Synthesis and study the biological activity of some six, five and fused ring heteroatome systems derived from 2-mercapto benzothiazole

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Received 16/3/2010 Accepted 5/3/2012

Abstract

In this paper ,new series of 2-hydrazino benzothiazole [1], 2-N-benzothiazole-N`-phenyl hydrazine carboxamide [2], 2-N-[(3)-N`-phenyl-5-(p-bromophenyl)-2`-hydroxy-1,3-oxazolin-2`-yl] benzothiazol hydrazine [3] , 2-N-benzothiazole-N`-1-naphthyl hydrazine carboxamide [4], 2-N-[(3`)-N`-(1-naphthyl)-5`-(p-bromo phenyl)-2`-hydroxy-1,3-oxazolin-2`-yl)] benzothiazol hydrazine [5], of 2-thiaacetic acid benzothiazole [6] ,2-thiaacetyl chloride benzothiazole [7], 5-amino-2-mercapto-1,3,4-thiadiazole [8], of 2-mercapto-[5-acetamid thiamethyl benzothiazol]-1,3,4-thiadiazole [9], 2-phenyl-5-chloromethyl-1,3,4-oxadiazole [10],and 2-[5-phenyl-1,3,4-oxadiazol-2`-thiomethyl] benzothiazole [11] have been synthesized. These compounds were characterized by FT-IR , spectrum, elemental analysis and the melting points were checked the purity of the prepared compounds was determined by TLC technique. The biological activity was also studied against Proteus vulgaris (G-) and Staphylococcus aureus (G+) with different concentrations.

تحضير ودراسة الفعالية البايولوجية لبعض الحلقات السباعية ، السداسية ،والخماسية غير المتجانسة اللمشتقة من 2-مركبتو بنزوثايازول .

ابتسام خليفة جاسم سوسن حارث شوكت علي عبيس عبدالشمري رؤى محمد ضيدان

الملخص

تم في هذا البحث تحضير عدد من المركبات تشمل 2-هيدرازينو بنزوثايازول (**1**)، N-2 بنزوثايازول -N فنيل هيدرازين كابوكسمايد (**2**) ، N--2 – N-(3)-] - فنيل - 5-(p –بروموفنيل)-2-هيدروكسي 3,1-اوكسازولين-2-يل] بنزوثايازول هيدرازين (**3**) ، N-2 –بنزوثايازول-N - 1-نفثايل هيدرازين كاربوكسمايد (**4**) ، N-2 - [(3)-N –(1-نفثايل) - 5-(p – بروموفنيل)-2-هيدروكسي-3,1-اوكسازولين-2-يل)] بنزوثايازول هيدرازين (**5**) ، 2-ثايواسيتك اسدبنزوثايازول (**6**) ، 2-ثايواسيتيل كلورايد بنزوثايازول (**7**) ، 5-أمينو-2-مركبتو-1و3و4- ثاياديايازول (**8**) ، 2-مركبتو-5-[5-استامايد ثايامثيل بنزوثايازول] - 1و3و4-ثاياديايزول (**9**) ، 2-فنيل - 5-كلورومثيل - 1و3و4-اوكساديايزول (**10**) ، 2-[5-فنيل-1و3و4-اوكساديايزول -2-ثايومثيل] بنزوثايازول(11) . شخصت المركبات المحضرة بواسطة اطياف الاشعة تحت الحمراء والتحليل الدقيق للعناصر كذللك تم التاكد من نقاوة المركبات المحضرة عن طريق تقنية كروماتوكرافيا الطبقة الرقيقة . كذلك درست الفعالية البايولوجية ضد نوعين من البكتريا الموجبة والسالبة .

Introduction

Heterocyclic compounds are considered one of important types of organic compounds due to their applications in drug and industrial studies. Heterocyclic compounds are cyclic compounds in which one or more of the atoms of the ring are hetero atoms. The name comes from the Greek word heteros, which means "different". A variety of atoms such as (N, O, S, Se, P, Si, B and As) can be incorporated into the ring structure[(1)]. Oxazoline is one of a class of organic heterocyclic compounds containing a five member one unsaturated ring structure composed of one oxygen atom and one nitrogen atom, oxazoline can be represented by two forms [(2)].

