Synthesis of Some Heterocyclic Compounds Derived from 2-Mercapto Benzoxazole

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Abstract

New series of 2-mecapto benzoxazole derivatives (1-20) incorporated into fused to different nitrogen and suphur containing heterocyclic were prepared from 2-meracpto benzoxazole, when treated with hydrazine hydrate to afford 2-hydrazino benzoxazol (1). Compound (1) converted to a variety of pyridazinone andphthalazinone derivatives (2-4) by reaction with different carboxylic anhydride. Also, reaction of (1) with phenyl isothiocyanate and ethyl chloro acetate afforded 3-phenyl-1,3-thiazolidin-2,4-dione-2-(benzoxazole-2-yl-hydrazone) (6). Azomethines (7-10) were prepared through reaction of (1) with aromatic aldehyde, then (7, 8) converted to thaizolidinone derivatives (11, 12). Treatment of (1) with active methylene compounds afforded derivative (13). Reaction of (1) with CS_2 and NaOH gave 1,2,4-triazole derivative (14). Treatment of (1) with p-bromophenancyl bromide afforded another 1,2,4-triazole (15). The reaction of 2-mercapto benzoxazole with chloro acetic acid gave (16) followed by refluxing (16) with ortho-amino aniline giving benzimidazol (17). Moreover, the reaction of 2-mercapto benzoxazole with ethyl chloroacetate afforded (18), and then reaction of (18) with thiosemicarbazide and 4% NaOH leads to ring closure giving 1,2,4-triazole derivative (20). All compounds were confirmed by their melting point, FT-IR, UV-Vis spectra and ^{1}H-NMR spectra for some of them.

Key words: Benzoxazole, Thiazolidinone and 1,2,4-Triazole.

Introduction:

Benzoxazole nucleus have been reported various types of biological activites such as antidepressant, antifungal, analgesic [1], anti-inflammatory [2], anticancer and antimicrobial [3].Pyridazinone derivatives as important scaffolds in drug discovery with many of their analog have been used in the treatment of various human pathological states [4]. Recently it was found that pyridazinone derivatives could be used as anticonvulsant activity [5].4-thiazolidinone derivatives play a vital role due to their wide range of biological activity [6] and industrial applications [7]. It is also well established that various derivatives of 1,2,4-triazole exhibit broad spectrum of pharmacological properties such as antibacterial and antifungal activites [8].In the current study, we aimed to synthesize new heterocyclic compounds derivative from 2-mercapto benzoxazole containing pyridazinone, thiazolidinone,triazole, benzimidazole moieties with predictable biological activites.

Materials and Methods:

Melting points were taken in open capillary tubes on a Gallenkamp melting apparatus and are uncorrected. The IR spectra (KBr Discs) were recorded with a Shimadzu FTIR 8400.

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The UV-Visible spectra were measured in ethanol using a Shimadzu UV-Vis 160-A spectrophotometer. ^{1}H-NMR spectra were recorded on Bruker model Ultra Shield 300 MHz spectrophotometer, using TMS as the internal standard in DMSO-d6. Starting chemical compounds were obtained from Fluka or BDH companies.

Preparation of 2-hydrazino Benzoxazole (1):

A mixture of 2-mercapto benzoxazole (1.51g, 0.01mole) and hydrazine hydrate (10ml) was refluxed for 3hrs., ethanol (15 ml) was added and refluxed for 4 hrs. The separated precipitate was filtered and washed with cold water and recrystallized from ethanol.

General procedure for preparation of 1-benzoxazole-2-yl-1,2-di-hydropyridazine-3,6-dione (2), 2-benzoaxazole 2-yl-2,3,4a,5,8-8a hexa hydro phthalazin-1,4-dione(3) and 2-benzoaxazole 2,3-dihydrophthalazine-1,4-dione (4):

Maleic anhydride or 1,2,3,6-tetrahydro phthalic anhydride or phthalic anhydride (0.01 mole) in 30 ml acetic acid was added to hydrazide (1), (1.49g, 0.01 mole) and the reaction was refluxed for 7hrs. then the mixture was poured on crushed ice, the formed solid product was filtered off and recrystallized from pet. ether (40-60^{o}C).

Preparation of N-pheny-2-benzoaxazole-2-yl-hydrazine carbothioamide (5):

A mixture of compound (1) (1.49g, 0.01mole) and phenyl isothiocyanate (1.31 ml, 0.01mole), in absolute ethanol (20ml) was refluxed for 3 hrs and cooled. The solid product was filtered and recrystallized from ethanol.

Preparation of 3-phenyl-1,3-thiazolidine-2,4-dione-2-(benzoaxazole-2-yl-hydrazone) (6):

Ethyl chloro acetate (1.23g, 0.01mole) was added drop wise to a stirred solution of compound (5) (2.84g, 0.01mole) and anhydrous sodium acetate (0.01 mole) in 20 ml ethanol absolute. The reaction mixture was refluxed for 6 hrs. The solid product was filtered and recrystallized from ethanol.

Preparation of Schiff bases (7-10) :

To a stirring solution of compound (1) (0.01 mole) in ethanol absolute (15 ml), the appropriate different aldehyde from (0.01 mole) was added, and then the mixture was refluxed for 6hrs. and cooled to room temperature. The precipitate was filtered and recrystallized from appropriate solvent.

Preparation of thiazolidenones (11, 12):

A mixture of Schiff bases (7, 8) (0.02 mole) and mercapto acetic acid (0.26ml, 0.04mole) in dry benzene (30 ml) was refluxed for 10hrs. the mixture was concentrated and recrystallized from methanol.

Preparation of compound (13):

To a solution of compound (1) (1.49g, 0.01 mole) in ethanol absolute 30 ml ethyl cyano acetate (0.01 mole) was added. The reaction mixture was heated at refluxed for 6hrs. and after cooling the precipitate was filtered and recrystallized from methanol and water.

