Synthesis and characterization of some new derivatives of 2-mercapto benzothiazole and evaluation their biological activity

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Abstract

This work involves the synthesis of some 2-mercapto benzothiazole [1] (2-MBT) derivatives. Compound [1] was reacted with α,β-unsaturated carbonyl compounds (Micheal reaction) to give five new derivatives [2-6], then amide [2] reacted with phenacyl bromide or 4-nitro phenacyl bromide in absolute ethanol to give oxazole derivatives [7-8]. Furthermore, the reaction of amide [2] with α-chloro acetic acid or α-bromo propionic acid in absolute ethanol afforded oxazolone derivatives [9-10]. Moreover, 2-MBT [1] reacted with ethyl α-bromo acetate in absolute ethanol giving ester [11] which on reaction with hydrazin hydrate afforded the corresponding hydrazide [12]. The hydrazide [12] was converted to pyrazole derivatives [13] and [14] when reacted with acetyl acetone or ethyl aceto acetate, respectively. In addition, treatment of hydrazide [12] with malic anhydride or phthalic anhydride in acetic acid afforded pyridazine [15], and phthalazine derivatives [16].

The synthesized compounds were characterized by their IR, UV spectra and C.H.N. analysis data. Some of these derivatives showed biological activities.

الخلاصة

يتضمن هذا البحث تحضير عدد من مشتقات المركب 2- مركبتوبنزوثايـازول الجديـدة (2-MBT)، حيث تم مفاعلة المركب 2-MBT مع مركبات الكاربونيل α,β-غير المشبعة فـي وسـط قاعـدي لتحـضير المشتقات [2-6]، ومن ثم مفاعلة مشتق الامايد [2] مع بروميد الفيناسيل أو 4-نيترو بروميد الفيناسيل لتحضير مشتقات الاوكسازول [7-8]، وكذلك تم مفاعلة مشتق الامايد [2] مع α-كلورو حـامض الخليـك أو مـع α-بروموحامض البروبونيك في الايثانول المطلق للحصول على مشتقي الاوكسازولون [9-10]. من ناحية أخرى تم مفاعلة المركب 2-MBT مع α-بروموا سيتات الاثيل باستخدام كاربونات الصوديوم اللامائية للحصول على

مشتق الاستر [11] والذي تم مفاعلته مع الهيدرازين المائي في الايثانول المطلق للحصول على مشتق الهيدرازيد [12] والذي تم مفاعلته مع كل من الاستيل اسيتون أواسيتو اسيتات الاثيل للحصول على مشتقي البايرازول [14-13] على التوالي، ومن مفاعلة مشتق الهيدرازيد [12] مع انهدريد حامض الماليك أوانهدريد الفثاليك وباستخدام حامض الخليك تم الحصول على مشتق البيردازين [15] والفثالازين [16] على التوالي.

وقد تم تشخيص المركبات باستخدام طيف الأشعة تحت الحمراء وطيف الأشعة فوق البنفسجية، بالإضافة إلى التحليل الدقيق للعناصر لبعض منها، كما تم تقييم الفعالية البايولوجية لهذه المشتقات على بعض الأنواع من البكتريا.

Introduction

2-Mercapto benzothiazole and its derivatives have been shown to possess antifungicidal [1], antiasthamtics [2], antitumer, antiinflammatory [3] and anticonvulsant [4] activities. In addition, 2-MBT and its derivatives were used as herbicides and plant growth regulators [5]. In industry 2-MBT is used as accelerator for rubber vulcanization and as antioxidant as well as stabilizer for (P.V.C.) against light [6,7].

These observations promoted us to synthesize the title compounds as possible biologically active agents.

Experimental

Melting points were recorded on Gallen-Kamp MFB-melting point apparatus, IR spectra were recorded on a Pye-Unicam SP3-100 spectrophotometer as KBr discs, and the UV spectra were performed on Cintra-5 GBC Scientific Equipment UV-Visible spectrophotometer. Elemental analysis of these compounds was carried out on C.H.N. analyzer type 1106 Carlo-Erba.

