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Synthesis of Heterocyclic Compounds Derived from 2-Mercapto Quinoline

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Abstract

2-Mercapto quinoline was used as precursor for synthesis of new heterocyclic derivatives of quinoline nucleus such as pyrazole (3), pyrazolone (4), 1,3,4-oxadiazole (5) and 1,2,4-triazole (8). New Schiff bases (9a-e) were obtained from the reaction of hydrazide derivative (2) with miscellaneous aldehydes and ketones. All synthesized compounds were characterized by physical and spectral data.

Introduction

There is continuing interest in quinoline derivatives due to their large variety of industrial and biological activities[1-3]. It was reported that quinoline derivatives which in corporating another heterocyclic ring displayed an impressive properties, for example, the presence of pyrazole or pyrazolone moiety with quinoline have antimicrobial[4,5] and industrial importance[5-7] while the presence of 1,3,4-oxadiazole or 1,2,4-triazole nucleuses shows diverse therapeutic uses[8-10]. Biocidal activities of shiff's bases of 2-mercapto quinoline have also been established[11,12]. Based on these considerations we aimed to obtain this class of quinoline derivatives.

Experimental

A- Materials

All chemical used were supplied from Fluka and BDH except for the starting material 2-mercapto quinoline which was supplied from Aldrich.

B- Instrumentation

Melting points were recorded using electro thermal melting point apparatus and are uncorrected. Infrared spectra were recorded as KBr disc on SHIMADZU-FT-IR-8400 spectrometer. The UV-Visible spectra were measured in ethanol using SHIMADZU UV-Vis 160A spectrometer. The progress of the reactions was monitored by TLC using aluminum silica gel plates 60 F_{245}.

Synthesis of ethyl (quinoline-2-yl thio) acetate (1)[13]:

Ethyl chloroacetate (0.01mol) was added drop wise to a hot solution of 2-marcapto quinoline and sodium hydroxide in ethanol as a solvent. The mixture was refluxed for 2 hrs. then it filtered and the filtrate poured onto ice and left for 1 hr. The formed solid was collected and recrysallized from ethanol.

Synthesis of 2-(quinoline-2-yl thio) acetohydrazide (2)[14]:

To a hot solution of hydrazine hydrate (0.01mol) in ethanol (10ml) a solution of compound (1) in ethanol (10ml) was added and the mixture was stand for 2 hrs. then (5ml) of benzene was added. The solvent was removed and the precipitate recrystallized from ethanol.

Synthesis of 3,5-Dimethyl-1-[(quinoline-2-yl thio)acetyl]-1H-pyrazole(3)[15]:

A mixture of acetylacetone (0.002mol) and compound (2) (0.002mol) was heated under reflux for 8 hrs. The mixture was allowed to cool and the precipitate recrystallized from ethanol.

Synthesis of 5-methyl-2-[(quinoline-2-yl thio)acetyl]-2,4-dihydro-3H-pyrazole-3-one(4) [15]:

A mixture of ethylacetoacetate (0.002mol) and compound (2) (0.002mol) was heated under reflux for 8 hrs. The mixture was allowed to cool and the precipitate recrystallized from ethanol.

Synthesis of 5-[(quinoline-2-yl thio)methyl]-1,3,4-oxadiazole-2-thiol(5)[16]:

To a mixture of compound (2) (0.003mol) in (10ml) ethanol KOH (0.003mol) in (30ml) ethanol was added at (0-4 ˚C). The mixture was stirred for few minutes then (3ml) of CS_2 was carefully added at the same temperature. Then the mixture was stand for 5 hrs afterwards the solvent was evaporated the residue was poured into ice water and acidified with (10%) HCl. The solid product was filtrated, washed with water and recrystallized from ethanol.

Synthesis of 2-[({5-(4-nitrophenyl thio)}-1,3,4-oxadiazole-2-yl)thio]quinoline(6)[17]:

P-nitro flouro benzene (0.001mol) was added gradually to a mixture of compound (5) (0.001mol) and KOH (0.001mol) in ethanol under stirring then the resulted mixture was refluxed for 1hr and poured into ice-water. The solid product was filtered, dried and recrystallized from methanol.

