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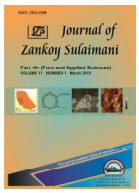

Synthesis and evaluation antimicrobial activity of some new S-substituted Quinazolinone containing pentagonal, hexagonal heterocyclic ring

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Abstract

New 1,2,4-triazine, imidazole ,2-aminothiazole, phthalazine and oxazoline derivatives of 2-mercapto-3-phenyl-4(3H)-quinazolinone were synthesized via an important intermediate compound(2) In which formed from reaction of compound(1) with chloroacetyl chloeide in dimethylformamide. The following different steps show the details of this work: The first step involves the conversion of compound (2) in to thiosemicarbazide and thiourea derivatives through its reaction with thiosemicarbazide,thiourea respectively to give compounds 3 and 4. Then cyclization of compounds 3 and 4 by using alkaline media 4N NaOH and concentrated H2SO4 to give compounds (5, 6 and 7) respectively. The second step involves treating compound (2) with hydrazine hydrate in dimethylformamide to give compound (8). Then reaction of prepared compound (8) with different aromatic anhydrides in acetic acid as a solvent to gives compounds (9-13). The third step involves preparation of compounds (14, 15 and 16) via reaction of compound (8) with (1-naphthyl isocyanate, phenylisocyanate and phenyl thioisocyanate) respectively in absolute ethanol. Then cyclization of compounds 14, 15 and 16 with alkaline media in the presence of 4N NaOH and p-bromophenacyl bromide to give compounds (17-22) respectively. The fourth step involves reaction of the prepared compound (8) with carbon disulfide in the presence of potassium hydroxide producing compound (23). The obtained salt (23) was treated with hydrazine hydrate to afford the desirable compound (24). The structure of newly synthesized compounds were identified by spectral methods such as FTIR, 1H-NMR, 13C-NMR, some other physical Properties and some specific reactions.

Introduction:

Quinazolinone has been considered as a magic moiety possessing myriad spectrum of medicinal activities. Diversity of biological response profile has attracted considerable interest of several researchers across the globe to explore this skeleton for its assorted therapeutic significance [1]. 1,2,4-Triazines and their derivatives have been widely studied in terms of their synthetic methodologies and reactivity since some of these derivatives were reported to have promising biological activities [2].The synthesis of 1,2,4-triazines and their derivatives are well documented and their methods of preparation are manifold and varied [3].On the other hand imidazole is a planer heterocyclic compound with five-member ring has three carbon atoms and two nitrogen atom at 1,3 positions. purine, histamine, histidine and nucleic acid , including imidazole ring[4], Imidazole derivatives possess a broad spectrum of pharmacological activities such as (Anti-fungal and Anti-bacterial activity)[5] ;Anticonvulsant[6] and anti-Parkinson[7]. The synthesis of new compounds

and testing their biological and pharmacological activities are the major goals of drug development projects. Nitrogen-containing heterocyclic compounds have received much attention as shown by the numerous studies published on their applicability in different areas, especially as drugs. [8,9] Phthalazines are examples of nitrogen heterocycles that possess exciting biological properties. [10-12]They form the structural profile for several biologically active compounds and hence they are considered important key elements. Several reports in the literature have focused on the pharmacology of phthalazine derivatives. The oxazoline is a five-membered heterocyclic organic compound containing one atom of oxygen and nitrogen. It exists between oxazole and oxazolidine in terms of saturation [13] Compounds containing this ring are referred to oxazolines or oxazolyls and have a variety of chemical uses; particularly as ligands in asymmetric catalysis and as protecting groups for carboxylic acids [14].

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 (4000-600) cm^{-1} spectral range. ^{1}HNMR and ^{13}CNMR spectra were recorded on Burker 300 MHZ instrument using DMSO-d_6 as solvent and TMS as internal reference. Thin layer chromatography (TLC) was carried out using fertig follen precoated sheets type polygram Silica gel and the plates were developed with iodine vapor.

Synthesis of 2-mercpto-3-phenyl-4(3H)quinazolinone **(1) [15]**

A mixture of anthranilic acid (4.114g, 0.03mol), phenylisothiocyanate (3.61ml, 0.03mol) and triethylamine (3ml) in absolute ethanol (60ml) was refluxed 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 and FTIR spectral data of compound (1) are listed in table (1).

Synthesis of S-(α-Chloroaceto-2-yl)-3-phenyl-4(3H)quinazolinone **(2) [16]**

To a mixture of compound (1) (3g , 0.01mol) in dimethylformamide(16ml) and potassium hydroxide(0.662g , 0.01mol) dissolve in methanol(9ml), chloroacetyl chloride (1ml,0.01mol)was added and the mixture was refluxed for 4 hrs..After time refluxed expiration leaves the mixture stirring overnight, then the reaction mixture was poured in to ice water, the separated precipitate was filtered and recrystallized from ethanol to give a dusty crystal, physical properties and FTIR spectral data are listed in table (1).

Synthesis of 2-[(3-phenyl-4-oxo-3,4-dihydroquinazolinone-2-yl-thio)aceto]thio semicarbazide(3), and thiourea (4) **[17]**

A mixture of compound (2) (2 gm, 0.006 mol) with {thiosemicarbazide, thiourea } respectively and sodium acetate (0.49 gm ,0.006 mol) in absolute ethanol (20 ml) was refluxed for (10-14 hrs.).The reaction mixture was filtered and poured on ice water. The precipitate was filtered, dried and recrystallized from suitable solvent to give crystals. Physical properties and FTIR spectral data of products are listed in table (1).

Synthesis of 2-[(3-mercapto-1,6-dihydro-1,2,4-triazin-5-yl) thio]-3-phenyl-4(3H) quinazolinone(5),and 2-[(2-thione-1,3-dihydroimidazol-4-yl)thio]-3-phenyl-4(3H)-quinazolinone (6) **[18]**

In round bottom flask (0.0012 mol) of compounds 3, 4 were refluxed with 4N sodium hydroxide solution (10 ml) for (8-10 hrs.), The mixture was cooled, poured on ice water, stirred and neutralized by gradual addition of (1:1) hydrochloric acid. The formed precipitate was filtered, dried and recrystallized from suitable solvent. Physical properties and FTIR spectral data of compounds (5, 6) are listed in table (1).

Synthesis of 2-[(2-aminothiazol-5-yl)thio]-3-phenyl-4(3H)quinazolinone(7) **[19]**

(0.4 gm, 0.001 mol) of Compound (4) was dissolved in cold concerted sulfuric acid (10 ml),the reaction mixture was refluxed for overnight, and then the mixture was cooled and poured ice and neutralized by (10%) sodium bicarbonate to remove the acid impurities. The formed precipitate was filtered and washed with water and recrystallized from ethanol. Physical properties and FTIR spectral data of this compound are listed in table (1).

Synthesis of 2-[(3-phenyl-4-oxo-3,4-dihydroquinazolin-2-yl)thio]acetohydrazide(8) **[20]**

To a solution of compound (2) (4 gm, 0.012 mol) in DMF (30ml), hydrazine hydrate 80% (2 ml, 0.024 mol) was added with continuous stirring and the resulting mixture was refluxed for (4hrs). After cooling the mixture white precipitate was formed. The precipitate was filtered and recrystallized from ethanol to give the pure product. Physical properties and FTIR spectral data of the product are listed in table (2).

Synthesis of S-[(7-nitro-1,2-dihydrophthalazin-3,10-dione-1-yl)aceto]-3-phenyl 4(3H)quinazolinone (9), S-[(hexahydro diazepine-3,7-dione-1-yl)aceto]-3-phenyl-4(3H) quinazolin one(10), S-[5,6,7,8-tetraphenyl-1,2-dihydrophthalazin-3,10-dione-1-yl)aceto]-3-phenyl-4(3H)quinazolinone(11), S-[(tetrahydropyridazin-3,6-dione-1-yl)aceto]-3-phenyl-4(3H)quinazolinone(12) **[21]**

A mixture of hydrazide derivative (8) (1gm, 0.003 mol) and 4-Nitrophthalic anhydride or Glutaric anhydride or 3.4,5,6- Tetraphenylphthalic anhydride or Succinic anhydride (0.003mol) In acetic acid (10ml) respectively was heated under reflux for 7 hrs. Then cooling the mixture by poured on ice bath to give the precipitate which was filtered and recrystallized from suitable solvent. Physical properties and FTIR spectral data of the products are listed in table (2).