General procedure for Preparation of 2-MBT derivatives [2-6] by Michael reaction (8):

To a stirring solution of 2-MBT [1] (0.01 mole) and triethyl amine (0.01 mole) in ethanol (30 ml), α,β-unsaturated carbonyl compounds (0.01 mole) was added. The mixture was refluxed for (6 hrs). After cooling, the precipitate was filtered and recrystallized from an appropriate solvent. Table (1).

Preparation of 3-(2'-ethylene-4'-aryl-1',3'-oxazol-2'-yl) benzothiazole-2-thion [7-8] (9):

To a stirring solution of amide compound [2] (0.01 mole) in absolute ethanol (30 ml), phenacyl bromide or 4-nitro phenacyl bromide (0.01 mole) was added. The mixture was refluxed for (8 hrs) and left to stirring overnight and cooled. The precipitate was filtered and recrystallized from ethanol. Table (1).

Preparation of 3-(2'-ethylene-4'-oxo-5'-alkyl-1',3'-oxazol-2'-yl) benzothiazole-2-thion [9-10] [9]:

To a stirring solution of amide compound [2] (0.01 mole) in absolute ethanol (30 ml), α-chloro acetic acid or α-bromo propionic acid (0.01 mole) was added. The mixture was refluxed for (24 hrs) then left stirring overnight at room temperature then cooled. The precipitate was filtered and recrystallized from benzene. Table (1).

Preparation of 2-thio(α-ethyl acetate) benzothiazole [11] [10]:

To a stirring solution of 2-MBT [1] (0.01 mole) and anhydrous potassium carbonate (0.01 mole) in absolute ethanol (50 ml), α-bromo ethyl acetate (0.01 mole) was added. The mixture was refluxed for (6 hrs) and cooled. The precipitate was filtered and recrystallized from ethanol-water. Table (2).

Preparation of 2-thio(α-acetic acid hydrazide) benzothiazole [12] [11]:

To a stirring solution of compound [11] (0.01 mole) in absolute ethanol (30 ml), hydrazine hydrate (99%) (0.015 mole) was added. The mixture was refluxed for 4 hrs and cooled. The precipitate was filtered and recrystallized from ethanol. Table (2).

Preparation of 2-thio acetyl [3'-methyl-5'-(hydroxy or methyl) pyrazolin-1'-yl] benzothiazole [13-14] [12,13]:

To a stirring solution of compound [12] and ethyl aceto acetate (0.001 mole) or acetyl acetone (0.001 mole) in absolute ethanol (30 ml), acetic acid (0.1 ml) was added. The mixture was refluxed for (7 hrs) and cooled. The precipitate was filtered and recrystallized from ethanol. Table (3).

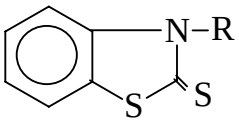
Preparation of 2-thio acetyl [3',6'-dioxo pyridazine-1'-yl] benzothiazole [15] [13]:

A stirring mixture of compound [12] (0.001 mole) and maleic anhydride (0.001 mole) in acetic acid (10 ml) was refluxed for (7 hrs). After cooling, the solution poured into crushed ice water (50 gm). The precipitate was filtered and recrystallized from acetic acid. Table (3).

Preparation of 2-thio acetyl [3',8'-dioxo-1',2',3',8'-tetrahydro phthalazin-1'-yl] benzothiazole [16] [13]:

A stirring mixture of hydrazide [12] (0.001 mole) and phthalic anhydride (0.001 mole) in acetic acid (30 ml) was refluxed for (6 hrs). After cooling, the solution poured into crushed ice water (50 gm). The precipitate was filtered and recrystallized from acetic acid. Table(3).