Synthesis of 4-amino-5-[(quinoline-2-yl thio)methyl]-1,2,4-triazole-3-thiol(8)[18]:

A mixture of compound (2) (0.003mol) and KOH (0.004mol) in ethanol (30ml) was cooled and (5ml) of CS_2 was added with stirring then the mixture was refluxed for 1hr. the product (xanthate salt) (7) was filtered, washed with ether and dried . The mixture of salt and (3ml) of hydrazine hydrate in (2ml) of water was refluxed until the emission of H_2S gas stopped (detected by using soaked paper with CH_3COOPb) then it cooled, filtered and the filtrate was acidified with diluted hydrochloric acid. The solid product was collected and recrystallized from ethanol.

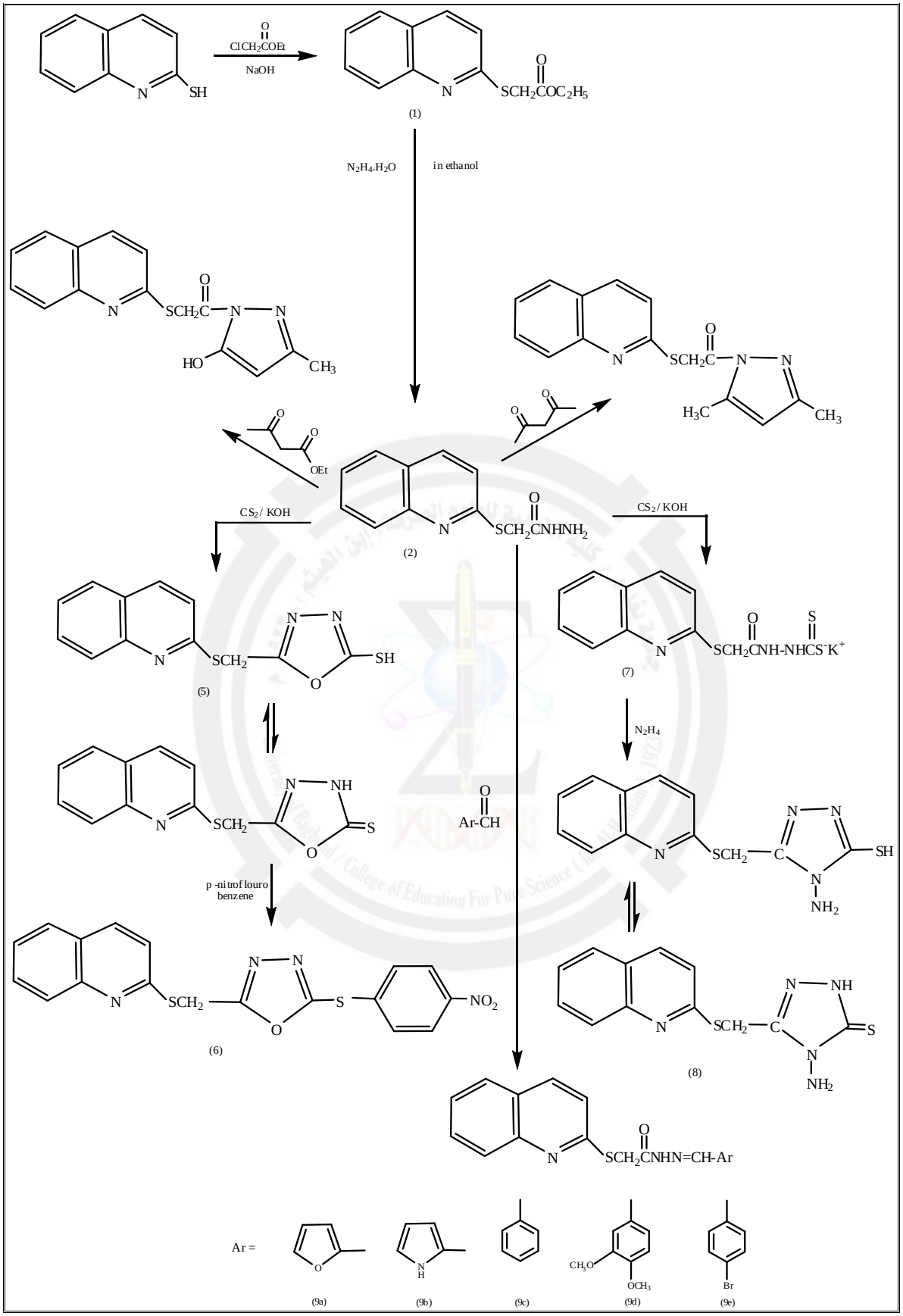
Synthesis of Schiff bases (9a-e)[19]:

A mixture of compound (2) (0.001mol) and selected aldehyde or ketone (0.001mol) in absolute ethanol was refluxed for (3-6 hrs). The mixture then was cooled, filtrated and recrystallized from ethanol.