Synthesis of S,S′-bis(1,1′,2,2′-tetrahydropyromillitazine,3,3′,10,10′-tetraoxo-1,1′-yl) aceto]-3-phenyl-4(3H)quinazolinone(13) **[21]**

A mixture of hydrazide derivative (8) and pyromellitic anhydride. (1.95 gm, 0.006 mol) and (0.654 gm, 0.003 mol) In acetic acid (15ml) was heated under reflux for 7 hours. Then cooling the mixture by adding on ice bath to give the precipitated product which was filtered and recrystallized from suitable solvent. Physical properties and FTIR spectral data of the product are listed in table (2).

Synthesis of 2-[(3-phenyl-4-oxo-3,4-dihydroquinazolinone-2-yl-thio)aceto]1-naphthylsemicarbazide(14), phenylsemicarb azide(15) and phenylthio semicarbazide (16) **[21]**

To a solution of compound (8) (2 gm ,0.006 mol) in absolute ethanol (25 ml), 1-naphthyl isocyanate(0.006 mol, 1.014 gm) or phenylisocyanate (0.006 mol, 0.714 gm) or phenyl thioisocyanate (0.006 mol, 0.81 gm) was refluxed for (5-6 hrs.). The reaction was cooled and the formed solid was filtered off, recrystallized from suitable solvent. Physical properties and FTIR spectral data of the products are listed in table (3).

Synthesis of 2-[(3-hydroxy-4-(α-naphthal)-1,4-dihydro-1,2,4-triazin-5-yl)thio]-3-phenyl-4(3H)quinazolinone(17), 2-[(3-hy droxy-4-phenyl-1,4-dihydro-1,2,4-triazin-5-yl) thio]-3-phen yl-4(3H)quinazolinone (18), 2-[(3-mercapto-4-phenyl-1,4-di hydro-1,2,4-triazin-5-yl)thio]-3-phenyl-4(3H)quinazolinone (19) **[18]**

The compound (14) (1 gm, 0.002 mol) or compound (15) (1 gm, 0.002 mol) or compound (16) (1 gm, 0.002 mol) was refluxed in 4N sodium hydroxide solution (25 ml) for (5-6 hrs.). Cooled, the mixture was cooled, poured on ice water, stirred and filtered to give the compound (19). Physical properties and FTIR spectral data are listed in table (3).

Synthesis of S-[5(P-Bromophenyl)-2-hydroxy-3-(α-naphthyl or phenyl)-2,3-dihydro-1,3-oxazole-2-yl) hydrazine]-3-phen yl-4-oxo-3,4-dihydro-quinazolin-2-yl-ethanethioate(20, 21) ,S-[5(P-Bromophenyl)-2-mercapto-3-(phenyl)-2,3-dihydro-1,3-oxazole-2-yl)hydrazine]-3-phenyl-4-oxo-3,4-dihydro-qui nazolin-2-yl-ethanethioate(22) **[18]**

A mixture of compound (14) (1 gm, 0.00202 mol) or compound (15) (1 gm, 0.00224 mol) or compound (16) (1 gm, 0.00216 mol) with *P*-Bromophenacyl bromide (0.002 mol) in abs. ethanol (30 ml) was refluxed for (6-7) hrs. The mixture was cooled and neutralized with ammonium hydroxide solution. The precipitate was filtered off, washed with water, dried and recrystallized from suitable solvent. Physical properties and FTIR spectral data are listed in table (3).

Synthesis of Potassium 2-[(3-phenyl-3,4-dihydroquinazolin one-2-yl-thio)aceto]di thiocarbazate(23) **[18]**

To a stirred solution of KOH (1.34g, 0.024mol) in ethanol (20 ml), hydrazide derivative (8) (2.6g, 0.008mol) and then CS_2 (0.24mol, 1.44ml) were added and stirred overnight, dry ether (20 ml) was added and the precipitate was filtered, washed with ether and dried. The salt (23) was obtained in almost quantitative yield

and was employed in the next step without further purification. Physical properties and FTIR spectral data of compound (23) are listed in table (4).

Synthesis of 2-[(4-amino-3-mercapto-1,4-dihydro-1,2,4-triazin-5-yl)thio]-3-phenyl-4(3H)quinazolinone(24) **[18]**

A suspension of potassium salt (23) (1 gm, 0.0022 mol) in excess hydrazine hydrate 80% (7 ml) was refluxed until the evolution of H_2S was ceased, during and the color of the reaction mixture changed and a homogeneous solution resulted. After cooling, the reaction mixture was acidified with 10% HCl to yield a precipitate and ethanol-water was used for recrystallization. Physical properties of compound (24) are listed in table (4).

Anti-microbial activity test [22]

The test was performed according to the disk diffusion method. Some of prepared compounds were tested against two strain gram +ve (*Staphylococcus aura* and *Bacilles*) and two strain gram –ve bacteria (*Escherichiacoli* and *pseudomanacruginosa*). 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 121 °C. The sterile disks were impregnated with different compounds (800µg/disk). Agar plates were surface inoculated uniformly with 100 °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 for 1 hr. to permit good diffusion and then transferred to an incubator at 37 °C 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 the prepared compounds (1-7)

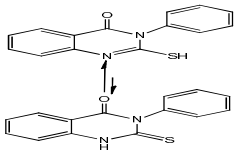
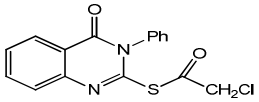
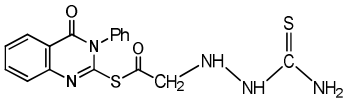
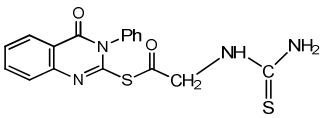
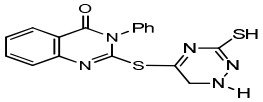
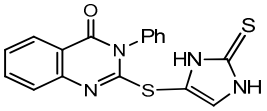
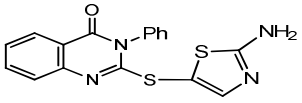
Com.No.	Physical Properties				Major FTIR Absorption cm^{-1}				
	Structures	M. P. C°	Yield %	Color	ν(N-H)	ν(C-H) aliph.	ν(C=O)	ν(C=N)	Others
1		297-299	89	white	3245	-	1662	1622	ν(C-H) arom. 3028 3064 ν (C=S) 1226
2		158-160	96	White	-	2910	1735 keton 1681 Amid	1662	ν (C-Cl) 644
3		239-240	83	White	3245	2952 2820	1735 Keton 1683 Amide	1622	ν(NH_2) asym.3447 Sym.3364 ν(C=S) 1226
4		143-145	84	White	3247	2920 2850	1735 Keton 1683 Amide	1620	ν(NH_2) asym.3416 Sym.3364 ν (C=S) 1257
5		211-212	80	Grey	3245	2921 2850	1664 Amide	1622	ν(S-H)2617
6		183-184	89	white	3245	2921 2850	1664 Amide	1622	ν(C=C) 1650 ν (C=S) 1228
7		174-176	75	Pale grey	3245	2921 2850	1662 Amide	1608	ν(NH_2) asym.3525 Sym.3452

Table 2 - Physical properties and FTIR spectral data cm^{-1} of the prepared compounds (8-13)

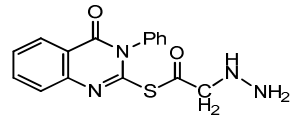
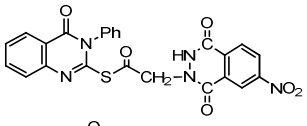
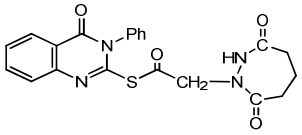
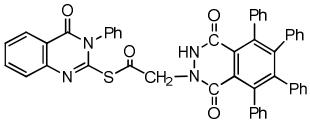
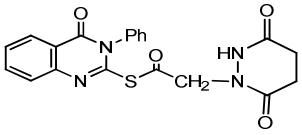
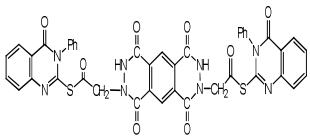
Com.No.	Physical Properties				Major FTIR Absorption cm^{-1}				
	Structures	M. P. C°	Yield %	Color	ν(N-H)	ν(C-H) aliph.	ν(C=O)	ν(C=N)	Others
8		260-262	60	White	3253	2923 2850	1716 Keton 1681 Amide	1616	$\nu(NH_2)$ asym. 3456- Sym. 3348
9		278-280	85	white	3247	2957 2850	1755 Keton 1685 Amide	1602	νNO_2 Asym. 1510 Sym.1355
10		220-222	87	White	3114	2923 2852	1733 Keton 1683 Amide	1616	
11		266-268	80	Pale orange	3346		1741 Keton 1687 Amide	1602	
12		198-200	79	white	3114	2920 2850	1731 Keton 1687 Amide	1616	
13		269-270	76	Pale grey	3257	2920	1749 Keton 1664 Amide	1620	