1,3-Oxazoline

Chiral oxazolines especially chiral bis (oxazoline), have been widely applied in many catalytic asymmetric reaction as versatile ligands[(3,4)]. Oxazoline-base ligands were also found to be effective for the asymmetric addition of diethyl zinc to aldehydes [(3,5)]. In particular the ligand combining the oxazoline ring and hydroxyl group or an amino group have been reported to show excellent catalytic activity in the asymmetric addition of diethyl zinc to aldehydes [(6-11)]. The growing patent literature from the sixties demonstrates that the 1,3,4-thiadiazoles are becoming of great interest, this is primarily due to the large number of uses of 1,3,4-thiadiazoles in the most diverse areas, for example in drug synthesis, scintillation materials, dye stuffs industry, photography and corrosion inhibitors. Numerous 1,3,4-thiadiazoles have been synthesized and reported to be biologically versatile compounds having bactericidal, fungicidal, muscle relaxant properties…etc., some 1,3,4-thiadiaozles derivatives possess central nervous system (CNS) depressant activity [(12,13)]. 1,3,4-Oxadiazole is the most thermally stable isomer which has attracted special attention, this is primarily due to the large number of uses in many diverse areas, including drugs, scintillation materials, dyes[(14)] and surface active agents [(15)]. The biological significance of oxadiazole ring is well documented in the literature. Thus, it has been shown that many substituted-1,3,4-oxadiazoles have biological and medical uses as antibacterial [(16)], antifungal [(17)], antimalarial [(18,19)] and anti-inflammatory [(20)] activities when probably substituted in (2) and (5) positions. Further, it was suggested that (-SH) group attached to a heterocyclic nucleus may include fungicidal activity [(21)].

Instruments

1) Melting points were measured using hot stage **Gallen Kamp** melting point apparatus and were uncorrected.

2) The F.T.IR spectra in the range (4000-600) cm^{-1} were recorded using KBr disk on a **SHIMADZU** F.T.IR 8300 spectrophotometer Japan.

3) Thin Layer Chromatography (TLC) was carried out using Fertigfollen precoated sheets type PolyGram silg, and the plates were developed with iodine vapor.

1- Preparation of 2-hydrazino benzothiazole [1]

To 2-mercapto benzothiazole (1.67 g, 0.01 mol) dissolved in ethanol, was added hydrazine hydrate (99%) (0.32 g, 0.317 ml, 0.01 mol) and the mixture was then refluxed for 6 hours, excess solvent was distilled off. The resulting solid then was separated out on cooling filtered and recrystallized from ethanol [(22)], m.p. (203-205 ^{o}C), yield (80%).

2-Preparation of 2-N-benzothiazole-N`-phenyl hydrazine carboxamide [2]:

A mixture of 2-hydrazido benzothiazole [1] (1 g, 0.006 mol) and phenyl isocyanate (0.71 g, 0.006 mol) was refluxed in absolute ethanol (30 ml) for 6 hours, then cooled and filtered,

the formed solid was recrystallized from benzene [23], m.p. (214-216 °C), yield (81%).

3-Preparation of 2-N-[(3)-N`-phenyl-5-(p-bromophenyl)-2`-hydroxy-1,3-oxazolin-2`-yl] benzothiazol hydrazine [3]:

A mixture of compound [2] (0.85 g, 0.003 mol) and p-bromo phenacyl bromide (0.83 g, 0.003 mol) in absolute ethanol (30 ml) was refluxed for 8 hours, cooled and neutralized with ammonium hydroxide solution. The precipitate was filtered off, washed with water, dried and recrystallized from ethanol giving the final product [23] m.p. (178-180 °C), yield (74%).

4-Preparation of 2-N-benzothiazole-N`-1-naphthyl hydrazine carboxamide [4]:

Compound [4] was synthesized by the same method described for the preparation of compound [2] using 1-naphthyl isocyanate (0.5 g, 0.003 mol) [23] m.p. (223-225 °C), yield (96%).