All physical data were reported in Table(1). All spectral data were reported in Table (2).

Results and discussion

2-Mercapto quinoline has been chosen as a starting material for synthesis of new heterocyclic compounds through converting it to the corresponding ester (1) via reacting 2-mercapto quinoline with chloro ethylacetate in the presence of NaOH then by treating the resulted ester with hydrazine hydrate we produced the hydrazide derivative (2) which was useful intermediate for the preparation of new heterocyclics scheme (1). IR spectrum of compound (1) showed the disappearance of stretching band of (SH) group at 2550 cm^{-1} and appearance of stretching bands at 1735 cm^{-1} for (C=O), 1161 cm^{-1} and at 1093 cm^{-1} for (C-O) respectively[19,20].



Scheme (1)

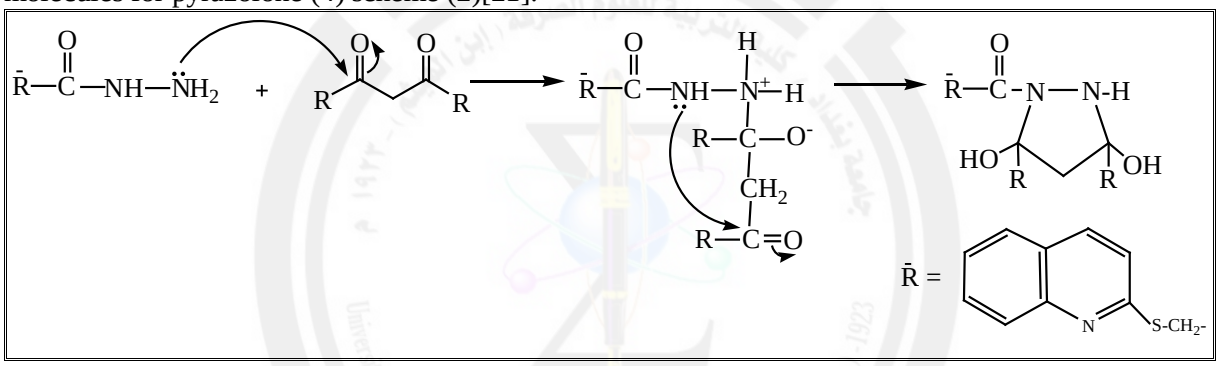
U.V spectrum showed absorption band at 336 nm and at 323 nm with high intense attributed to (π–π*) and (n–π*) transitions for ester. IR spectrum of compound (2) revealed the

appearance of three stretching bands of (NH) and (NH_2) groups at 3276-3199 cm^{-1} and (C=O) stretching band shifted to the lower frequency at 1650 cm^{-1} comparing with that of ester due to tautomerisim. U.V spectrum exhibited two absorption bands at 254 nm and at 213 nm attributed to (π–π^*) and (n–π^*) transitions. ^{1}HNMR was more informative, characteristic peaks were observed at 3.95 (s, 2H, of SCH_2), 8.85 (br. s, H of NH amide), 7.95(m, 2H of pyridine) and 7.25, 7.72 (t, H of benzene), Fig (1).