Table (1): Physical properties of compounds (2-10):



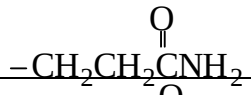
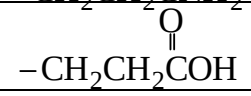
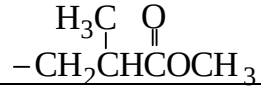
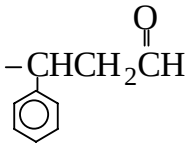
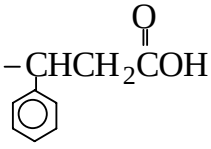
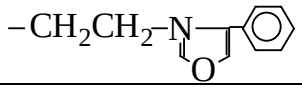
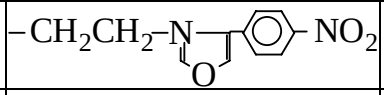
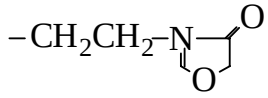
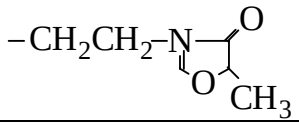
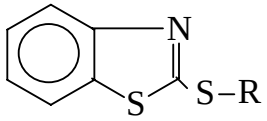
Comp. No.	R	M.p. (°C)	Yield %	Purification solvent	Molecular formula
2		138-140	83	1:1 Ethanol-water	$C_{10}H_{10}S_2N_2O$
3		175-177	80	2:1 Ethanol-water	$C_{10}H_9S_2NO_2$
4		148-150	61	Ethanol	$C_{12}H_{13}S_2NO_2$
5		171-173	53	Ethanol	$C_{16}H_{13}S_2NO$
6		184-186	66	1:1 Ethanol-water	$C_{16}H_{13}S_2NO_2$
7		85-87	60	Ethanol	$C_{18}H_{14}S_2N_2O$
8		98-10	79	Ethanol	$C_{18}H_{13}S_2N_3O_2$
9		108-110	38	Benzene	$C_{12}H_{10}S_2O_2N_2$
10		119-121	42	Benzene	$C_{13}H_{12}S_2O_2N_2$

Table (2): Physical properties of compounds (11, 12):



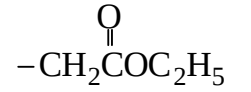
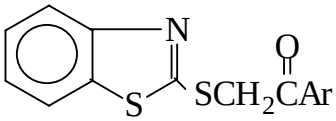
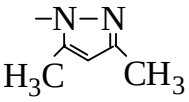
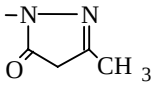
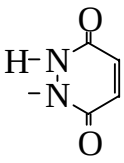
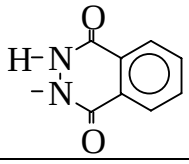
Comp. No.	R	M.p. (°C)	Yield %	Purification solvent	Molecular formula
11		44-46	80	1:1 Ethanol-water	$C_{11}H_{11}S_2O_2N$
12		160-162	92	Ethanol	$C_9H_9S_2N_3O$