5-Preparation of 2-N-[(3`)-N`-(1-naphthyl)-5`-(p-bromo phenyl)-2`-hydroxy-1,3-oxazolin-2`-yl)] benzothiazol hydrazine [5]

Compound [5] was synthesized by the same method described by the preparation of compound [3] using compound [16] (0.68 g, 0.003 mol) instead [23] m.p. (179-181 °C), yield (62%).

6-Preparation of 2-thiaacetic acid benzothiazole [6]:

To a stirred solution of (2-MBT) (1.67 g, 0.01 mol) in (25 ml) of ethanol and excess of KOH was added slowly. Chloro acetic acid (0.94 g, 0.01 mol) was added gradually with stirring, the mixture was refluxed for 2 hours after that the mixture was cooled and filtered, the filtrate was poured into ice-water, the crude product was recrystallized from ethanol [24] m.p (228-230 °C), yield (62%).

7-Preparation of 2-thiaacetyl chloride benzothiazole [7]:

To a solution of 2-thioacetic acid benzothiazole (0.4 g, 0.002 mol) and thionyl chloride (10 ml) was refluxed for 7 hours. Excess thionyl chloride was evaporated, the formed solid was recrystallized from benzene[25] m.p. (307-309 °C), yield (90%).

8-Preparation of 5-amino-2-mercapto-1,3,4-thiadiazole [8]:

Potassium hydroxide (2.24 g, 0.04 mol) was dissolved in absolute ethanol (20 ml) and carbon disulfide (4.57 g, 3.62 ml, 0.06 mol) was added to the solution. After the addition of carbon disulfide thiosemicarbazide (3.38 g, 0.04 mol) in absolute ethanol (20 ml) was added and the mixture was stirred and refluxed for 6 hours most of the residue was dissolved in water (15 ml) and carefully acidified with concentrated hydrochloric acid (3.5 ml) the precipitate was filtered and washed with cold water and recrystallized from ethanol [25] m.p. (229-231 °C), yield (92%).

9-Preparation of 2-mercapto-[5-acetamid thiamethyl benzothiazol]-1,3,4-thiadiazole [9]:

To a solution of [7] (0.4 g, 0.0016 mol) in absolute ethanol (25 ml), triethyl amine (0.23 ml, 0.0016 mol) was added with stirring followed by the addition of compound [8] (0.22 g, 0.0016 mol) to the reaction mixture which was refluxed for 4 hours. Triethyl amine hydrochloride was filtered off, the solution was concentrated to one-third of its original volume and carefully treated with concentrated hydrochloric acid, and the precipitate was collected by filtration and recrystallized from ethanol [25] m.p. (120-122 °C), yield (57%).

***10-Preparation of 2-phenyl-5-chloromethyl-1,3,4-oxadiazole [10]*:**

A mixture of benzohydrazine (1.36 g,0.01 mol), chloro acetic acid (0.92 g, 0.01 mol) and phosphorous oxychloride (5 ml) was refluxed for 5 hours, the mixture was cooled, poured on ice-water and made alkaline by adding sodium bicarbonate solution. The resulting solid filtered, dried and recrystallized from (a mixture of acetone and

ethanol) to give the titled compound [26] m.p. (107-109 ^{o}C), yield (70%).

11-Preparation of 2-[5-phenyl-1,3,4-oxadiazol-2`-thiomethyl] benzothiazole [11]:

A mixture of (2-MBT) (0.42 g, 0.0025 mol) and 5-phenyl-2-chloromethyl-1,3,4-oxadiazole (0.5g, 0.0025mol) was refluxed in pyridine (15 ml) for 4 hours. The mixture was then poured into ice-water the resulting solid was then washed and recrystallized from ethanol[27,28] m.p. (121-123 ^{o}C), yield (65%).

Results and Discussion

1- Preparation of 2-hydrazino benzothiazole [1]:

2-Mercapto benzothiazole with hydrazine hydrate in ethanol was refluxed for 6 hours to afford the hydrazine benzothiazole [1]. The structure of the hydrazine benzothiazole [1] was confirmed from its melting point and F.T.IR spectrum. The F.T.IR spectrum of compound [1] indicates the disappearance of the thiol bond at (2534.3 cm^{-1}) and appearance of doublet bands of NH_2 group asymmetric and symmetric at (3313.5, 3201.6 and ν NH stretching band at 3128.3 cm^{-1}).