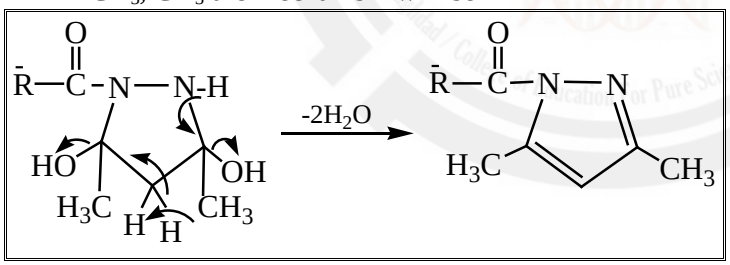
In ^{13}CNMR Fig (2) the observed peaks were identical with the chemical structure of compound (2), whereas it appeared eleven peaks of carbon of quinoline. Compound (2) was treated with active methylene compounds such as acetylacetone and ethylacetoacetate to give the corresponding pyrazole and pyrazolone derivatives (3) and (4) respectively. IR spectra of compound (3) and (4) exposed the absence of stretching bands of (NH) and (NH_2) groups at 3199-3276 cm^{-1} and the appearance of stretching bands of (C=N) endocyclic around 1600 cm^{-1}, (C-H) of (CH_3) at 2922-2856 cm^{-1} for compound (3) and (C=O amide) at 1668 cm^{-1} for compound (4).

U.V spectrum showed two absorption bands at 251 nm and at 215 nm for (π–π^*) and (n–π^*) transitions of compound (3) and two absorption bands at 336 nm at 325 nm for (π–π^*) and (n–π^*) of compound (4).

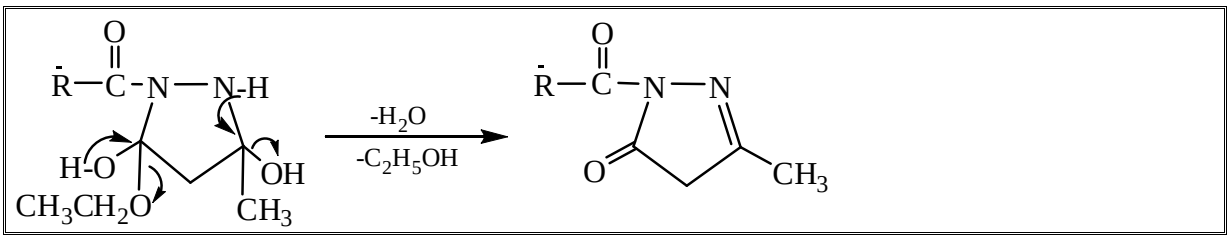
The mechanism for the formation of pyrazole ring includes nucleophilic attack of NH_2 electrons of compound (2) at carbonyl groups of acetylaceton and ethyl acetoacetate with ring closure and elimination of two molecules of H_2O for pyrazole (3) and elimination of H_2O and C_2H_5OH molecules for pyrazolone (4) scheme (2)[21].