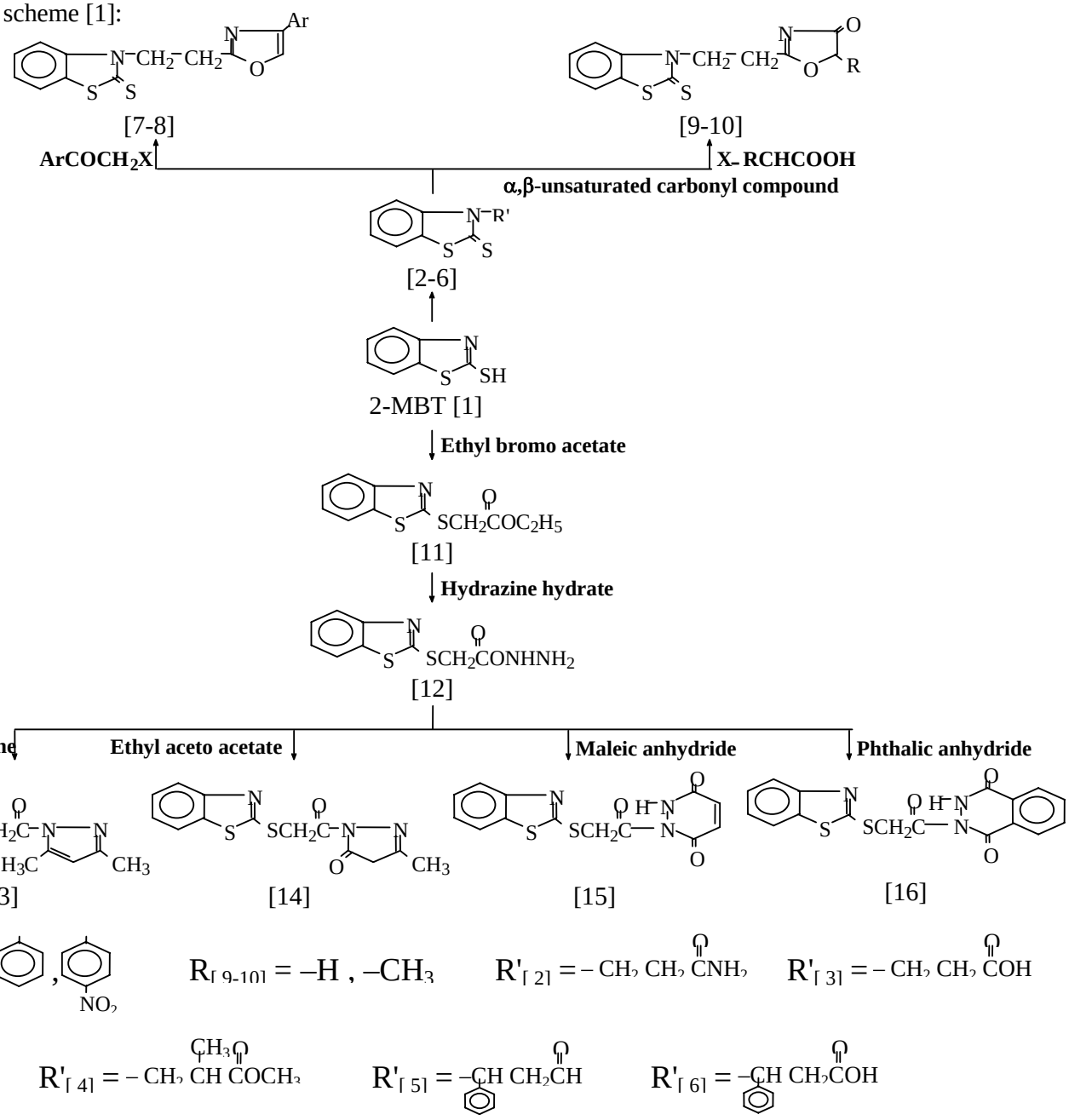
Table (3): Physical properties of compounds (13-16):



Comp. No.	Ar	M.p. (°C)	Yield %	Purification solvent	Molecular formula
13		38-40	76	Ethanol	$C_{14}H_{13}S_2N_3O$
14		90-92	70	Ethanol	$C_{13}H_{11}S_2N_3O_2$
15		178-180	68	Acetic acid	$C_{13}H_9S_2N_3O_3$
16		192-194	66	Acetic acid	$C_{17}H_{11}S_2N_3O_3$

Results and discussion

The preparation of titled compounds was carried out according to the following scheme [1]:



Scheme [1]