Table 3 (A) - Physical properties and FTIR spectral data cm^{-1} of the prepared compounds (14-19)

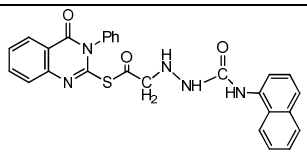
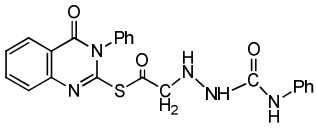
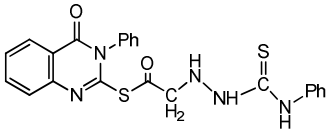
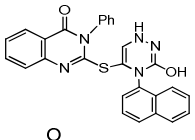
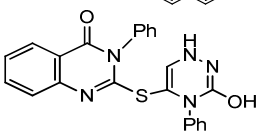
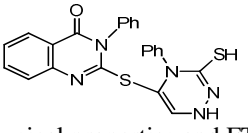
Com.No.	Physical Properties				Major FTIR Absorption cm^{-1}				
	Structures	M. P. C°	Yield %	Color	ν(N-H)	ν(C-H) aliph.	ν(C=O)	ν(C=N)	Others
14		228-230	84	white	3245	2966 2945	1710 Keton 1689 Amide	1650	δ(N-H) 1618
15		246-248	80	White	3263	2972	1712 Keton 1683 Amide	1658	δ(N-H) 1620
16		264-266	75	white	3355	2925 2858	1715 Keton 1691 Amide	1620	ν (C=S) 1299
17		300>	70	white	Overlap with ν(O-H)	2920 2850	1647 Amide	1608	ν(O-H) 3382
18		300>	68	White	Overlap with ν(O-H)	2920 2869	1670 Amide	1604	ν(O-H) 3436
19		284-286	75	white	3260	2920 2850	1647 Amide	1625	

Table 3 (B) - Physical properties and FTIR spectral data cm^{-1} of the prepared compounds (20-22)

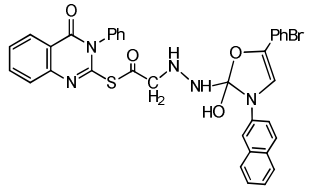
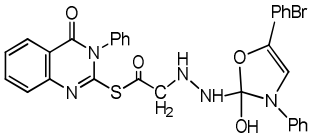
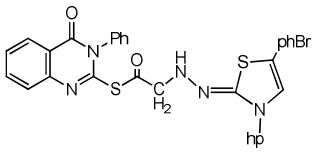
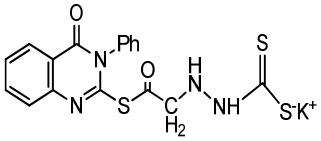
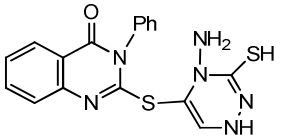
Com.No.	Physical Properties				Major FTIR Absorption cm^{-1}				
	Structures	M. P. C°	Yield %	Color	ν(N-H)	ν(C-H) aliph.	ν(C=O)	ν(C=N)	Others
20		278-280	84	white	3275	2975 2923	1710 Keton 1685 Amide	1598	νO-H 3465 ν(C-Br)613 νC-O-C Asym. 1298 Sym 1145
21		194-195	76	White	3298	2974 2894	1708 Keton 1683 Amide	1602	νO-H 3450 ν(C-Br)620 νC-O-C Asym. 1267 Sym. 1172
22		182-184	80	white	3275	2914 2850	1707 Keton 1683 Amide	1610	ν(C-Br) 650 νC-O-C Asym. 1267 Sym 1199

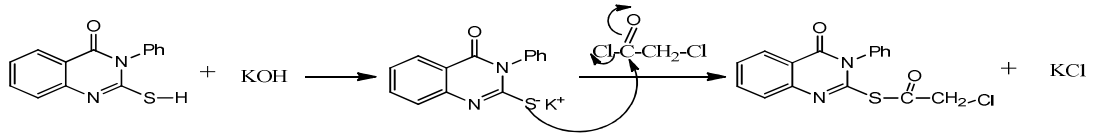
Table 4 - Physical properties and FTIR spectral data cm^{-1} of the prepared compounds (23-24)

Com.No.	Physical Properties				Major FTIR Absorption cm^{-1}				
	Structures	M. P. C°	Yield %	Color	ν(N-H)	ν(C-H) aliph.	ν(C=O)	ν(C=N)	Others
23		174-175	89	white	3220	2927 2850	1707 Keton 1689 Amide	1622	ν(C=S) 1228
24		196-198	78	White	3210	2920 2850	1679 Amide	1600	$\nu(NH_2)$ 3563 Asym. 3336 Sym.

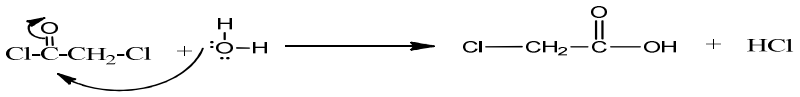
Results and Discussion:

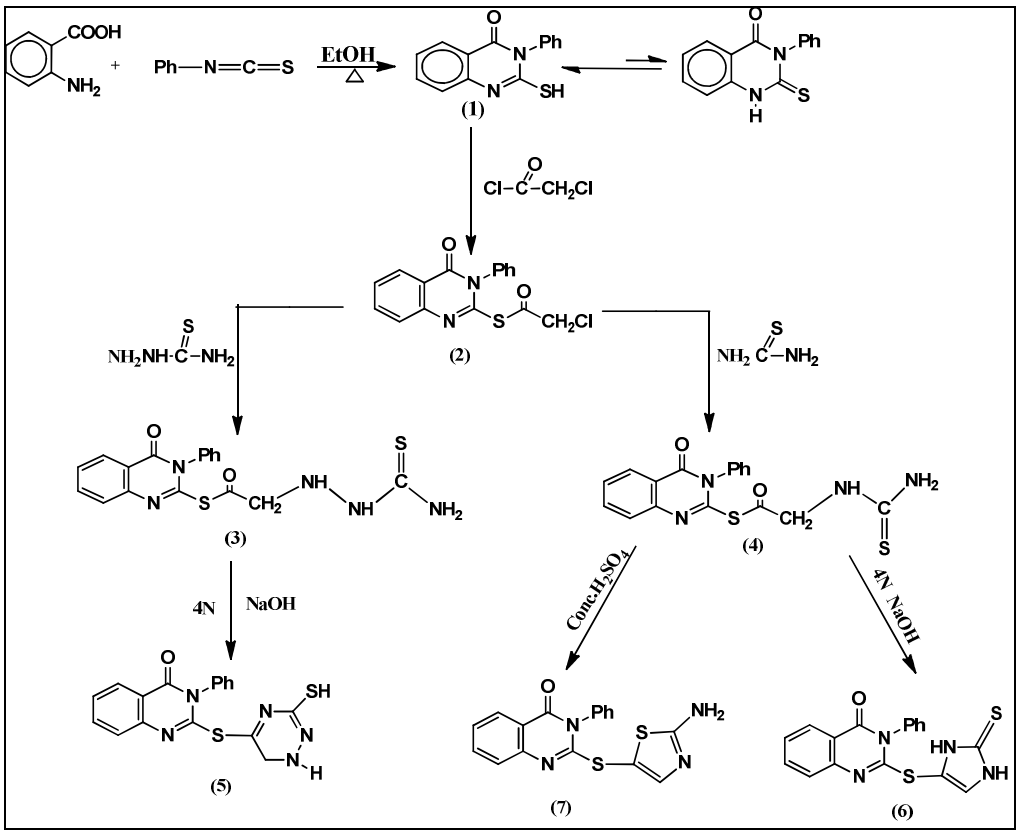
The present work involves the application of various synthetic methods in preparation of different new compounds containing pentagonal, hexagonal hetero rings such as 1,2,4-triazine,imidazole and 2-aminothiazole linked to compound (2). These different syntheses performed in this work were summarized in scheme (1).