Preparation of 2-N-benzothiazole-N`-phenyl hydrazine carboxamide [2]:

Compound [2] was synthesized from the reaction of compound [1] with phenyl isocyanate. The compound was characterized by its melting point and F.T.IR spectroscopy.

The F.T.IR spectrum of compound [2] indicated the disappearance of NH_2 band (3313.5 and (3201.6 cm^{-1}) of the starting material and the appearance of N-H band at (3278.8 cm^{-1}) and carbonyl group at (1660.6 cm^{-1}).

Preparation of 2-N-[(3)-N-phenyl-5-(p-bromophenyl)-2-hydroxy-1,3-oxazolin-2-yl] benzothiazol hydrazine [3]:

Compound [3] was synthesized from the reaction with compound [2] with p-bromo phenacyl bromide. The compound was characterized by its melting point and F.T.IR spectroscopy. The F.T.IR spectrum of compound [3] indicated the disappearance of carbonyl group band at (1660.6 cm^{-1}) of the compound [2] and appearance of N-H band at (3272.9 cm^{-1}) and O-H band at (3451.9 cm^{-1}) and bands at (1250.0 cm^{-1}), (1016.4 cm^{-1}) belong to the asymmetric and symmetric (C-O-C) band. It is assume that the S_N2 mechanism.

Preparation of 2-N-benzothiazole-N`-1-naphthyl hydrazine carboxamide [4]:

Compound [4 was synthesized from the reaction of compound [1] with 1-naphthyl isocyanate. The compound was characterized by its melting point and F.T.IR spectroscopy. The F.T.IR spectrum of compound [4] indicated the disappearance of NH_2 bands at (3313.5 and 3201.6 cm^{-1}) of the starting material and appearance of N-H band at (3261.4 cm^{-1}) and carbonyl group band at (1683.6 cm^{-1}).

Preparation of 2-N-[(3`)-N-(1-naphthyl)-5`-(p-bromo phenyl)-2-hydroxy-1,3-oxazolin-2-yl)] benzothiazol hydrazine [5]:

Compound [5] was synthesized from the reaction of compound [4] with p-bromo phenacyl bromide. The compound was characterized by its melting point and F.T.IR spectroscopy. The F.T.IR spectrum of compound [5] indicated the disappearance of carbonyl group band at (1683.0 cm^{-1}) of the compound [4] and appearance of N-H band at (3259.4 cm^{-1}) and O-H band at (3459.4 cm^{-1}) and ppearance of the C=C band at (1564.1 cm^{-1}), bands at (1253.6 and 1010.0 cm^{-1}) belong to the asymmetric and symmetric (C-O-C).

Preparation of 2-thiaacetic acid benzothiazole [6]:

Compound [6] was synthesized from the reaction of 2-mercapto benzothiazole with chloro acetic acid. The compound was characterized by its melting point and F.T.IR spectroscopy. The F.T.IR spectrum of compound [6] indicated the disappearance of S-H band at (2754.2 cm^{-1}) and appearance of the carbonyl group band at (1712.4 cm^{-1}) of the acid and appearance of O-H group band at (3450 cm^{-1}) and C-H aliphatic at (2900 cm^{-1}), which displayed broad band in the region (3450.0 cm^{-1}), and the mechanism of the

reaction may be considered as S_N2 mode reaction through the nucleophilic attack of the sulfide anion at the saturated carbon Cl-CH_2-CO_2H carrying the leaving group.