If R = CH_3, CH_3 the mechanism will be



If R = CH_3, OC_2H_5 the mechanism will be

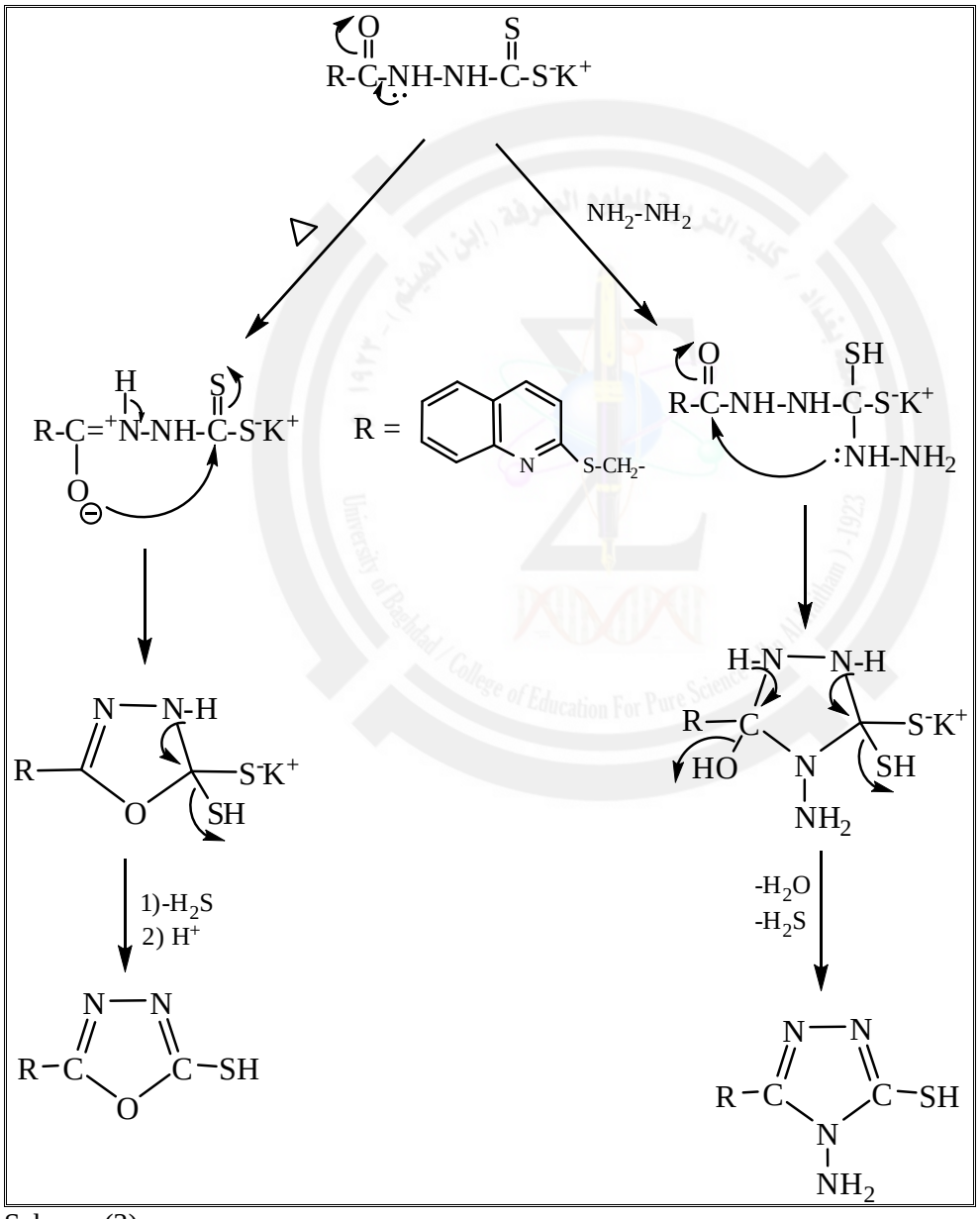


Scheme (2)

On the other hand, the reaction of compound (2) with carbon disulfide in the presence of KOH caused the conversion of hydrazide derivative to the 1,3,4-oxadiazole derivative (5). IR spectrum displayed the disappearance of stretching band of (NH) and (NH_2) groups and the appearance of stretching band of (NH) group at 3085 cm^{-1}. The other observed bands were at 2763 cm^{-1} (SH weak),

1627 cm^{-1} for (C=N) endocyclic, 1213 cm^{-1} for (C=S) and 1145 cm^{-1} which was characteristic for (C-O-C) of oxadiazole[22]. Moreover U.V spectrum of this compound demonstrated two absorption bands at 250 nm and 278 nm for (π–π*) and (n–π*) transitions.

The synthesis of compound (6) was preformed by the alkylation of oxadiazole derivatives (5) with aryl halide (ρ-nitro flouro benzene). In the IR spectrum the absence of stretching bands of (SH) and (C=S) and the appearance of stretching bands of ($-NO_2$) at 540 cm^{-1} asymmetrical and at 1370 cm^{-1} symmetrical were noticed U.V spectrum of compound (6) displayed two absorption bands at 220 nm and 308 nm for (π–π*) and (n–π*) transitions. The reaction between (xanthate salt) (7) and carbondisulphide in basic medium produced triazole derivative (8) which showed IR stretching bands at: 3360-3240 cm^{-1} of (NH_2) group, 1620 cm^{-1} of (C=N) endocyclic and at 1520 cm^{-1} of (N-C=S) moiety. U.V spectrum of compound (8) showed an absorption band at 282 nm for (π–π*) and (n–π*) transitions. The mechanism of the formation of oxadiazole and triazole included in scheme (3).