Preparation of 1,2,4-triazole [4,3-b] benzoxazole-1-(2*H*)thione (14):

To ethanolic sodium hydroxide solution prepared by dissolving sodium hydroxide (0.01mole) in ethanol absolute (30 ml), (0.01 mole) of compound (1) and (0.02mole) CS_2 were added. The mixture was refluxed in water bath at 80^{o}C for 10hrs. then allowed to cool down to room temperature, poured into water, neutralized by dilute acetic acid and the solid product was recrystallized from chloroform

Preparation of compound (15) :

A mixture of compound (1) (1.49g, 0.01 mole) and p-bromophenylphenacylbromide (0.01 mole) in ethanol absolute (30 ml) was heated under reflux for 5 hrs. and cooled. The solid product was filtered and recrystallized from ethanol.

Preparation of benzoxazole-2-yl-mercapto acetic acid (16) :

To (1.51g, 0.01mole) of 2-mercapto benzoxazole in (20 ml) of ethanol absolute, (0.01 mole) of KOH was added followed by (0.095g, 0.01mole) of monochloro acetic acid. The reaction mixture was heated under reflux for 8hrs. The hot solution was evaporated under reduced pressure, the solid was filtered, washed with cold distilled water and recrystallized from ethanol.

Preparation of 2-(1*H*-benzimidazol-2yl-thio methyl) benzoxazole (17):

Compound (16) (2.49g, 0.01mole) was refluxed for 10 hrs with o-phenylenediamine (1.08g, 0.01mole) in 4N hydrochloric acid (20 ml). The mixture was neutralized with ammonia to precipitate benzimidazole. The product was filtered and recrystallized from ethanol.

Preparation of ethyl-(benzoxazole-2-thio) acetate (18):

Ethyl chloro acetate (1.23g, 0.01mole) was added drop wise to a stirred solution of 2-mercapto benzoxazole (1.51g, 0.01mole) and KOH (0.56g, 0.01mole) in (20 ml) ethanol absolute. The mixture was refluxed for 5 hrs, and the precipitate was filtered, washed with water and recrystallized from chloroform.

Preparation of 2-[(benzoxazole-2-yl-thio) acetyl] hydrazine carbothioa-mide(19):

To stirring solution of compound (18) (2.37g, 0.01mole) in ethanol absolute (20 ml) was added thiosemicarbazide (0.91g, 0.01mole). the mixture was refluxed for 4hrs. and cooled to room temperature. The cold was filtered and recrystallized from ethanol and water.

Preparation of 5-(benzoxazole-2-yl-thio methyl)-(4*H*), 1,2,4-triazole-3-thiol (20):

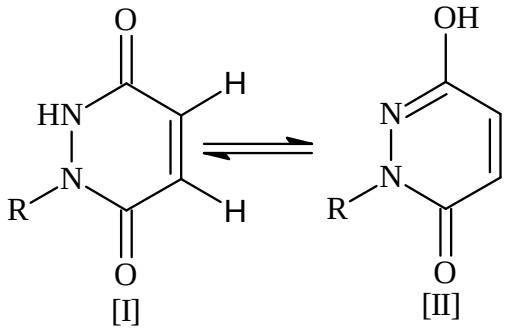
To solution of compound (19) (2.829g, 0.01mole) and (4% of NaOH, 10 ml) was refluxed for 3hrs. the mixture was acidified with dil.HCl and the product was collected and recrystallized from ethanol.

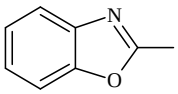
Results And Discussion:

New benzoxazole derivatives containing fused heterocyclic moiety were prepared following the reaction sequence depicted in schemes (1 & 2). 2-mercapto benzoxazole was reacted successfully with hydrazine hydrate. The starting material for the synthesis of targeted compounds is 2-hydrazino benzoxazole (1). Treatment of (1) with carboxylic anhydride, e.g., maleic anhydride, 1,2,3,6-tetraphthalic anhydride and phthalic anhydride gave compounds (2-4).

The structures of compounds (2-4) were confirmed by physical properties and spectral data, which are listed at Table (1). FTIR spectra of (2) show two broad bands at 3455 cm^{-1} and 3200 cm^{-1}, which assignable to O-H and N-H stretching vibration. The spectrum also shows absorption of C=O of pyridazine ring at 1720 while the C=O stretching of amide occure at 1635 cm^{-1}.

From the above mentioned we can suggest that compound (2) and (3, 4) can be exist in two tautomeric forms: keto [I] and enol forms [II].



R= 

The UV Spectrum of compound (3) was obtained in ethanol exhibited the the characteristic bands at (358 nm) responsible for (n→ π*) transition and (261, 214 nm) due to ($\pi \rightarrow \pi$*) transition.

While ^{1}H-NMR spectra of compound (4) show (δ ppm, DMSO-d_6); 7.3-8.2 (m, 8*H*, Ar-H) and 9.0 (s, 1*H*, NH Phthalazine).

Treatment of (1) with phenylisothiocyanate afforded the corresponding thiosemicarbazide (5). The FT-IT spectra of (5) display C=S stretching band at 1271 cm^{-1} and NH stretching band at 3209 cm^{-1}.

Refluxing of compound (5) with ethyl chloro acetate afforded 4-thioazolidone derivative (6). The structure of (6) was confirmed by the precence of C=O stretching band at 1697 cm^{-1} and C=N stretching at 1643 cm^{-1} combined with the disappearance of NH_2 stretching band.

Condensation hydridazide (1) with aryl aldehydes in absolute ethanol gave Schiff bases (7-10). The formation of these Schiff bases was indicated by the presence in their IR spectra of the azomethine CH=N stretching at 1600-1644cm^{-1}.