Preparation of 2-thiacetyl chloride benzothiazole [7]:

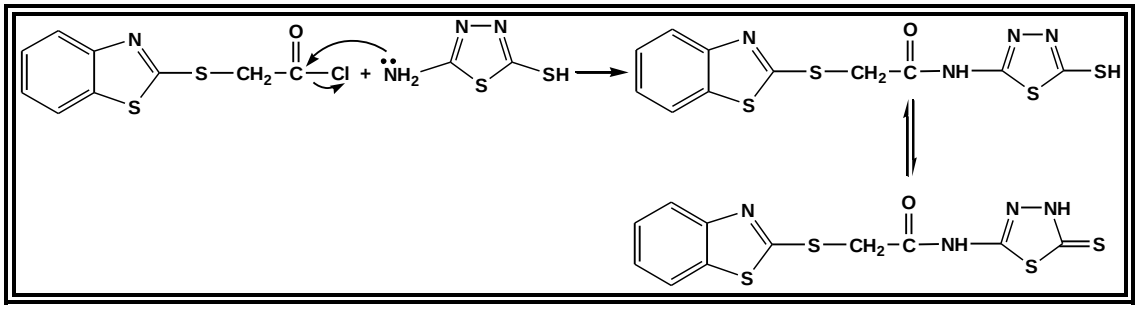
Compound [7] was synthesized from the reaction of 2-thiacetic acid benzothiazole with thionyl chloride. The compound was characterized by its melting point and F.T.IR spectroscopy. The F.T.IR spectrum of compound [7] indicated the disappearance of broad band of O-H at (3450.0 cm^{-1}) and appearance of the carbonyl group of the acid chloride at (1730.2 cm^{-1}) and C-H aliphatic (2854.4 cm^{-1}) and (C-Cl) at (758.0 cm^{-1}).

Preparation of 5-amino-2-mercapto-1,3,4-thiadiazole [8]:

Compound [8] was synthesized from the reaction of carbon disulfide with thiosemicarbazide in ethanol.The compound was characterized by its melting point and F.T.IR spectroscopy.The F.T.IR spectrum of compound [8] indicated the appearance of S-H band at (2773.4 cm^{-1}) and NH_2 band asymmetric and symmetric at (3336.6-3251.8 cm^{-1}) and appearance of thione band at (1342.4 cm^{-1}) and N-H band of the tautomerism appeared at (3130.0 cm^{-1}).

preparation of 2-mercapto-[5- acetamid thiamethyl benzothiazol]-1,3,4-thiadiazole [9]:

Compound [9] was synthesized from the reaction of [7] with compound [8]. The compound was characterized by its melting point and F.T.IR spectroscopy. The F.T.IR spectrum of compound [9] indicated the appearance of N-H band at (3263.3 cm^{-1}) and the carbonyl band at (1666.3 cm^{-1}) and aromatic (C-H) at (3116.7 cm^{-1}) and C-H aliphatic at (2854.4 cm^{-1}) and appearance of S-H band at (2525.0 cm^{-1}) and appearance of thione band at (1365.5 cm^{-1}) and N-H band tautomerism and (N-N) band at (1242.0 cm^{-1}) and assume that alkylation step involves S_N2 mechanism. The mechanism of the reaction is shown in Scheme below.



Scheme: Mechanism steps for the preparation of compound [9].

The compound was characterized by its melting point and F.T.IR spectroscopy.The F.T.IR spectrum of compound [10] indicated the disappearance of NH_2 bands in benzohydrazine at (3301.9 cm^{-1}) and (3201.6 cm^{-1}) N-H band at (3147.6 cm^{-1}) and disappearance of carbonyl group at (1658.6 cm^{-1}) and appearance of C=N band at (1550.6 cm^{-1}) and (C-O-C) asymmetric, symmetric at (1242.0 cm^{-1}) and (1018.3 cm^{-1}) and C-H aliphatic at (2854.4 cm^{-1}), C-Cl at (856.3 cm^{-1}) and (540.0 cm^{-1}).

Preparation of 2-[5-phenyl-1,3,4-oxadiazol-2-thiomethyl] benzothiazole [11]:

Compound [11] was synthesized from the reaction of 2-MBt with 2-phenyl-5-chloromethyl-1,3,4-oxadiazole in pyridine.The compound was characterized by its melting point and F.T.IR spectroscopy.The F.T.IR spectrum of compound [11] indicated the disappearance of S-H band of 2-MBt and the appearance of C-S-C band at (750.0 cm^{-1}), and the C-H band at (2981.7 cm^{-1}).