As starting material S-(α-chloroaceto-2-yl)-3-phenyl-4(3H) quinazolinone (2) was prepared by reaction of compound (1) with chloroacetyl chloride in the presence of potassium hydroxide solution in dry DMF according to the following equation:



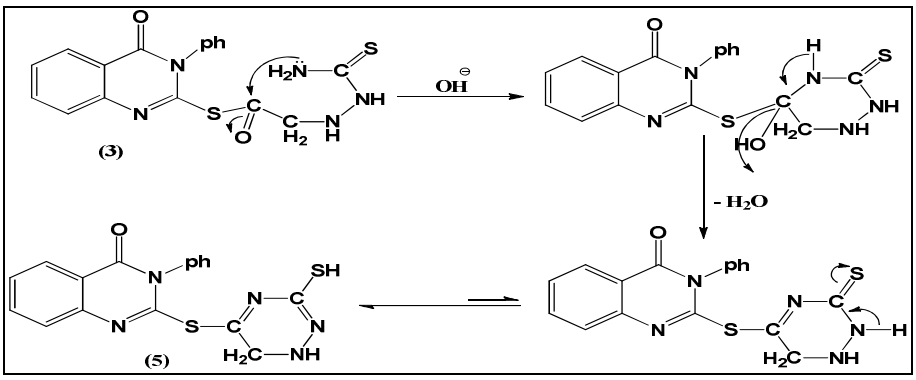
The reaction should be carried in dry condition otherwise water would react with chloroacetyl chloride according to the following equation:





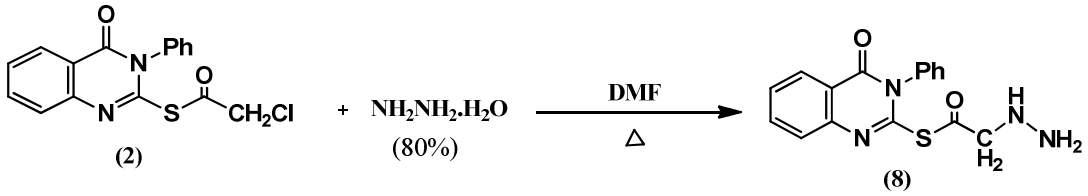
Scheme (1): Preparation of new derivatives of 2-mercapto-3-phenyl-4(3H)-quinazolinone compounds (1-7).

The structure of compound (2) was confirmed by physical properties which are listed in table (1).FTIR spectra showing the absorption at ν cm^{-1} 2910 for C-H aliph. ; 1735 for C=O (keton); 1681 for C=O (amid) and 644 for C-Cl.^{1}HNMR spectrum showed singlet signal at δ= (4.00) ppm due to (-$\underline{CH_2}$-Cl) protons and multiple signals at δ= (7.27-8.09) ppm due to aromatic rings protons as listed in table(5).Also silver nitrate alcoholic test confirmed the presence of chlorine group [23]. The compound (2) was converted to {thiosemicarbazide (3) and thiourea (4)} derivatives by reaction with (thiosemicarbazide and thiourea) respectively in absolute ethanol. FTIR spectral date showing the absorption at (3425 cm^{-1}) asym. (3309 cm-1) sym. for NH_2, (3245 cm^{-1}) for NH, (1735 cm^{-1}) for C=O keton, (1683 cm^{-1}) for C=O amide,(1267 cm^{-1}) for C=S of compound (3). (3416 cm^{-1}) asym. (3367 cm^{-1}) sym. for NH_2, (3245 cm^{-1}) for NH, (1735 cm^{-1}) for C=O keton, (1683 cm^{-1}) for C=O amide, (1257 cm^{-1}) for C=S, of compound (4). Treatment of compounds (3 and 4) with (4N NaOH) solution afford intramolecular cyclization to give the 1,2,4-triazine (5) and imidazole (6). Mechanism of reaction involved nucleophilic attack lead to intramolecular cyclization [14] as shown in scheme (2).

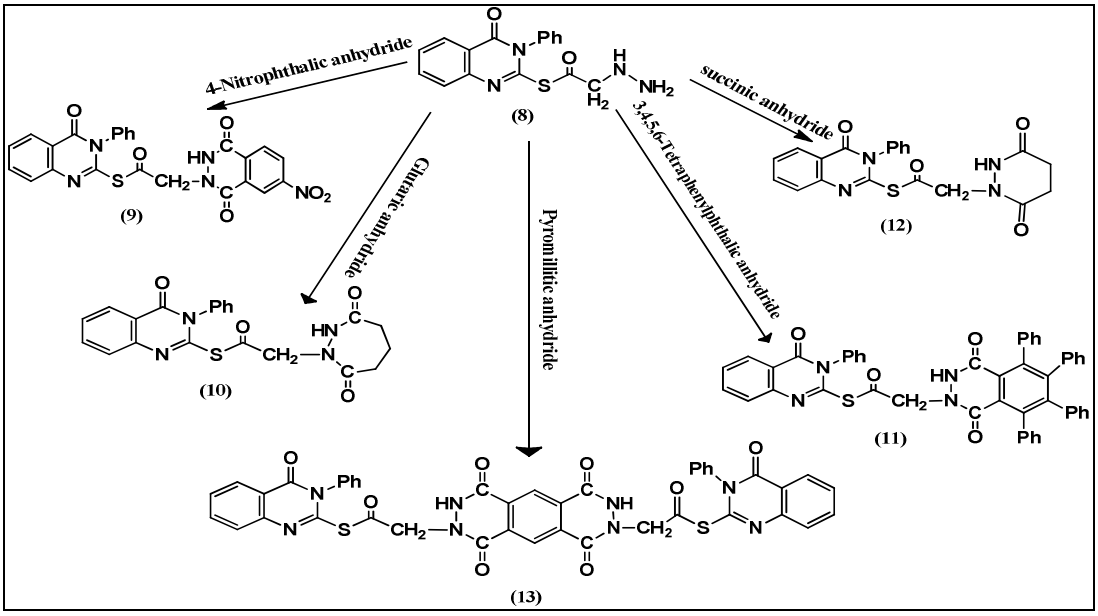


Scheme (2): Mechanism of reaction involves nucleophilic attack leading to intramolecular cyclization

These compounds were identified from FTIR spectra, that shows results listed in table (1). ^{1}H-NMR spectrum of compound (5) showed doublet signal at δ= (2.72) ppm due to (-C<u>H</u>$_2$-) protons, singlet signal at δ= (3.78) ppm due to(S-H) proton, singlet signal at δ= (7.19-7.95) ppm due to (Ar-H) protons, and signals at δ= (11.6)ppm due to (N-H) as shown in Table (5) and showed in figure (1). And the treating of compound (4) with conc. H_2SO_4 under reflux condition affected intramolecular cyclization through the loss of H_2O giving the 2- amino thiazole derivatives (7). The FTIR spectrum of compound (7) showed the disappearance of the (C=O) keton bands of compound (4) at 1735 cm^{-1} and appearance of bands at (3525, 3452) cm^{-1} for asymmetric and symmetric stretching bands of (NH_2), ^{1}H-NMR spectrum of compound (7) showed singlet signal at δ= (4.20) ppm due to (-NH_2) protons, singlet signal at δ= (7.20) ppm due to (=CH-N) proton and signals at δ= (7.34-8.10) ppm due to (Ar-H) protons, as shown in table (5). The hydrazide derivative (8) was found a suitable route for this synthetic approach. So when compound (2) was refluxed with hydrazine hydrate in dimethylformamide as a solvent it gave the expected hydrazide derivative (8). The equation below shows the details of this reaction:

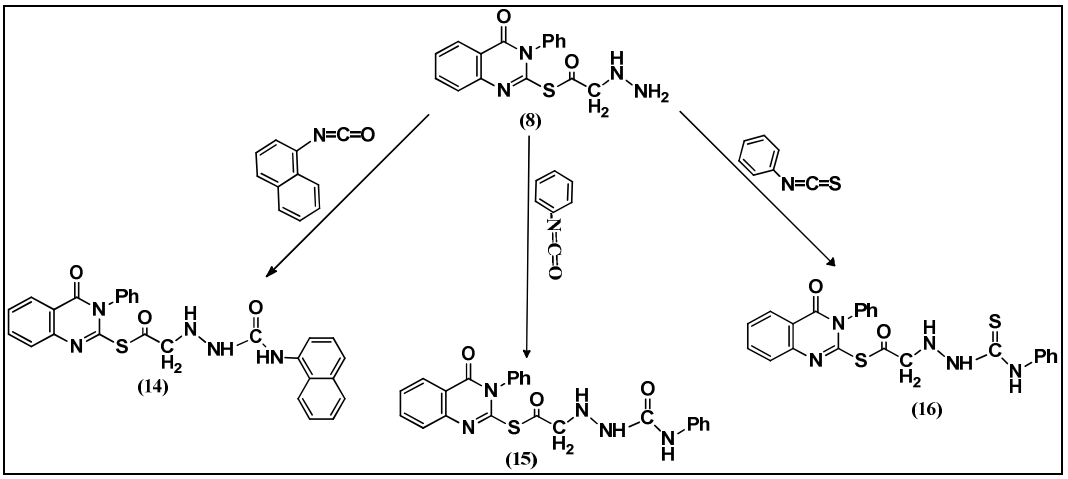


FTIR spectrum of prepared compound (8) confirmed its formation through the appearance of bands at (3456 and 3348) cm^{-1} which was assigned to the asymmetric and symmetric stretching bands of (NH_2) and (NH) groups. In addition to the disappearance of C-Cl band at 644cm^{-1} of compound (2). ^{1}H-NMR spectrum of compound (8) showed doublet signal at δ= (2.82) ppm due to (-C<u>H</u>$_2$-) protons, singlet signal at δ= (3.40) ppm due to (-N<u>H</u>$_2$) protons, signals at δ= (7.37-8.26) ppm due to aromatic rings protons, and singlet signal at δ= (9.55) ppm due to (N-H) proton as shown in table (5) and showed in Figure (2). ^{13}C-NMR spectral data of compound (8) are listed in Table (6) and shown in figure (3).The compounds (9-13) were synthesized by the reaction of hydrazide derivative (8), with (4-Nitrophthalic anhydride, Glutaric anhydride, 3,4,5,6-Tetraphenyl phthalic anhydride, succinic anhydride, Pyromellitic anhydride) respectively, in the presence of acetic acid as solvent and catalyst. These compounds were summarized in scheme (3).



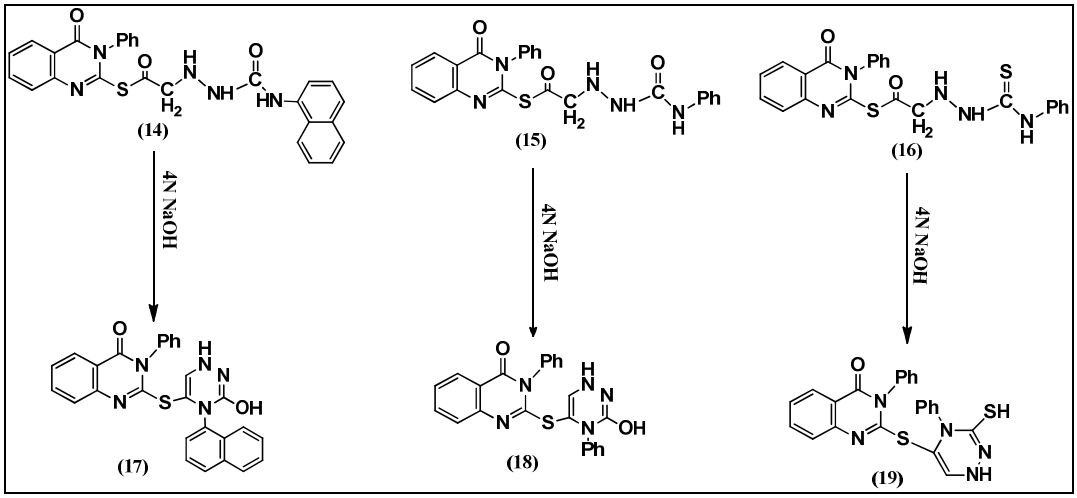
Scheme (3): Preparation of new derivatives of 2-mercapto-3-phenyl-4(3H)-quinazolinone for compounds (9-13).

The FTIR spectra of compounds (9-13) show the disappearance of the two bands of (-NH_2) group of hydrazide derivative (8) FTIR spectral data of compounds (9-13) at (3456 and 3348) cm^{-1}. And appearance of a band due to (-NH) group at the range (3346-3114) cm^{-1}. Two carbonyl groups of compounds (9-13) appeared at (1735-1703) cm^{-1} for cyclic carbonyl and at (1687-1664) cm^{-1} for the amide carbonyl. And the hydrazide derivative (8) was converted to compounds (14-16) via reaction with α-naphthyl isocyanate, phenylisocyanate and phenyl thioisocyanate in absolute ethanol as shown in scheme (4).



Scheme (4): Preparation of new derivatives of 2-mercapto-3-phenyl-4(3H)-quinazolinone for compounds (14-16).

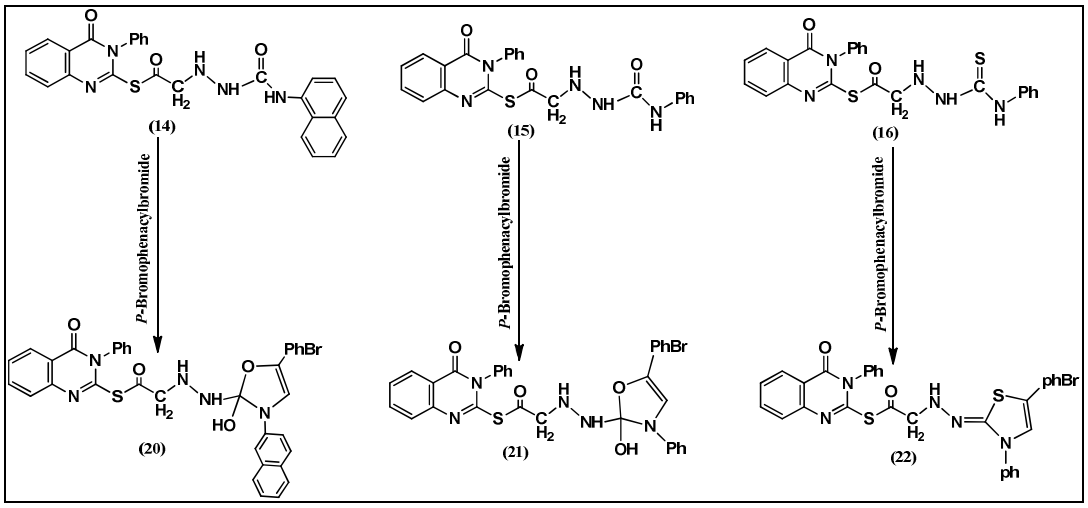
FTIR spectral data showed absorption at (3245,3263,3255) cm^{-1} for NH , (1710,1712,1715) cm^{-1} for C=O keton, (1689,1683,1691) cm^{-1} for C=O amide in compound (14, 15, 16) respectively together with appearance of a band at (1299)cm^{-1} for C=S of compound (16) and disappearance of ν NH2 at (3456 cm^{-1}) Asym., (3348 cm^{-1}) sym. Reaction of compounds (14, 15 and 16) with 4N NaOH under refluxing condition effected intramolecular cyclization through the loss of H_2O giving the 1,2,4-triazine derivatives. These compounds (17-19) were synthesized according to reaction scheme (5).



Scheme (5): Preparation of new derivatives of 2-mercapto-3-phenyl-4(3H)-quinazolinone for compounds (17-19).

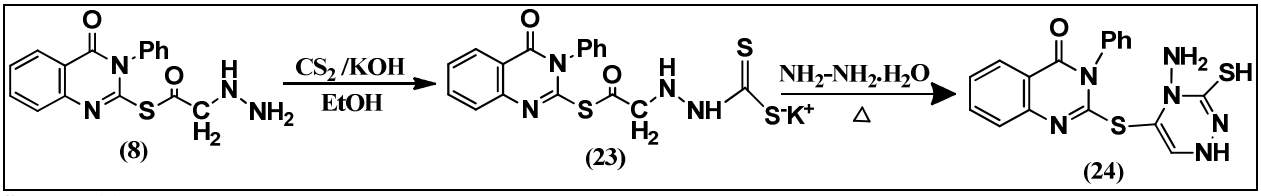
The FTIR spectra showed the disappearance of two carbonyl groups of the starting materials (14, 15) at 1710, 1715, 1689 and 1691 cm^{-1}. In addition to the appearance of abroad OH bands for compounds (17, 18) at 3436 and 3382 cm^{-1} respectively. ^{1}H-NMR spectrum of compound (19) showed a singlet signal at δ= (3.38) ppm due to (S-H) proton, singlet signal at δ= (7.17) ppm due to (=C<u>H</u>-NH) proton, signals at δ= (7.35-

7.69) ppm due to aromatic rings protons, and singlet signal at δ= (8.08) ppm due to (N-H) proton as shown in table (5). The compounds (20-22) were synthesized according to the reaction scheme (6).