While ^{1}H-NMR spectra of compound (7) show (δppm) 4.2 (s, 1*H*, NH); 7.0-7.8 (m, 8*H*, Ar-H) and 80 (s, 1*H*, =CH).

Moreover, treatment of Schiff bases (7, 8) with mercaptoactic acid in dry benzene gave thiazolidenone derivatives (11, 12), structures of these compounds were confirmed by the presence of C=O stretching band at 1690 cm^{-1} due to thiazolidinone ring was the characteristic evidence for success of cyclization step.^{1}H-NMR of compound (12) shows (δppm) 4.1 (s, 1*H*, NH); 7.1-7.8 (m, 7*H*, Ar-H), 5.8 (s, 1*H*,N-CH) and 9.5 (s, 1*H*, OH).

Treatment of (1) with active methylene compound such as ethyl cyano acetate produced prazolon derivative (13). In IR spectrum of (13), the carbonyl stretching was observed at 1718cm^{-1}, whereas the amino group appearance as two bands at 3311 and 3115cm^{-1}.

^{1}H-NMR spectra of (13) shows (δppm) 1.2-1.5 (d, 2*H*, CH_2); 5.5 (s, 2*H*, NH_2); (7.3-8.7) (m, 4*H*, ArH).

Condensation of (1) with CS_2 in alkaline medium afforded 1,2,4-triazolo [4, 3, a] benzoxazole-3-2*H*-thiol (14). The IR spectrum showed N-H stretching absorption in 3267 cm^{-1} and C=S at 1330cm^{-1} with a weak absorption near 2660 due to SH stretch because of thiol-thion-tautomeriism, while ^{1}H-NMR spectra of compound (14) show, δ, 6.3 (s, 1*H*, NH); 7.3-8.7 (m, 4*H*, Ar-H); 13(s, 1*H*, SH).

The interaction of (1) with p-bromophenacyl bromide give rise to the formation of 4-(p-bromo phenyl)-6*H*-1,2,4-triazino [5,4,b] benzoxazole (15). ^{1}H-NMR spectra of compound

(15) show δ 5.5 (s, 1*H*, proton triazine), 6.1-7.7 (m, 8*H*, aromatic NH of trazine).

In order to synthesize benzoxazole-2-yl-mercapto acetic acid (16), the starting material-2-mercapto benzoxazole reacted with monochloro acetic acid. Condensation of (16) with o-phenylenediamine yielded benzimidiazole (17).

Structure of compound (17) was confirmed by spectra data, which showed the disappearance of bands at 3414cm^{-1} and at 1695 cm^{-1} attributed to O-H and C=O of carboxylic in compound (16), while ^{1}H-NMR spectra of compound (17) show δ 4.2 (s, 2*H*, SCH_2); 7.3-7.9 (m, 8*H*, Ar-H); 12.1 (s, 1*H*, NH of amidazole).

Moreover, treatment of 2-mercapto benzoxazole with ethyl chloro acetate afforded (18), which displayed C=O stretching band at 1734 cm^{-1}. Refluxing of (18) with thiosemicarbazide in dry benzene give acyl thiosemicarbazide (19), which upon ring closure with 4% NaOH afforded 5-(benzoxazole-2-yl-thiomethyl)-4*H*-1,2,4-triazole-3-thiol (20), which exists in a tautomericthiol-thione equilibrium as andicated by C=S stretching band at 1236 cm^{-1} and S-H stretch at 2550 cm^{-1}.

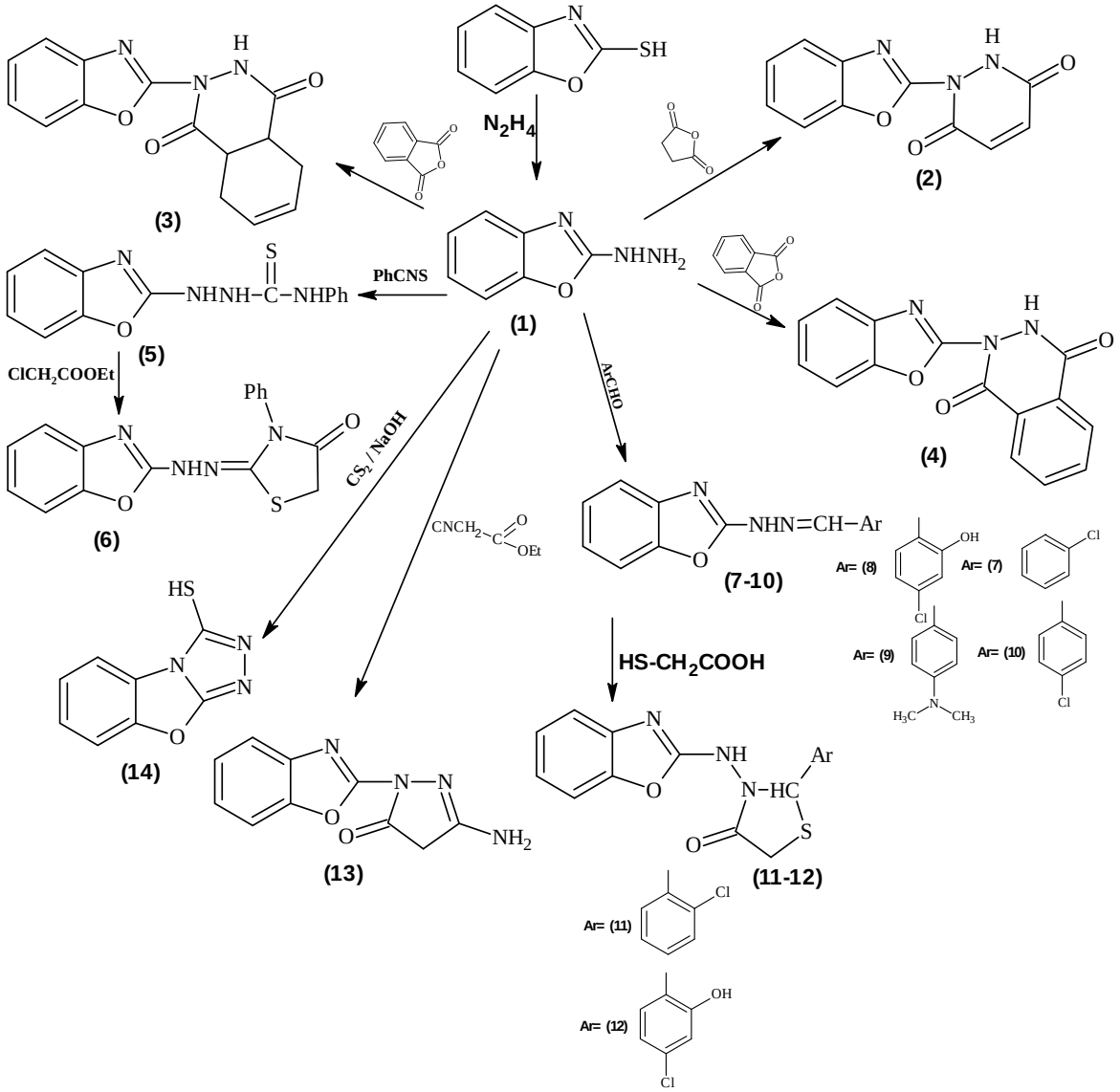
Table(1): Physical Properties and Spectral Data of the Prepared Compounds