Table (1): physical properties of the prepared compounds.

Comp. No.	M.P.^{O}C	Yield%	Recryst Solvent	Elemental Analysis C. H. N. calcd/found
1	203-205	80	EtOH	-
2	214-216	81	C_6H_6	59.15/59 4.22/4.0 19.71/19.01
3	178-180	74	EtOH	54.88/53.98 3.53/3.45 11.64/11.2
4	223-225	96	C_6H_6	-
5	179-181	62	EtOH	-
6	228-230	62	EtOH	55.95/55.45 3.62/3.1 7.25/7.0
7	307-309	90	C_6H_6	-
8	229-231	92	EtOH	-
9	120-122	57	EtOH	-
10	107-109	70	Acetone+EtOH	55.52/55.0 3.59/3.0 14.39/14.01
11	121-123	65	EtOH	-

Table (2): F.T.IR spectral data of the prepared compounds.

No	ν N-H (cm^{-1})	ν C-H arm (cm^{-1})	ν C-H aleph (cm^{-1})	ν C=N (cm^{-1})	ν C=C (cm^{-1})	ν C=O ester (cm^{-1})
1	3128.3	3051.2	-	1647.1	1554.5	-
2	3278.8	3080.0	-	1606.6	1537.2	-
3	3272.9	3031.8	-	1620.09	1500.0	-
4	3261.4	3051.18	-	1618.17	1564.16	-
5	3259.4	3041.53	-	1614.31	1564.1	-
6	-	3070.0	2900.0	1583.4	1500.0	1712.4
7	-	3062.7	2854.4	1542.9	1400.0	1731.02
8	-	-	-	1604.7	1546.8	-
9	3263.3	3116.7	2854.4	1550.6	1458.0	-
10	-	3024.1	2854.4	1550.6	1481.2	-
11	-	3060.8	2981.7	1606.5	1548.7	-

No	ν NH_2 (cm^{-1})	ν C=O amide (cm^{-1})	Others
1	3313.5-3201.6	-	C-S 752.2
2	-	-	C=S 1330.8
3	-	-	S-H 2560.0
4	-	1728.1	-
5	-	735.8	-
6	-	1690.3	-
7	-	-	-
8	-	1735.8	O-H 3440.8
9	-	-	p-CH_3 821.6
10	-	1620.1	C-O-C 1249.8-1022.2
11	-	1692.1	O-H 3440.8, C-S 732.9

Table (4): Concentrations used within the test.

Compound concentration	**Prepare stock**		**Concentration**
Stock	0.01 gram	2 ml DMSO	5 mg/ml
	Prepare concentrations		
	Stock	**DMSO**	
Concentration (a)	0.4 ml	0.6 ml	2 mg/ml
Concentration (b)	0.5 ml	0.5 ml	2. 5 mg/ml
Concentration (c)	0.6 ml	0.4 ml	3 mg/ml