Scheme (6): Preparation of new derivatives of 2-mercapto-3-phenyl-4(3H)-quinazolinone for compounds (20-22).

The oxazoline derivatives are considered important branch of heterocyclic compounds due to their biological activities. The reaction of compound (14, 15 and 16) with *P*-Bromo phenacylbromide under refluxing condition affected an intermolecular cyclization through SN_2 mechanism and tetrahedral nucleophilic substitutions [19] giving the oxazoline derivatives (20, 21 and 22) respectively. The structure of oxazoline derivatives were confirmed by FTIR spectroscopy. FTIR spectrum showed a broad band of (OH) group at (3450-3465) cm^{-1} , strong sharp bands of (NH) at 3275 cm^{-1}, (C-H) aliphatic at (2974 - 2914) cm^{-1}, band of (C=O) at 1683 cm^{-1}, ν(C=C) of oxazoline ring at 1610, respectively. ^{1}H-NMR spectrum of compound (21) showed doublet signal at δ= (3.35) ppm due to (-C<u>H</u>$_2$-) protons, doublate signal at δ= (4.69) ppm due to (-CH$_2$-N<u>H</u>) protons, singlet signal at δ= (5.04) ppm due to (O-H) proton, singlet signal at δ= (7.06) ppm due to oxazole ring protons, signals at δ= (7.42-8.49) ppm due to aromatic rings protons, and doublet signal at δ= (9.54) ppm due to(N<u>H</u>) oxazole ring protons as shown in table (5) and in figure (4). Compound (8) has been used for the preparation of compound (23) by the reaction of hydrazide derivative (8) with CS_2 in ethanolic/KOH to give the dithiocarbazate salt (23) in excellent yield, which was then cyclized by refluxing with 80% hydrazine hydrate to give a moderate yield of triazine derivative (24). These compounds (23, 24) were synthesized according to reaction. Shown in scheme (7).



Scheme (7): Preparation of new derivatives of 2-mercapto-3-phenyl-4(3H)-quinazolinone for compounds (23-24).

FTIR spectrum of compound (24) showed absorptions at (3563) cm^{-1} asym , (3336) cm^{-1} sym. due to ν(NH_2); (1600) cm^{-1} due to ν(C=N); The ν(N-H) group overlap with νNH_2.

Table 5: ^{1}H-NMR spectral data (δ ppm) for selected compounds

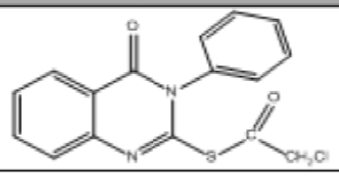
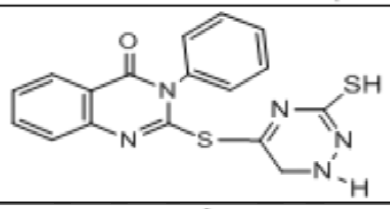
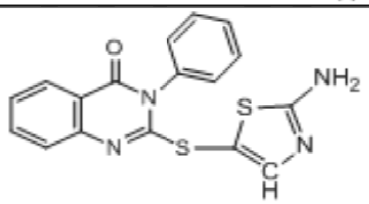
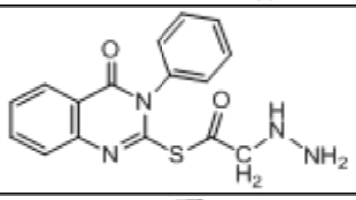
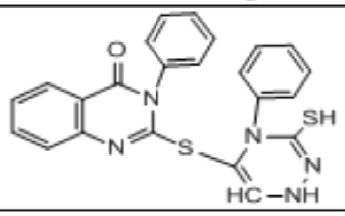
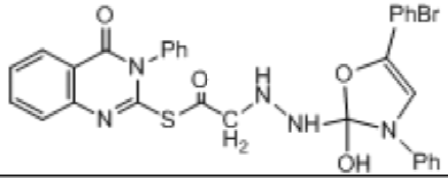
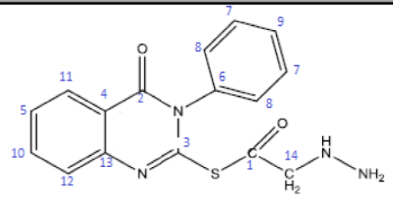
Comp. No.	Structures	^{1}HNMR Spectral data($^{\delta}$ppm)
2		4.00(s,2H, -CH$_2$-);7.27-8.09 (m,9H,Ar-H)
5		2.72 (d, 2H, CH$_2$); 3.78 (s,1H, S-H);7.19-7.95(m,9H,Ar-H); 11.6(s,1H,N-H).
7		4.20(s,2H,NH$_2$);7.20 (s,1H,=CH-N);7.34-8.10 (m,9H,Ar-H).
8		2.82 (d,2H,CH$_2$); 3.40 (s,2H,NH$_2$); 7.33-8.26 (m, 9H,Ar-H); 9.55 (s,1H,N-H)
19		3.38 (s, 1H, S-H); 7.17 (s, 1H, =CH-NH); 7.35-7.69 (m, 14H, Ar-H); 8.08 (s, 1H, N-H).
21		3.35(d, 2H, CH$_2$); 4.69(d, 1H, CH$_2$-NH); 5.04 (s, 1H, OH); 7.06 (s, 1H, oxazole ring); 7.42-8.49(m, 18H, Ar-H); 9.54(d, 1H, NH, oxazole ring).

Table 6: ^{13}CNMR spectral data (δ ppm) for selected compounds

Comp. No.	Compound structure	^{13}CNMR spectral data (δ ppm)
8		173.35(C1),158.55(C2),148.49(C3),135.78(C4),135.25 (C5),132.85(C6),129.16(C7)129.05(C8),128.88(C9),128.69 (C10),126.86(C11),116.99(C12),115.89(C13),56.20(C14)

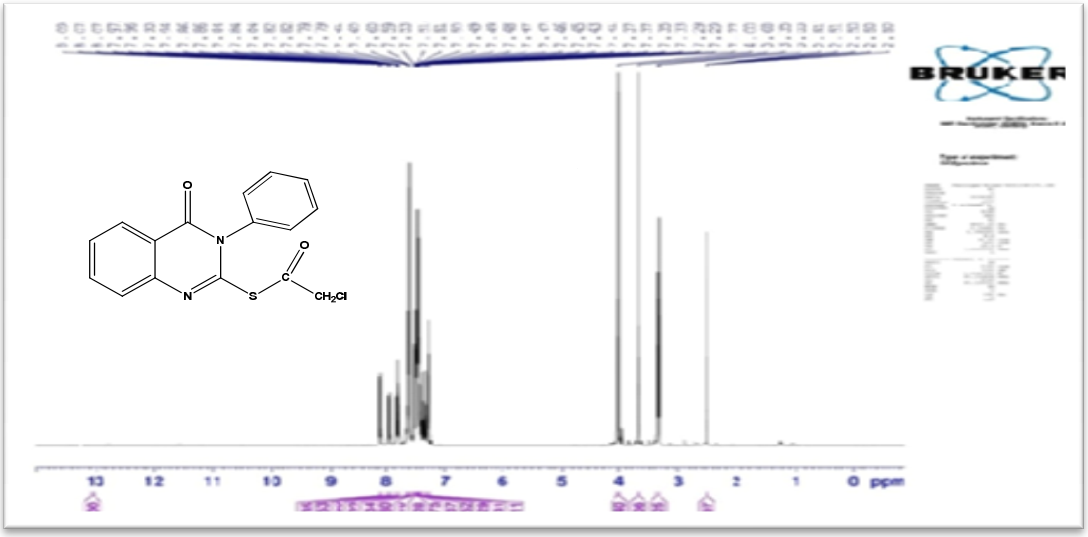


Figure 1 -[1]HNMR spectrum of compound (2)

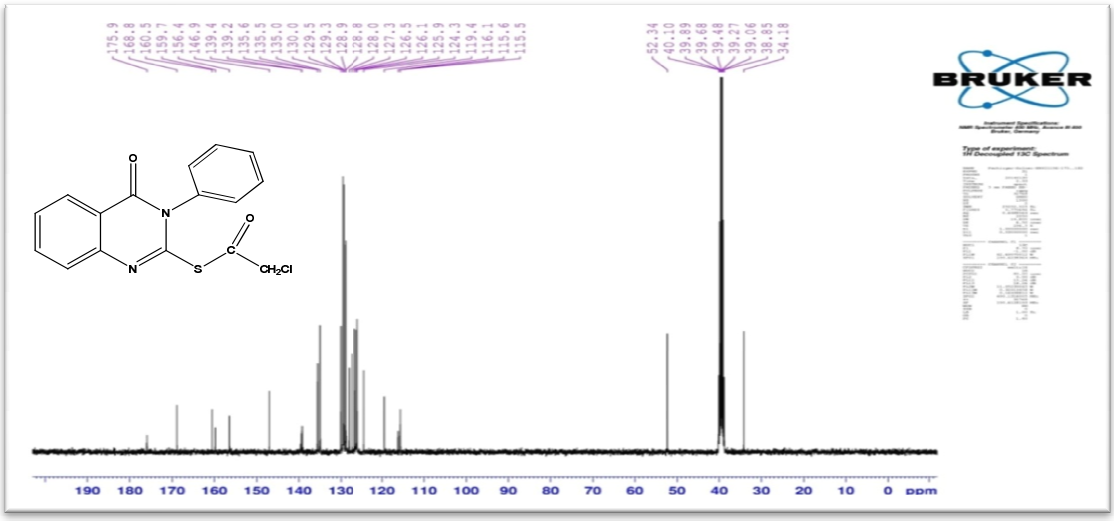


Figure 2-[13] CNMR spectrum of compound (2).