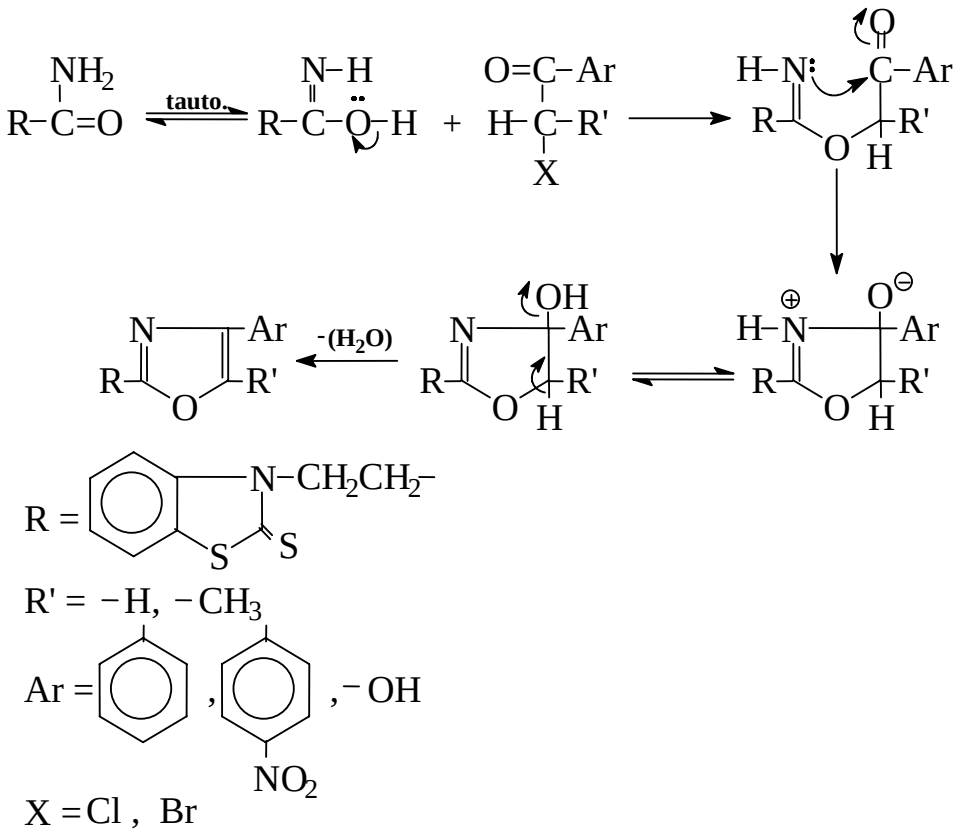
The derivative of 2-MBT [2-6] (Micheal adduct) have been prepared by the reaction of 2-MBT [1] with α,β-unsaturated carbonyl compounds in

alkaline solution by using triethylamine as a base and ethanol as a solvent (Micheal addition) (14,15).

The structures of these derivatives have been characterized and identified on the basis of their IR, UV and the C.H.N. analysis confirmed the structure of compounds [2-6], (tables 1 and 2). The IR spectra of compound [2] shows the appearance of characteristic (N-H) vibration bands at (3370 and 3500 cm-1) as well as at (2890 and 2970 cm-1) due to asymmetrical and symmetrical aliphatic (C-H) stretching vibrations, the spectra also shows the disappearance of the (S-H) stretching vibration of the starting material at (2600 cm-1) (18,19).

The reaction of 2-MBT [1] with phenacyl bromide, 4-nitro phenacyl bromide, α-chloro acetic acid or α-bromo propionic acid afforded oxazole or oxazolone derivatives [7-10].

The mechanism of the reaction of may be outlined as follows:



The IR spectrum of compound [8] shows the disappearance of the (N-H) vibration bands at (3370 and 3500 cm-1), and carbonyl vibration band at (1660 cm-1) of compound [2] and showed the appearance of (NO2) stretching vibration bands at (1360 and 1590 cm-1) caused by (NO2) stretching vibration (18,19).