Com. No.	Formul	M.p. °C	Yield%	Color	UV λ_{max}	Infrared data (υ, cm^{-1}) KBr disc
1	$C_7H_7N_3O$	210-212	74	White	205 343	3421, 3267 N-H, 3091 C-H ar. 1639 C=N, C-O-C 1157
2	$C_{11}H_7N_3O_3$	82-84	55	Pale brown	202 250 389	3450 O-H, 3221 N-H, 2930 C-H al., 1710 C=O, 1627 C=O amid
3	$C_{15}H_{11}N_3O_3$	110-112	59	Brown	214 261 358	3173 N-H, 2916 C-H al., 1718 C=O, 1655 C=O amid, 3309 O-H
4	$C_{15}H_9N_3O_3$	204 205	57	Nrown	215 356	3308 O-H, 3186 N-H, 3016 C-H ar., 1699 C=O, 1626 C=O amid
5	$C_{14}H_{12}N_4OS$	208 210	70	Yellow	211 302	3269, 3171 NH, 3028 C-H ar., 1271 C=S
6	$C_{16}H_{12}N_4O_2S$	175 177	62	Dark yellow	219 230	3209 N-H, 3024 C-H ar., 2929 C-H al., 1697 C=O, 1643 C=N
7	$C_{14}H_{10}N_3OCl$	211-213	77	White	218 263 318	3184 N-H, 3014 C-H, 1616 C=N, 1049 C-Cl
8	$C_{14}H_{10}N_3O_2Cl$	227 228	78	Yellow	202 228 338	3311 O-H, 3120 N-H, 3020 C-H ar., 1631 C=N, 1006 C-Cl
9	$C_{16}H_{13}N_4O$	182-184	80	Yellow	202 350	3309 N-H, 3045 C-H ar., 1626 C=N, 1010 C-Cl
10	$C_{14}H_{10}N_3OCl$	215-217	82	White	204 260	3308 N-H, 3026 C-H ar., 1710 C=O, 1045 C-Cl
11	$C_{15}H_{12}N_3O_2SCl$	230-231	70	Yellow	204 250 360	3298 N-H, 3095 C-H ar., 2906, 2818 C-H al., 1614 C=N
12	$C_{16}H_{12}N_3O_3SCl$		72	Yellow	220 380	3450 O-H, 3275 N-H, 1720 C=O, 1016 C-Cl
13	$C_{10}H_8N_4O_2$	220-221	66	White	201 219 315	3311, 3115 NH_2, 3020 C-H ar., 2949 C-H al., 1718 C=O, 1631 C=N