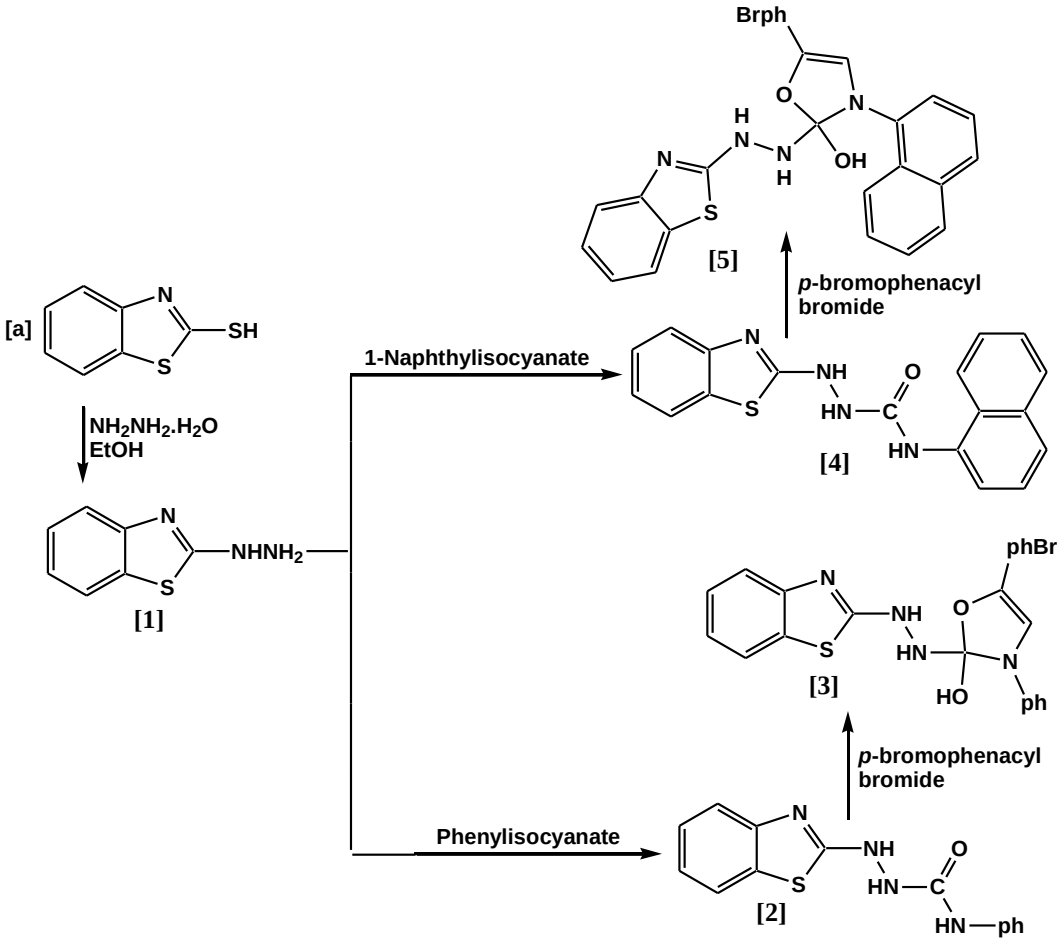
Table (5): Antibacterial activities of some of the prepared compounds.

Strains	Proteus vulgaris (G-)			Staphylococcus aureus (G+)		
Compound No.	Concentrations			Concentrations		
	a	B	c	A	B	c
1	S	S	S	Ms	Ms	S
2	-	-	-	-	-	-
3	-	-	-	-	R	-
6	-	-	R	-	Ms	Ms
8	Ms	Ms	Ms	R	Ms	Ms