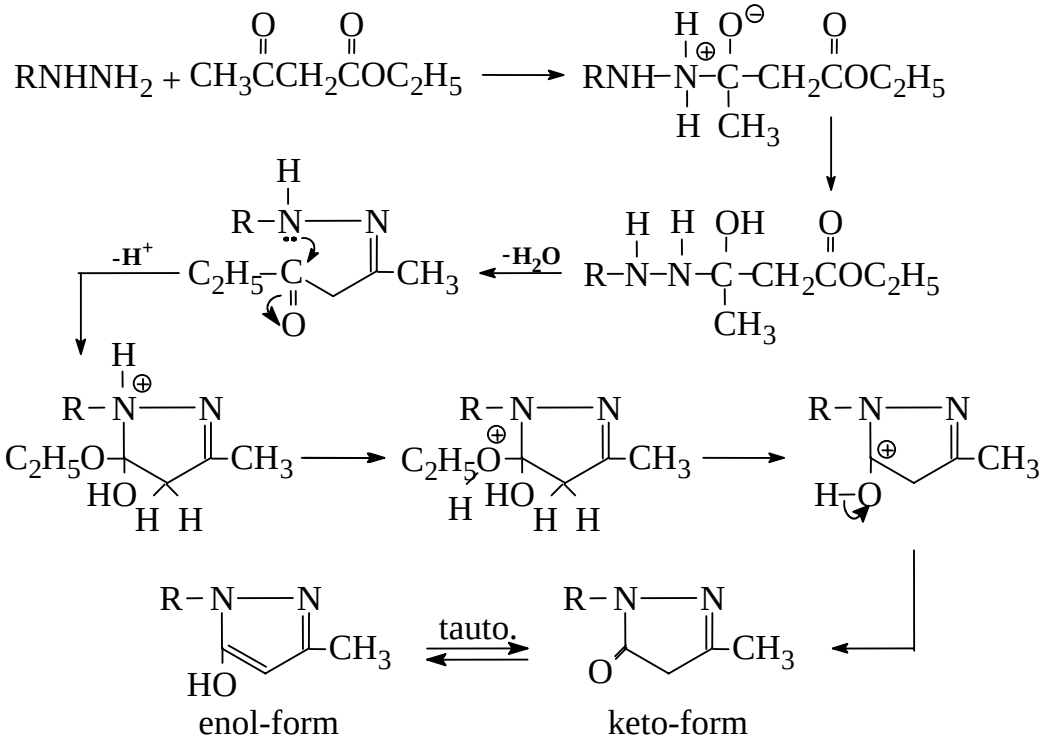
2-MBT was alkylated with ethyl bromo acetate in the presence of sodium bicarbonate to give ester derivative [11], the IR spectra of compound [11] clearly shows the disappearance of the thiol (S-H) vibration band of the starting material at (2600 cm-1), and the appearance of vibration band at (1740 cm-1) due to carbonyl group, and at (1170 cm-1) due to (O-C2H5) group as well as appearance of (C-H) aliphatic bands at (2860 and 2960 cm-1), in addition of IR spectra the structure of compound [11] have been characterized and identified on the basis of UV and C.H.N. analysis. Table (4-6) (18,19).

The treatment of ester [11] with hydrazine hydrate yielded acid hydrazide [12], the reaction proceeds by nucleophilic substitution of hydrazine to the ester carbonyl group giving the corresponding hydrazide [12] (16). Tables (4-6).

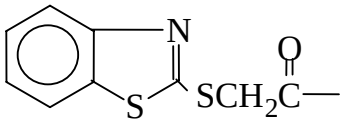
IR spectra of compound [12] shows the appearance of characteristic vibration bands near (3320 and 3270 cm-1) due to the asymmetrical and symmetrical (N-H) stretching vibration and at (1650 cm-1) due to carbonyl group which appears at (1740 cm-1) in ester [11] (18,19).

The reaction of hydrazide [12] with acetyl acetone or ethyl aceto acetate in presence of glacial acetic acid as catalyst afforded pyrazole [13] or pyrazolon derivative [14]. Table (5-6).

The mechanism of the formation of pyrazolon derivative [14] may be visualized as follow (17):