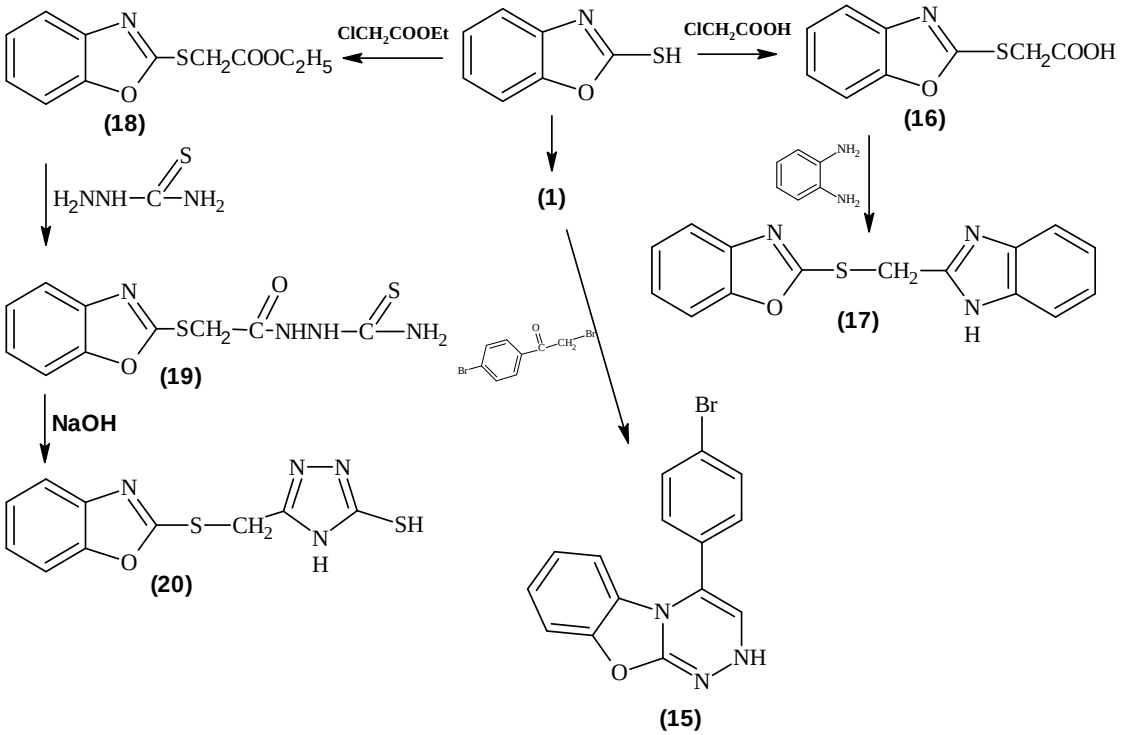
14	$C_8H_5N_3OS$	100-101	63	Brown	204 262	3207 N-H, 3084 C-H ar., 1643 C=N, 1330 C=S
15	$C_{15}H_{10}N_3OBr$	74-76	60	Brown	204 387	3244 N-H, 3016 C-H ar., 1633 C=N, 1604, 1570 C=C, 850γ C-H, 603 C-Br
16	$C_9H_7NO_3S$	121-122	60	Brown	240 330	3500-3200 O-H, 3080 C-H ar., 1695 C=O, 603 C-S
17	$C_{15}H_{11}N_3OS$	250-252	69	Yellow	211 250 360	3377, 3306 NH, 3051 C-H ar., 2960 C-H al., 1620 C=N
18	$C_{11}H_{11}NO_3S$	211-212	70	White	208 360	3090 C-H ar., 2935 C-H al., 1734 C=O ester, 1215 C-O, 1639 C=N
19	$C_{10}H_{10}N_4O_2S_2$	149-151	67	Yellow	203 360	3327, 3263 NH_2, 3158 N-H, 3064 C-H ar., 1663 C=O, 1242 C=S
20	$C_{10}H_{10}N_5OS_2$	231-232	55	Brown	215 380	3170 NH, 2550 SH, 1640 C=N, 1236 C=S

Table(2): Chemical Schiff's ^{1}H-NMR Spectra

Com. No.	^{1}H-NMR (DMSO-d_6) δppm
4	7.3-8.2 (m, 8*H*, Ar-H); 9.0 (s, 1*H*, NH phthalazine)
7	4.2 (s, 1*H*, NH); 7.0-7.8 (m, 8*H*, Ar-H); 8.0 (s, 1*H*, =CH)
12	4.1 (s, 1*H*, NH); 7.1-7.8 (m, 7*H*, Ar-H); 5.8 (s, 1*H*, N-CH); 9.5 (s, 1*H*, OH)
13	1.2-1.5 (d, 2*H*, CH); 5.5 (S, 2*H*, NH_2); 7.3-8.7 (m, 4*H*,Ar-H)
14	6.3 (s, 1*H*, NH); 7.3-8.7 (m, 4*H*, Ar-H); 13.0 (s, 1*H*, SH)
15	5.5 (s, 1*H*, Proton triazine); 6.1-7.7 (m, 8*H*, aromatis NH of triazine)
17	4.2 (s, 2*H*, SCH_2); 7.3-7.9 (m, 8*H*, Ar-H); 12.1 (s, 1*H*, NH of amidazole)


N2H4
PhCNS
ClCH2COOEt
CS2 / NaOH
ArCHO
HS-CH2COOH
(1)
(2)
(3)
(4)
(5)
(6)
(7-10)
(11-12)
(13)
(14)
Ar= (7)
Ar= (8)
Ar= (9)
Ar= (10)
Ar= (11)
Ar= (12)

Scheme 1


ClCH2COOEt
ClCH2COOH
SCH2COOC2H5
SH
SCH2COOH
(18)
(1)
(16)
H2NNH–C(=S)–NH2
(19)
(17)
NaOH
(20)
Br
(15)