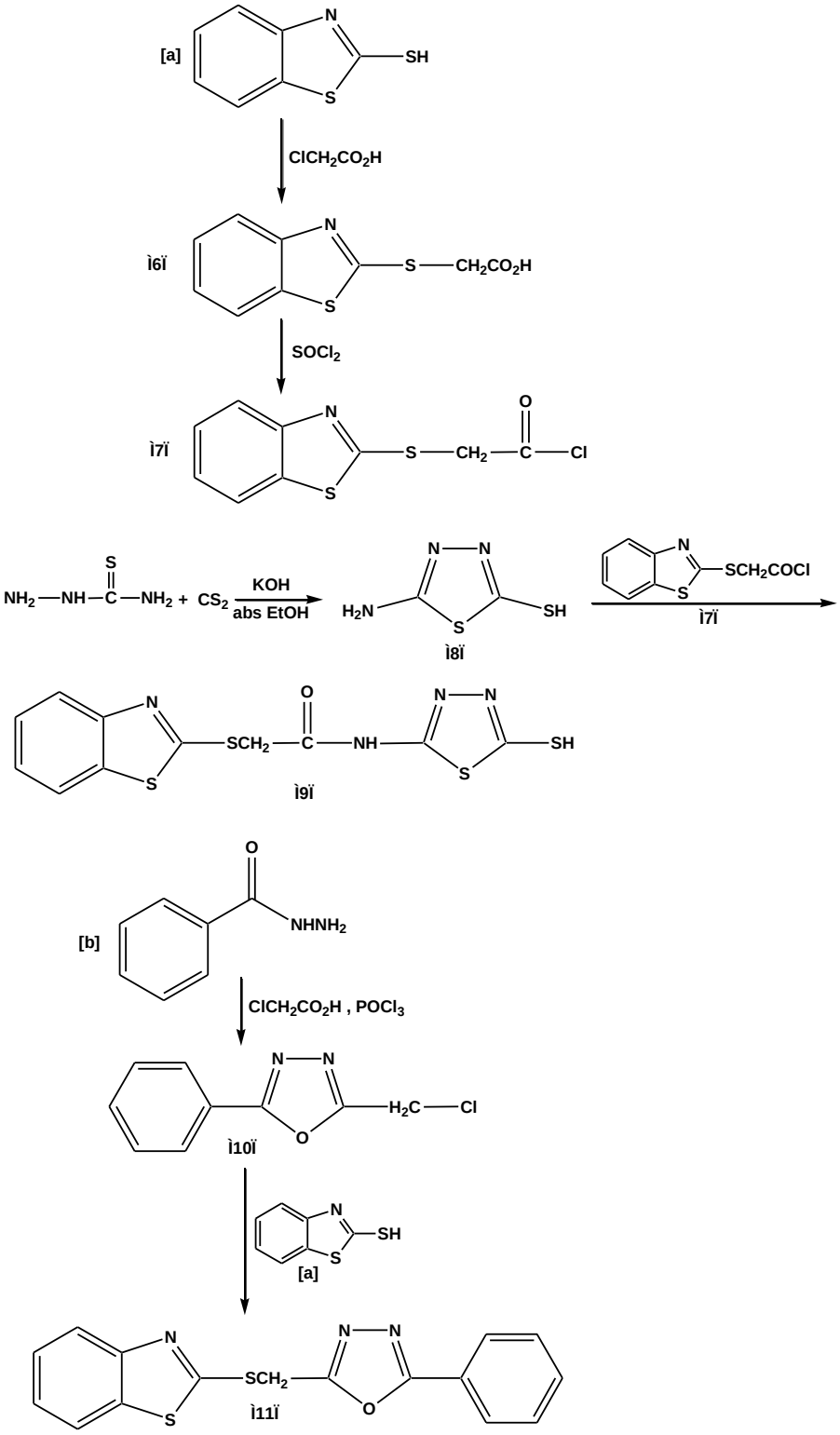
Key to symbols:
Sensitive (inhibition zone > 20 mm).
Moderately sensitive (inhibition zone 11-20 mm).
Resistant (inhibition zone 5-10 mm).
Inactive (inhibition zone <5 mm).

Microbiological Method

In this work the antimicrobial test was performed according to agar well diffusion method [29], and selected three concentration for ten derivative compounds as in table(4) The prepared compound were tested against two pathogenic microorganism, **Staphylococcus Aureus (G+)** and **Proteus vulgaris (G-)**. In the solidified media (Nutrient agar) ,suitable spaced apart holes were made (6 mm in diameter)these holes were filled with (0.1 ml) of prepared compound concentration that dissolve in DMSO(Di Methyl Sulfoxid) after spread the bacteria on agar . These plate were incubated at 37 ^{o}C for 24 hour ,the zone of inhibition of bacteria growth around the hole was absorbed and measured in mm and are represented by (R), (Ms) and (S) depending upon the diameter and clarity[30] as in table (5) .The preliminary screening results reveal that the compounds contained (pyrazole, 4-thiazolidenin, oxazepine, oxazoline, thiadiazole, oxadiazole, triazole, pyridazine moiety, triazole moiety imino and thiol groups in their structures [1] exhibit the highest antibacterial activity against **Proteus vulgaris (G-)** while the substituted thiadiazole and triazole compounds showed either low or no activity against both organisms.



Scheme (1).


[a]
SH
ClCH2CO2H
Ì6ï
CH2CO2H
SOCl2
Ì7ï
CH2
Cl
KOH
abs EtOH
NH2
CS2
H2N
Ì8ï
SCH2COCl
Ì7ï
SCH2
NH
Ì9ï
[b]
NHNH2
ClCH2CO2H , POCl3
H2C
Ì10ï
[a]
Ì11ï

Scheme (2).

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