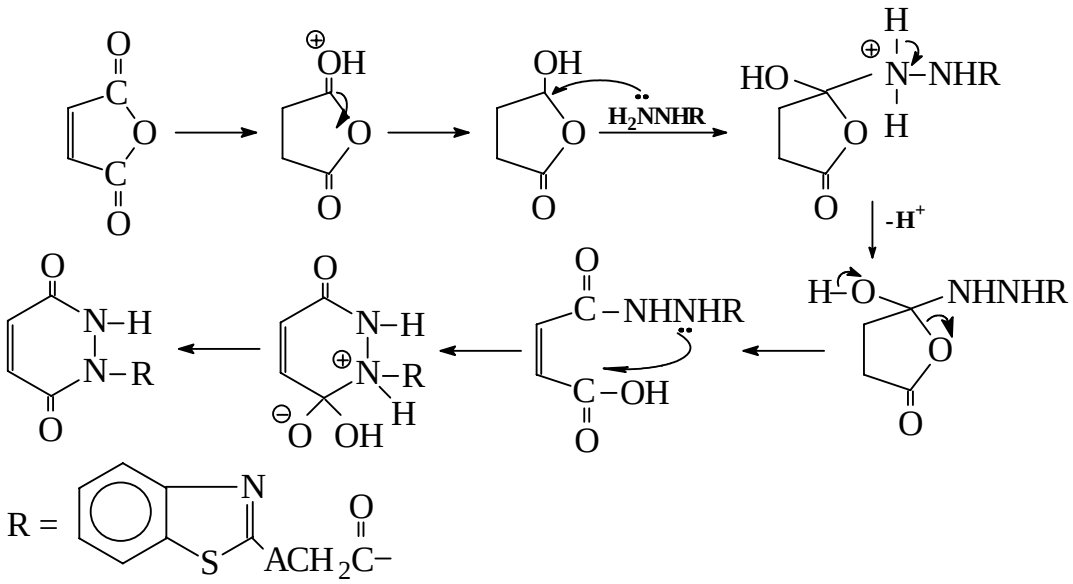
R =



IR spectra of compound [14] shows the disappearance of (N-H) vibration bands at (3320 and 3270 cm-1), which appears in hydrazide [12], and appearance of a vibration band at (3400 cm-1) for (O-H) group has been observed, which confirms the equilibrium between the enol and keto forms at (1670 cm-1) (18,19).

Hydrazide [12] reacted with malic anhydride or phthalic anhydride in presence of acetic acid as catalyst and solvent to give pyridazin [15] or phthalazin [16].

The mechanism of the reaction may be outlined as follow (17):



The IR spectrum of compound [16], (tables 5, 6), shows three main characteristic bands at (1680 and 1720 cm-1) due to carbonyl stretching vibration, and at (3450 cm-1) due to (O-H) stretching vibration which confirm the equilibrium between the enol-form and keto-form as follow (18,19):

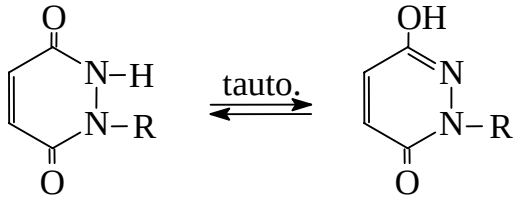


Table (4): Spectral data for compounds (2-6):

Comp. No.	UV (EtOH) λ_{max} (nm)	Characteristic bands of IR (cm^{-1}, KBr disc)					
		ν(C-H)$_{ar.}$ cm^{-1}	ν(C-H)$_{aliph.}$ Cm^{-1}	ν(C=O) cm^{-1}	ν(C=C) cm^{-1}	ν(C=S) cm^{-1}	ν others cm^{-1}
2	213.2, 226.8, 324.8	3100	2890 2970	1660	1450	1340	(N-H) 3370 s 3500 as (C-H) out of plane 780
3	236.4, 289.0, 312.6	3080	2870 2960	1670	1470	1340	(O-H) 2500-3200 (C-O) 1210 (C-H) out of plane 760
4	232, 279.6, 289.2	3100	2870 2960	1720	1440	1320	(C-O) 1250 (O-CH_3) 1140 (C-H) out of plane 750
5	214.4, 229.8, 278.4	3090	2880 2960	1740	1440	1380	(C-H)$_{ald.}$ 2740 (C-O) 1180 (C-H) out of plane 770, 745
6	244, 278.4, 288.4	3060	2860 2940	1680	1480 1600	1330	(O-H) 2500-3200 (C-O) 1240 (C-H) out of plane 770, 750

Table (5): Spectral data for compounds (7, 8):

Comp. No.	UV (EtOH) λ_{max} (nm)	Characteristic bands of IR (cm^{-1}, KBr disc)						
		ν(C-H)$_{ar.}$ cm^{-1}	ν(C-H)$_{aliph.}$ cm^{-1}	ν(C=N) cm^{-1}	ν(C=C) cm^{-1}	ν(C-O-C) cm^{-1}	ν(C=S) cm^{-1}	ν others cm^{-1}
7	224.4, 279.2, 298.8	3100 3120	2890 2980	1630	1440 1480	1260	1350	(C-S-C) 640
8	204.4, 235.2, 284.4, 304.0	3100 3120	2880 2960	1640	1440 1460	1260	1340	(-NO_2) 1310 1590 (C-S-C) 690