Scheme 2

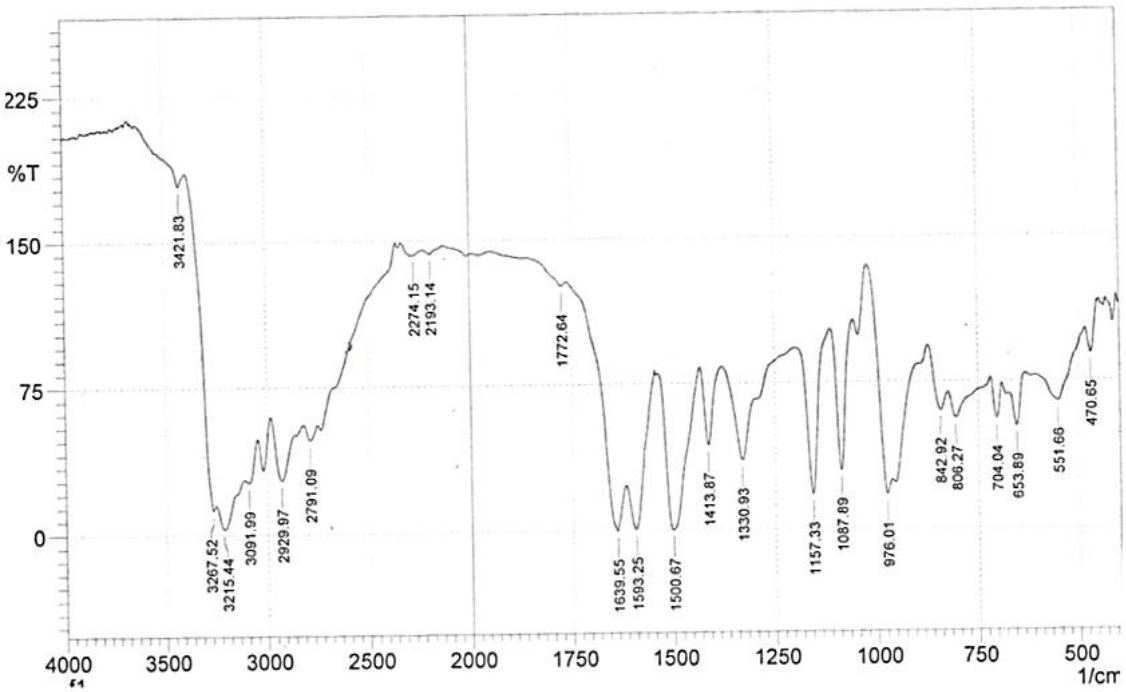
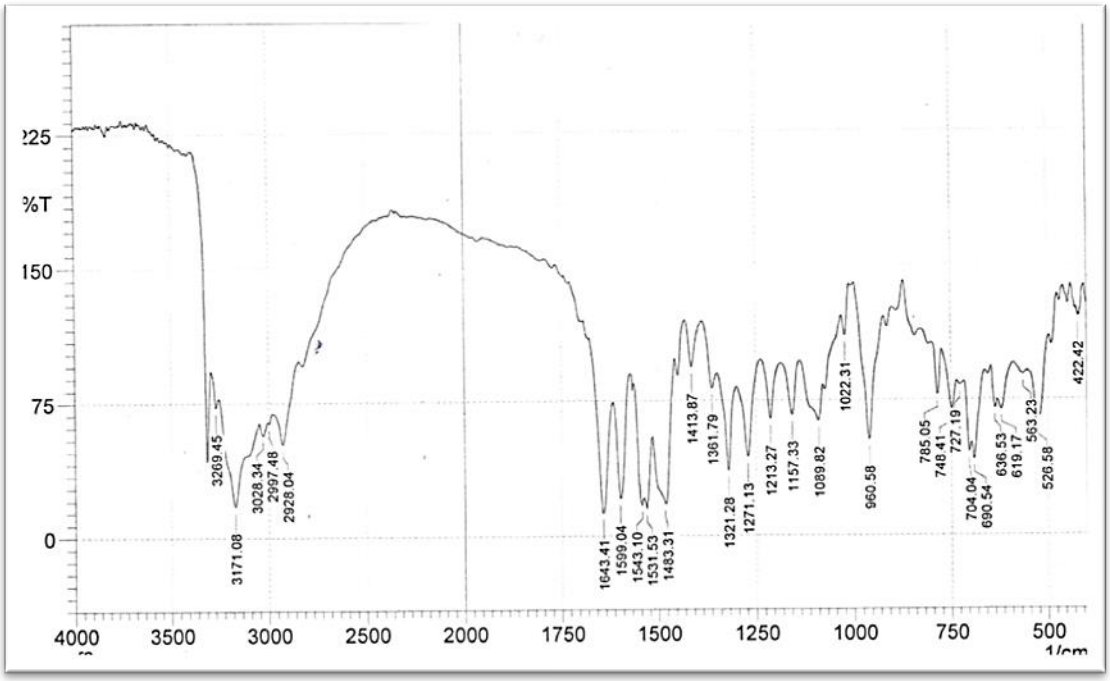
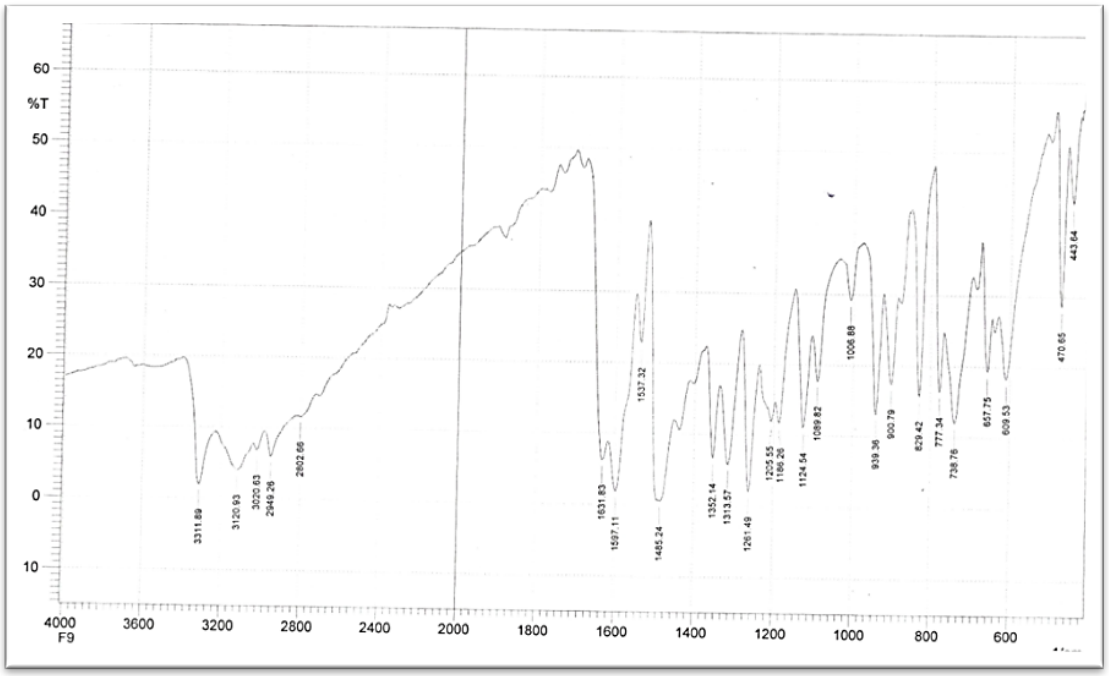