Scheme (3)

Compound (2) on reaction with various aromatic aldehydes and ketones yielded Schiff bases (9 a-e) proven by IR spectra through the disappearance of stretching band of NH_2 at 3295-3195 cm^{-1} and the appearance of stretching band of (NH) group at 3200-3300 cm^{-1} and of (C=N) exocyclic

group at 1640-1600 cm^{-1}. Moreover, Schiff bases exhibited absorption band in U.V region at higher wave number (red shift) due to increase in sequence caused by the presence of chromophores such as (NH_2), (NO_2) and (OH).

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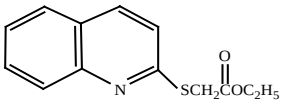
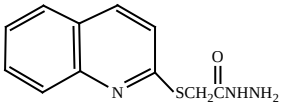
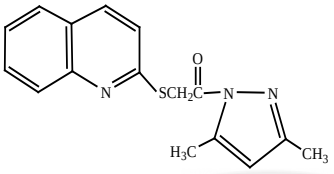
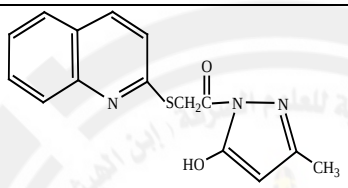
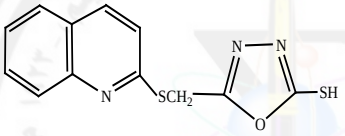
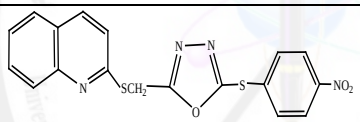
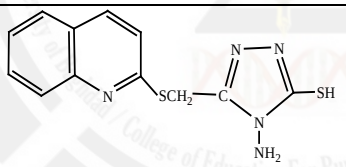
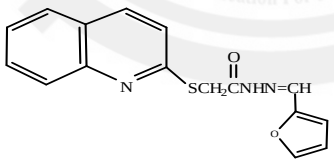
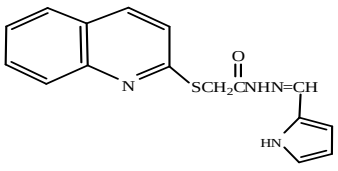
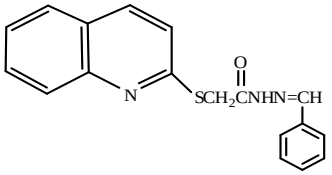
Table (1): Physical properties of prepared compounds

Comp. No.	Molecular Formula	Structural Formula	M.P. °C	R_f $CHCl_3$:ACOEt 1:1	Colour	Yield %
1	$C_{13}H_{13}O_2SN$		98-100	0.93	Yellowish White	87
2	$C_{11}H_{11}OSN_3$		133-134	0.29	Pink	85
3	$C_{16}H_{15}OSN_3$		78-80	0.40	Yellow	60
4	$C_{15}H_{13}O_2SN_3$		160-162	0.70 $CHCl_3$:ACOEt 2:1	Yellow	50
5	$C_{12}H_9OS_2N_3$		162-164	0.35 $CHCl_3$	Dark Yellow	60
6	$C_{18}H_{12}O_3S_2N_4$		58-60	0.72	Pale Yellow	79
8	$C_{12}H_{11}S_2N_5$		229-230	0.57	Yellow	40
9a	$C_{16}H_{14}OSN_4$		200-204	0.60	Yellow	88
9b	$C_{16}H_{14}O_2SN_3$		150-153	0.64	Pale Yellow	86
9c	$C_{18}H_{15}OSN_3$		180-183	0.72	White	80

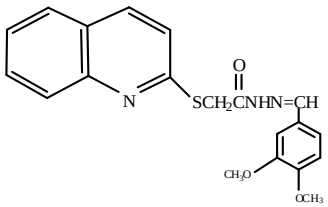
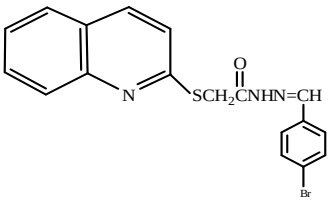
9d	$C_{20}H_{20}O_3SN_2$		**178-180**	**0.56**	**Yellowish White**	**75**
9e	$C_{18}H_{14}OSN_3Br$		**187-190**	**0.63**	**Yellow**	**80**