Table (6): Spectral data for compounds (9, 10):

Comp. No.	UV (EtOH) λ_{max} (nm)	Characteristic bands of IR (cm^{-1}, KBr disc)						
		ν(C-H)$_{ar.}$ cm^{-1}	ν(C-H)$_{aliph.}$ cm^{-1}	ν(C=O) cm^{-1}	ν(C=N) cm^{-1}	ν(C=C) cm^{-1}	ν(C=S) cm^{-1}	ν others cm^{-1}
9	225.6,278, 298.8	3100	2880 2960	1710	1640	1440	1370	(C-O-C) 1180
10	221.4, 222, 274.4, 299.2	3100	2890 2980	1690	1620	1440	1340	(C-O-C) 1180

Table (7): Spectral data for compounds (11, 12):

Comp. No.	UV (EtOH) λ_{max} (nm)	Characteristic bands of IR (cm^{-1}, KBr disc)						
		ν(C-H)$_{ar.}$ cm^{-1}	ν(C-H)$_{aliph.}$ cm^{-1}	ν(C=O) cm^{-1}	ν(C=C) cm^{-1}	ν(C-O) cm^{-1}	ν(C=S) cm^{-1}	ν others cm^{-1}
11	244.4, 267.6, 290, 300.4, 324.8	3080	2870 2950	1740	1440	1310	700	(O-C_2H_5) 1170
12	230.8, 279.6, 289.2, 299.6	3090	2880 2960	1650	1450	1310	710	(N-H) 3270 3320

Table (8): Spectral data for compounds (13-16):

Comp. No.	UV (EtOH) λ_{max} (nm)	Characteristic bands of IR (cm^{-1}, KBr disc)						
		ν(N-H) cm^{-1}	ν(C-H)$_{ar.}$ cm^{-1}	ν(C-H)$_{aliph.}$ cm^{-1}	ν(C=O) cm^{-1}	ν(C=N) cm^{-1}	ν(C=C) cm^{-1}	ν others cm^{-1}
13	216.8, 226.8, 324.4, 367.6	-	3020	2980	1720	1620	1440	(C-N) 1300
14	211.2, 237.7, 302.3	3320	3100	2930	1650 1670	1600	1470	(C-N) 1300 (O-H) 3400
15	226.8, 278.5, 324.8	3220	3100	2890 2960	1700 1690 1670	-	1520 1420	(N-N) 1040 (O-H) 3400
16	208, 228, 300, 345.2	3200	3100	2890 2980	1720 1680 1650	-	1510 1440	(O-H) 3450 (N-N) 1080

Table (9): Elemental analysis of some synthesized compounds:

Comp. No.	C%	H%	N%
	Calc. Found	Calc. Found	Calc. Found
2	50.42 50.38	4.20 4.17	11.76 11.73
7	63.90 63.86	4.14 4.18	8.28 8.21
10	53.42 53.36	4.10 4.12	9.58 9.51
11	52.17 52.14	4.34 4.30	5.53 5.55
12	45.18 45.11	3.76 3.71	17.57 17.51
13	55.44 55.40	4.29 2.23	13.86 13.80
16	55.28 55.30	2.98 2.91	11.30 11.23

Biological activity:

Applying the agar plate diffusion technique, some of the synthesized compounds were screened in vitro for antibacterial activity against Staphylococcus aureus, Escherichia coli and Proteus mirabilis. The zone of inhibition of bacterial growth around the disc was observed, the screening results given in the table (10).

Table (10): Screening results:

Comp. No.	*Staph. aureus*	*E. Coli*	*Proteus mir*
2	++	++++	+
8	+++	-	++
10	++	+++	+
11	+	++	++++
12	++	++++	+
14	+++	++	+++
16	-	++++	++

(-) = no inhibition (+++) = 16-20 mm

well = 5 mm (++++) = 21-25 mm

(+) = 6-10 mm Conc. = 10^{-3} mg/ml

(++) = 11-15 mm

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