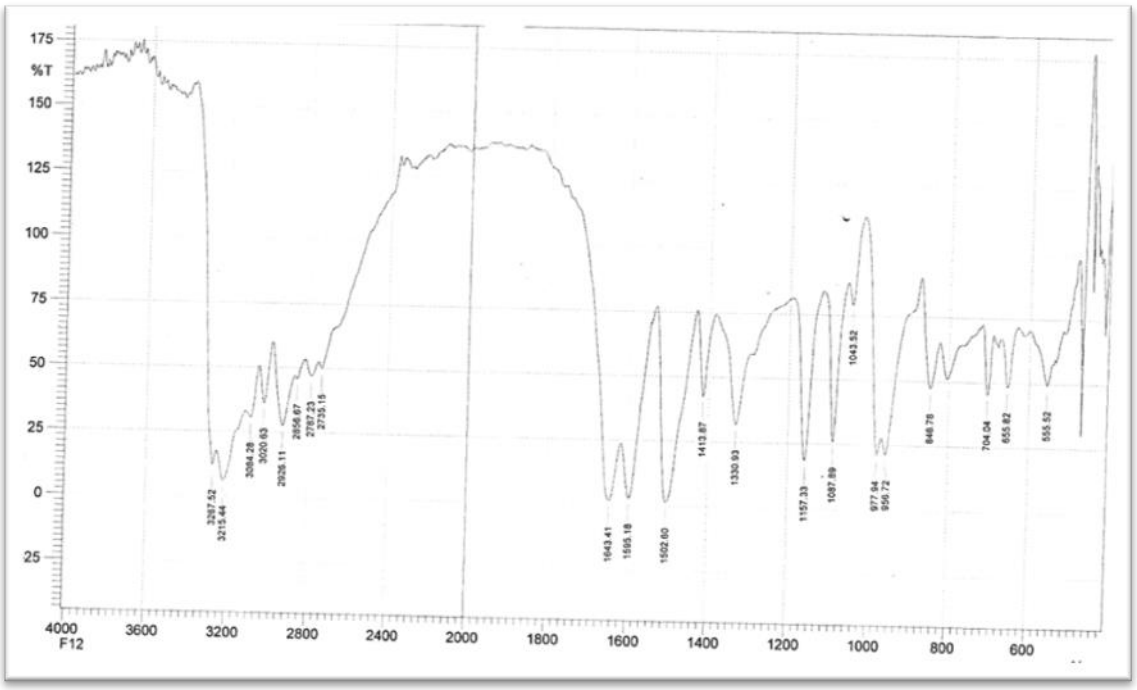
Fig (1): FT-IR Spectrum of Compound (1)



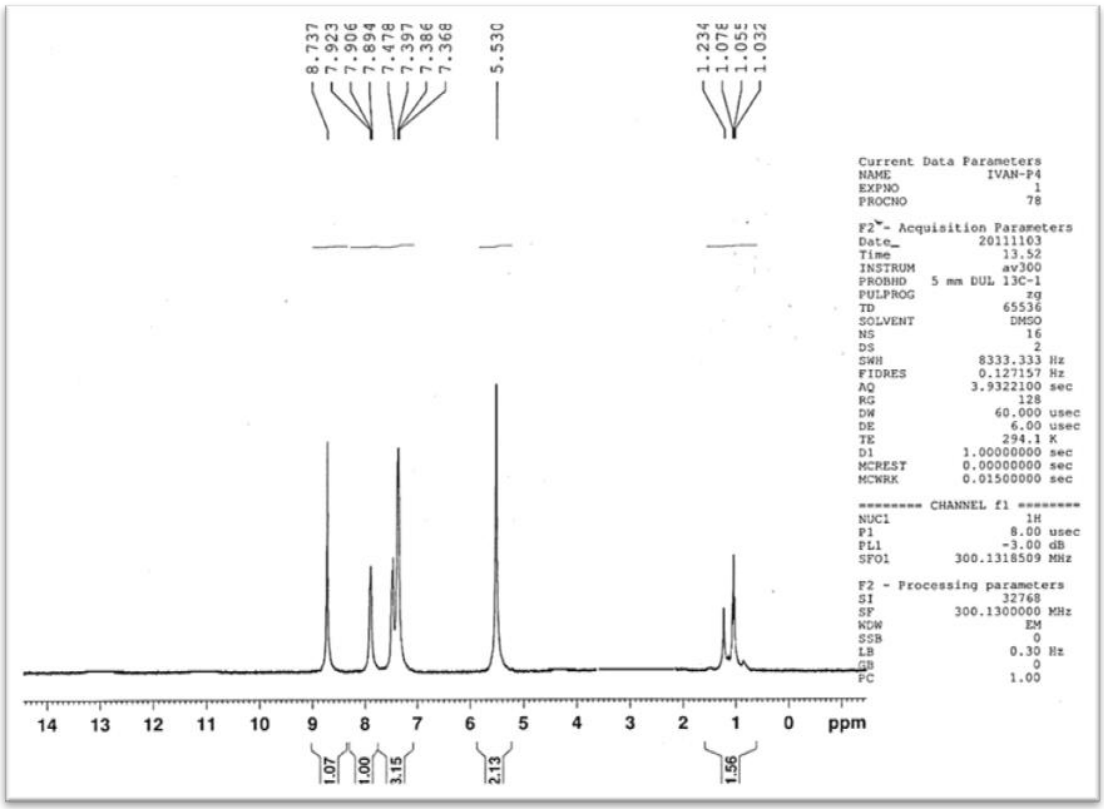
Fig(2): FT-IR Spectrum of Compound (5)