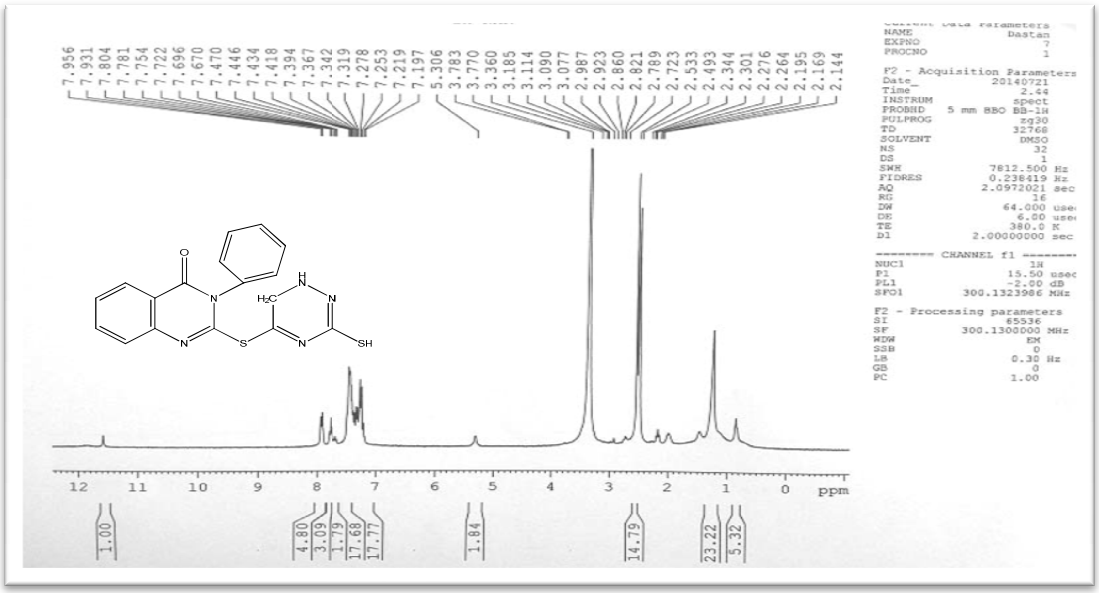


Figure 3 -[1]HNMR spectrum of compound (5)

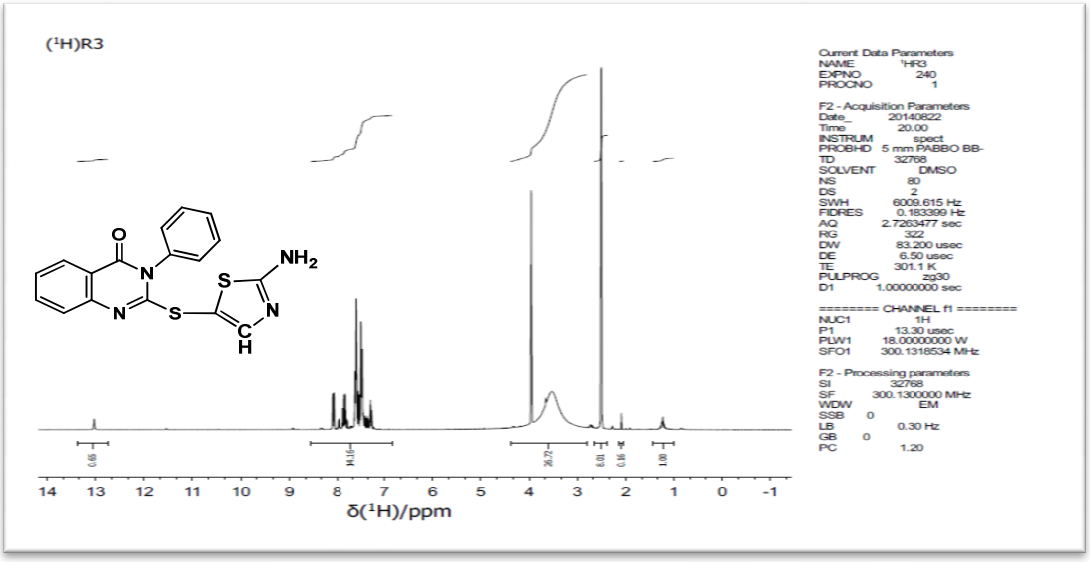


Figure 4 - ^{1}HNMR spectrum of compound (7)

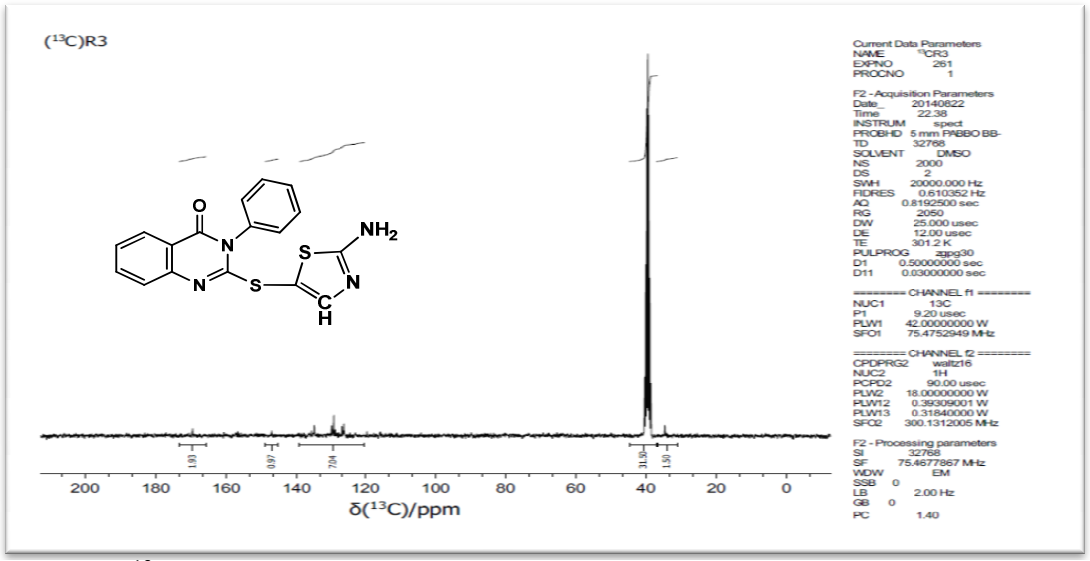


Figure 5-^{13} CNMR spectrum of compound (7).