Table (2): Electronic spectra and infrared data of prepared compounds

Comp. No.	U.V C_2H_5OH λ_{max} nm	Infrared data (υ_{max} cm^{-1}) (KBr disc)
1	**336, 323**	**(C-$H_{arm.}$) 3053; (C-$H_{alph.}$) 2975-2923; (C=O) ester 1735; (C=N) 1612; (C=C) 1591-1498.**
2	**336, 254, 213**	**(NH, NH_2) 3276-3199; (C-$H_{arm.}$) 3037; (C-$H_{alph.}$) 2979, 2918; (C=O) 1650; (C=N) 1614; (C=C) 1593-1490.**
3	**336, 251, 215**	**(C-$H_{arm.}$) 3030; (C-$H_{alph.}$) 2950, 2860; (C=O amide) 1668; (C=N) 1610; (C=C) 1590-1500.**
4	**336, 325**	**(OH) 3200; (C-$H_{arm.}$) 3033; (C-$H_{alph.}$) 2985; (C=O) 1700; (C=N) 1640; (C=C) 1600-1481.**
5	**322, 278, 250**	**(NH) 3085; (C-$H_{arm.}$) 3045; (C-$H_{alph.}$) 2935, 2850; (C-SH) 2763; (C=N) 1627; (C=C) 1606-1508; (C=S) 1213.**
6	**308, 220**	**(C-$H_{arm.}$) 3050; (C-$H_{alph.}$) 2995; (C=N) 1640; (C=C) 1620-1550; (NO_2) 1540as, 1370s.**
8	**282**	**(NH_2) 3240, 3380; (C-$H_{arm.}$) 3030; (C-$H_{alph.}$) 2985, 2920; (SH) 2650; (C=N) 1620; (C=C) 1600-1580; (N-C=S) 1520.**
9a	**302, 253, 214**	**(NH pyrol); (NH) 3175; (C-$H_{arm.}$) 3010; (C=O amide) 1670; (C=N) 1640-1590.**
9b	**336, 297**	**(NH) 3197; (C-$H_{arm.}$) 3110, 3004; (C=O amide) 1650; (C=N) 1649-1544; (C-O-C Furan) 1213.**
9c	**214, 253**	**(NH) 3220; (C-$H_{arm.}$) 3100; (C=O amide) 1695; (C=N) 1610-1580.**
9d	**249, 314**	**(NH) 3220; (C-$H_{arm.}$) 3030; (C-$H_{aliph.}$) 2950, (C=O amide) 1665; (C=N) 1640-1520; (C-O) 1110.**
9e	**315, 256**	**(NH) 3228; (C-$H_{arm.}$) 3037; (C=O amide) 1680; (C=N) 1650-1593; (C-O) 1135; (C-Br) 750.**

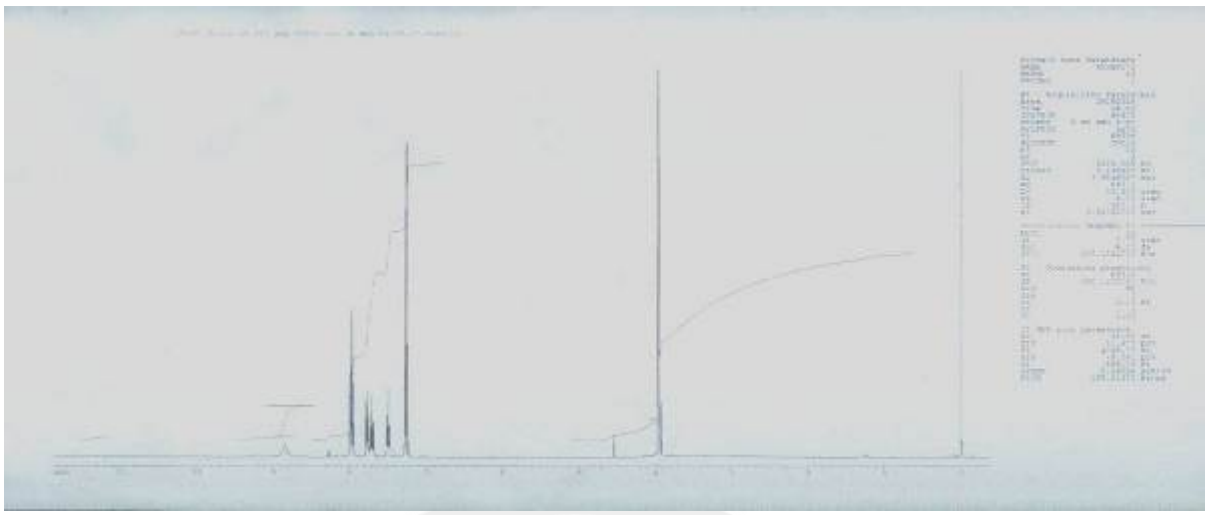


Fig. (1): ^{1}HNMR spectrum of compound (2)