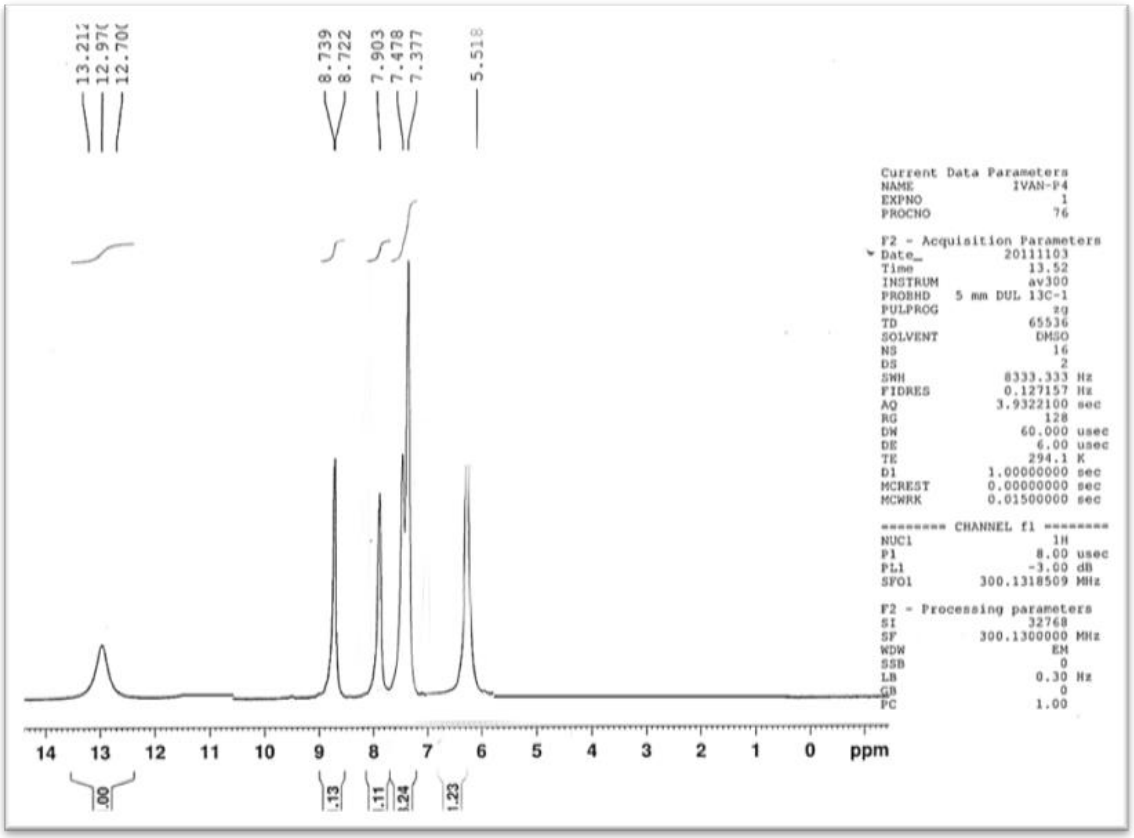
Fig(3): FT-IR Spectrum of Compund (8)



Fig(4): FT-IR Spectrum of Compound (14)



Fig(5): ^{1}H-NMR Spectrum of Compound (13)



Fig(6): ^{1}H-NMR Spectrum of Compound (14)

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****** جامعة بغداد- كلية التربية ابن الهيثم**

الخلاصة

تم تحضير سلسلة جديدة من مركبات حلقية غير متجانسة (1-20) مشتقة من 2-مركبتو بنزو أوكسازول تحتوي على ذرات مختلفة من النتروجين والكبريت وذلك عند معاملة المركب أعلاه مع الهدرازين اللامائي للحصول على 2-هايدرازوبنزو أوكسازول (1). ثم تحويل المركب إلى عدد من مشتقات البيردايازنون وفثالزينون (2-4) بتفاعله مع عدد من أنهدريدات الحوامض الكاربوكسيلية. تفاعل (1) مع فنيل آيزوثايوسيانيت وأثيل كلورو أستات فتكون 3-فنيل-1،3-ثايوزوليدين-2،4-ثنائي أون-2-(بنزوأوكسازول-2-يل-هايدرزون) (6). مركبات آزوميثين (7-10) حضرت من تفاعل (1) مع الألديهايدات الأورماتية، ثم تحول المركبات (7 و8) إلى عدد من مشتقات ثايوزوليدنون فتكون (11 و12). ومعاملة (1) مع مركب المثيلين الفعال أعطت المركب (13). ثم تفاعل (1) مع CS_2 و NaOH أعطى مشتق 1 و2 و4-ترايزول (14). ومعاملة (1) مع بارا-بروموفيناسيل برومايد أعطى 1، 2، 4-ترايزول (15). وتفاعل 2-مركبتو بنزو أوكسازول مع حامض كلورو أسيتك أعطى (16)، وعند تسخين المركب (16) مع أورثو-أمينو أثيلين فأعطى مشتق بنزايميدازول (17). تفاعل 2-مركبتو أوكسازول مع أثيل كلورو أسيتات أعطى (18). ومن ثم تفاعل (18) مع ثايوسيماكاربازايد في محيط قاعدي أدى إلى الغلق الحلقي الذي أعطى مشتق 1، 2، 4-ترايزول (20). وشخصت المركبات المحضرة جميعها عن طريق قياس درجة الإنصهار وأطياف الأشعة تحت الحمراء والأشعة فوق البنفسجية والرنين النووي المغناطيسي للبعض منها.