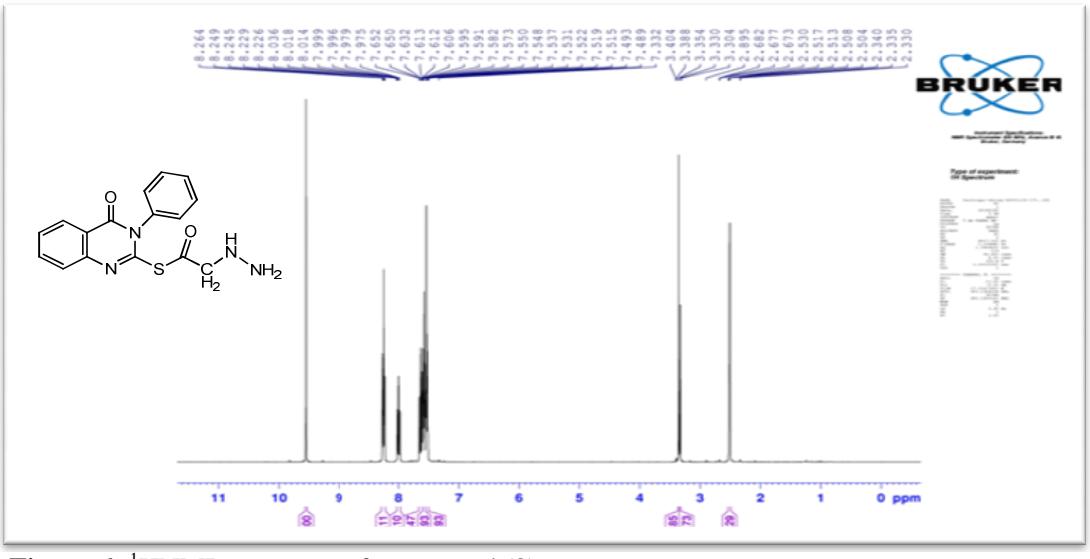


Figure 6 - ^{1}HNMR spectrum of compound (8)

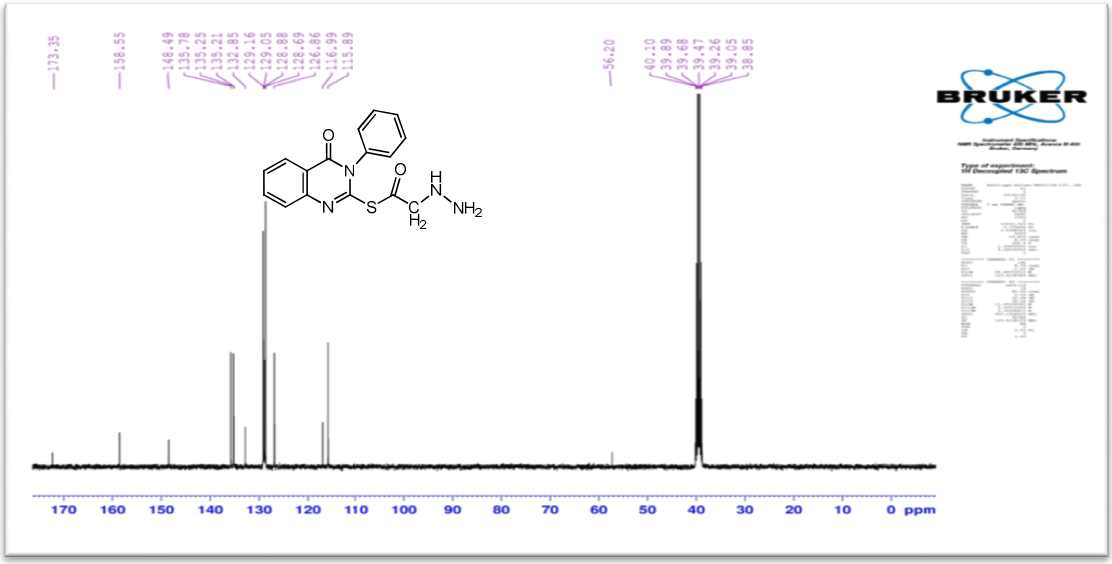


Figure 7-[13] CNMR spectrum of compound (8).

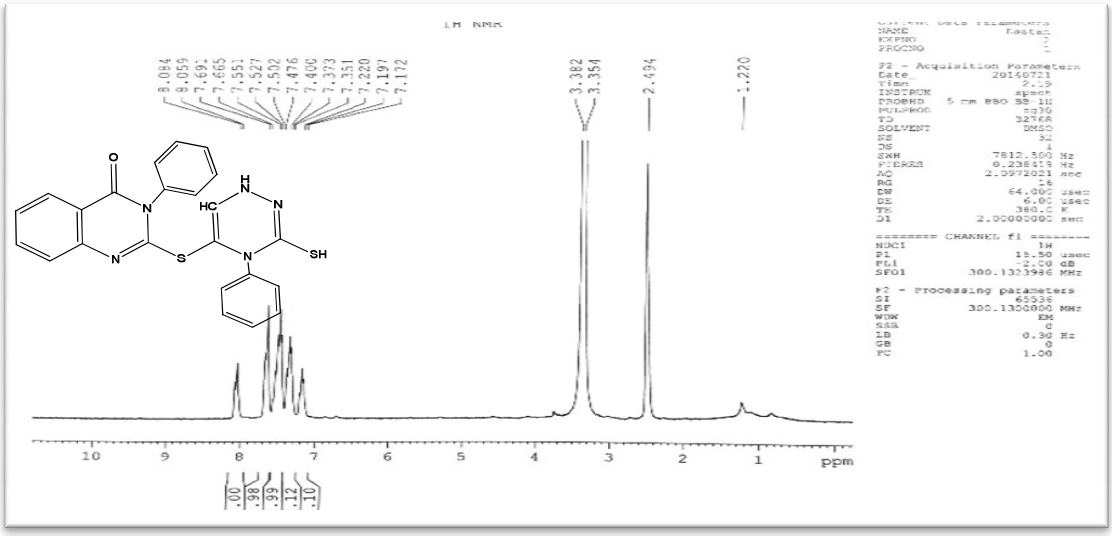


Figure 8 -[1]HNMR spectrum of compound (19)

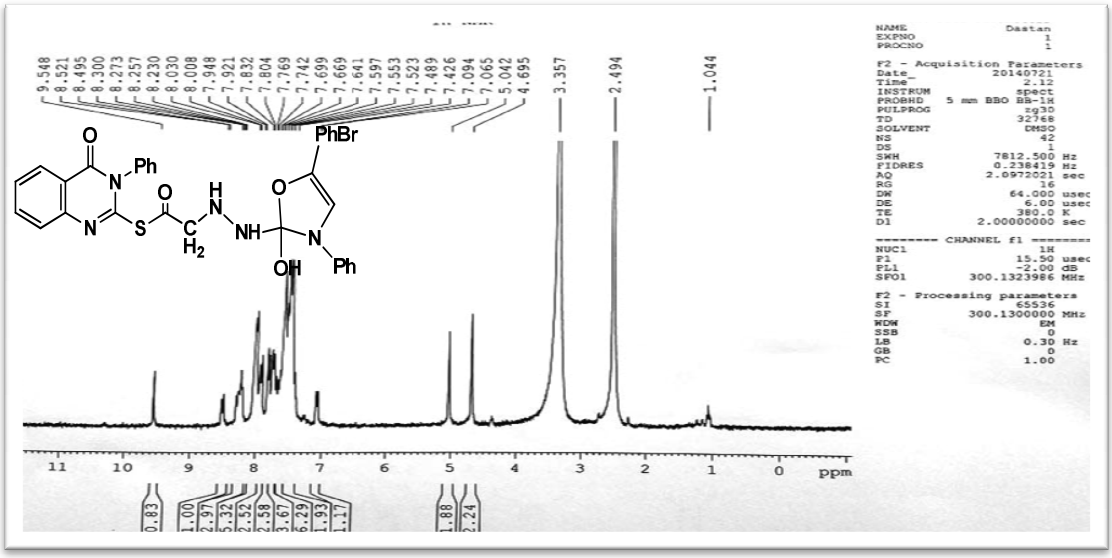


Figure 9 -[1]HNMR spectrum of compound (21)

Anti-microbial activity:

The results of antimicrobial activity are listed in table (7). 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. Compounds (9, 12) possess strong activity against ***Staphylococcus aureus***, while compounds (21, 22) possess moderate activity against same bacteria. Compounds (5, 17, and 19) possess moderate activity against ***Bacilliessubtilus*** while ***Pseudomonas aeruginosa*** was inhibited by compounds (9, 12). Compounds (5, 9 and 21) was found to possess good activity against ***Candidau*****.** All compounds in table (7) had not activity against ***Escherichia coli*** except compounds (12, 21 and 22) which possess weak activity against same bacteria.

Table 7: anti-microbial activity of some the tested of prepared compounds

Comp. No.	*Staphylococcus aureus*	*Bacilliessubtilus*	*Escherichia coli*	*Pseudomonas aeruginosa*	*Candidau*
5	-	15	-	-	20
6	-	10	-	-	15
9	15	-	-	18	20
12	18	-	5	16	12
17	-	14	-	-	15
19	-	12	-	-	13
21	12	3	5	-	16
22	10	10	2	-	12

Solvent: DMSO; [C]: 800µg/ml. Zone of inhibition: (-) no inhibition zone; (3-6) weak; (7-10) moderate; (11-20) strong.

References

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