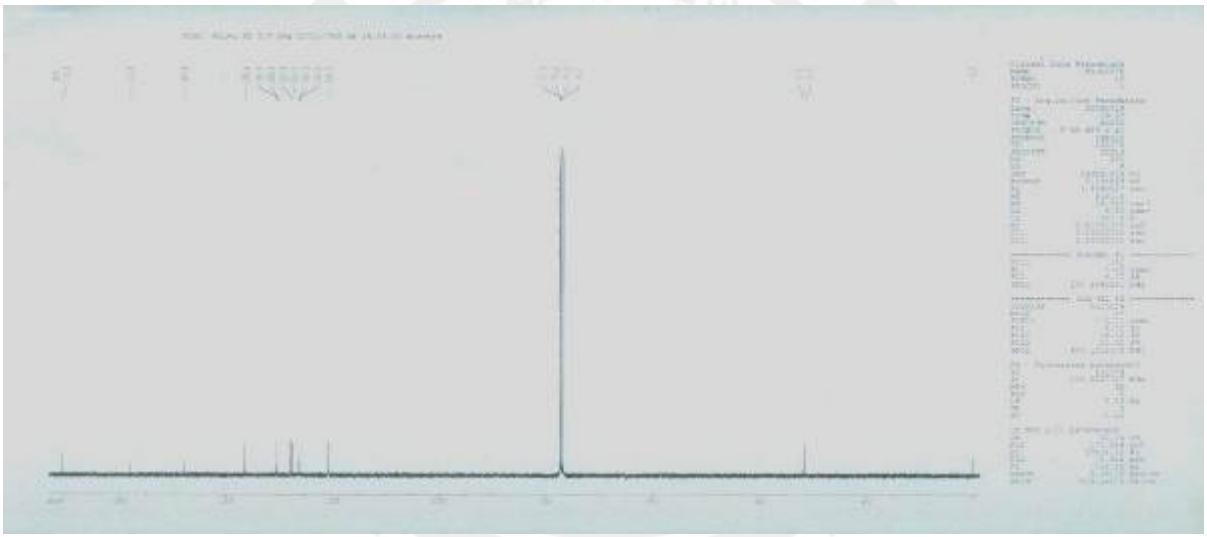


Fig. (2): ^{13}CNMR spectrum of compound (2)

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تحضير مركبات حلقية غير متجانسة مشتقة من 2- مركبتو كوينولين

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استلم البحث في : 30 نيسان 2012 قبل البحث في :2 تموز 2012

الخلاصة

أستعمل 2- مركبتو كوينولين مادة اساسية لتحضير مركبات حلقية غير متجانسة جديدة مثل3، 5- ثنائي مثيل-1-[(كوينولين-2- يل ثايو)اسيتال]-H1- بايرازول (3) ،و 5- مثيل-2-[(كوينولين -2- يل ثايو) اسيتال]-2، 4- ثنائي هايدرو-H3- بايرازول -3- ون (4) و5-[(كوينولين-2- يل ثايو) مثيل]- 4,3,1-اوكساديازول-2- ثايول(5) ،و4-امينو-5-[(كوينولين-2- يل ثايو) مثيل]- 4,2,1- ترايزول-3- ثايول (8) فضلا عن قواعد شف جديدة (9a-e) التي حضرت بمفاعلة 2-(كوينولين-2- يل ثايو)اسيتوهايدرازايد (2) مع الديهايدات وكيتونات مختلفة. شخصت المركبات المحضرة باستعمال الطرائق الطيفية والفيزيائية.

الكلمات المفتاحية: 2- مركبتو كوينولين، بايرازول، 4,3,1- اوكساديازول ، قواعد شف.