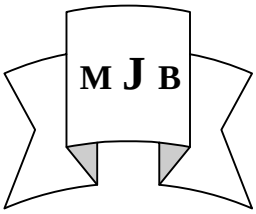
Synthesis, Characterization and Antimicrobial Activity of some New 2-Mercapto benzothiazole Heterocyclic Derivatives

Rafah F.Al-Smaisim Ayad M.R. Raauf Afrah Mohammed Hassan Salman*
Collage of Pharmacy, University of Al-Mustansriya, Iraq.
* De, Collage of Pharmacy,University of Al-Mustansriya, Iraq.



Abstract

New heterocyclic derivative of 2-Mercaptobenzothiazole have been synthesized: firstly, Schiff base of 2-(1,3-benzothiazol-2-ylthio) acetohydrazide derivatives (3-7) were prepared by refluxing 2-(1,3-benzothiazol-2-ylthio) acetohydrazide (2) with different aromatic aldehydes and ketones, then two of synthesized Schiff"s bases (4,5) were cyclized with acetic anhydride formed oxadiazole ring (8,9). Secondly, [(1,3-benzothiazol-2-ylthio)acetyl]hydrazinecarbothioamide (10) was prepared by reacted compound (2) with ammonium thiocyanate in dry benzene, then refluxing (10) with sodium hydroxide (2N) followed acidification by hydrochloric acid solution formed (11) . Thirdly, reacted (2) with acetylacetone afforded (12) .fourthly, compound (13) was formed by refluxe compound (2) with ethylacetoacetate; then refluxing (13) using absolute ethanol (98%) and formaldehyde with different primary amines formed (14-17) and with hydrazides derivatives formed (18-20). finally, dihydrophthalazine 1,4-dione derivative (21) was prepared by condensation of compound (2) with phthalic anhydride using absolute ethanol and glacial acetic acid. All structures of newly synthesized compounds were elucidated by elemental analysis and spectral data (IR and UV). Some of the synthesized compounds (4, 5,8,9,11,12,15,17,20 and 21) were screened for their antibacterial activity.

الخلاصة

تحضير مركبات حلقية غير متجانسة جديدة مشتقة من 2- مركبتو بنزوثايازول من خلال اجـراء التفـاعلات الاتيـة: اولاً : تحضيرقواعد شيف (2-7) للمركب2-(1,3-بنزوثايازول-2-يل ثايو) اسيتوهايدرازايد (2) من خلال تكاثف المركب (2) مع عدد من الالديهايدات و الكيتونات الاروماتية المختلفة. ثم اجراء الغلق الحلقي لاثنين من قواعد شف المحضرة(5و4) بمعاملتها مع(اسيتك انهيدريد)لتكوين مشتقات حلقية جديدة(9,8) التي تحتوي على حلقة الاوكسادايازول ً . ثانياً : مفاعلة المركب (2) مع الامونيوم ثايوسيانيت باستخدام البنزين الجاف كمذيب للحصول على المركب (10) ومن ثم صُعدَ المركب الاخير مع محلـول هيدروكسيد الصوديوم (2نورمال) وحمض الناتج بواسطة حامض الهيدروكلوريك للحصول على المركب (11). ثالثا: مفاعلـة المركب(2) مع الاسيتايل اسيتون لينتج المركب (12) .رابعاً: تصعيد المركب(2) مع الاثيل اسيتو اسيتيت لينتج المركب (13) ,ثم صُعد المركب (13)باستخدام الايثانول المطلق كمذيب و بوجود الفورملديهايد مع مجموعة من مشتقات الامينات الاولية لتحضير المشتقات (14-17) وكذلك مع مشتقات الهيـدرازين لتحـضير المـشتقات (18-20). واخيـراً : تـم تحـضير مـشتق دايهايدروفثاليزين 1,4-داي اون (21)من معاملة المركب (2) مع فثاليك انهيدريد وحامض الخليك المركز باستخدام الايثانول المطلق .شُخصت المركبات الجديدة المحضرة وذلك بتحليل العناصر وتحليل أطياف الاشعة تحـت الحمـراء والاشـعة فـوق البنفسجية.

تمت دراسةالفعالية البايلوجية لبعض المركبات المحضرة الجديدة (4,5,8,9,11,12,15,17,20, 21) ضد بعض انـواع مـن البكنيريا.

Introduction

The chemistry and pharmacology of benzothiazole derivatives have been of great interest because of its various biological activity [1,2]. The benzothiazole have recived the attention of medicinal chemists due to their wide range of biological activities

which include anti-inflammatory, analgesic, antibacterial activities [3,4]. Recently isatin-linked benzothiazole analogs on breast cancer and matching non-cancer cells [5].

The aim of the present work to synthesis new heterocyclic derivative of 2-Mercaptobenzothiazole and antimicrobial screening of some synthesized.

Materials and Methods

Apparatus and Chemicals

All reagents and solvents used were of Merck, Fluka and BDH.The melting points were determined in open capillaries tube on Stuart SMP10 Melting point apparatus. The purity of the compounds was confirmed by TLC using silica gel (0.5mm thickness, Merk) and visualized in iodine. The IR spectra were recorded in potassium bromide on Shimadzu FTIR-8400S. Spectral Wave length (λ_{max}) measurements were recorded on UV 1650 Shimadzu spectrophotometer by using 1 cm quartz cell.

The elemental analyses (C, H, and N) were performed using Perkin-Elmer 240C analyzer. Their results were found to be in good agreement with calculated values.

Experimental:

Ethyl (1,3-benzothiazol-2-ylthio)acetate (1) [6]

2-Mercaptobenzothiazole (0.2mol) and ethylchloroacetate (0.02 mol) in dry acetone in the presence of K_2CO_3 (20g) was refluxed for 10 hr and the reaction mixture poured into ice and neutralized with dil.HCl, the solid thus obtained was washed several times with water and recrystallized from chloroform; yield 80 %, as a white crystal. m.p. 58-59 °C.

2-(1, 3-benzothiazol-2-ylthio) acetohydrazide (2) [6]

A mixture of compound (1) (0.1mol) and hydrazine hydrate (0.13 mol, 98%) in ethanol (200ml) was refluxed for 6 hr, after cooling; the solid product was filtered, dried and recrystallized from ethanol, yield 66 %, as off-white crystal. m.p. 191-192 °C.

2-(1,3-benzothiazol-2-ylthio)-*N*'-(arylmethylene)acetohydrazide (3-7) [6]

To a stirred solution of compound (2) (0.01 mole) in absolute ethanol (30 ml), the appropriate aldehyde or ketone (0.01 mole) (3-7) was added. The mixture was refluxed for 4 hr and cooled to room temperature. The precipitate was filtered and recrystalized from appropriated solvent Table 1.

2-{3-acetyl-5-[(1,3-benzothiazol-2-ylthio)methyl]-2,3-dihydro-1,3,4-oxadiazol-2-yl}-*N*,*N*-dimethylaniline(8)[7]

4-{3-acetyl-5-[(1,3-benzothiazol-2-ylthio)methyl]-2,3-dihydro-1,3,4-oxadiazol-2-yl}benzene-1,3-diol (9) [7]

A solution of redistilled acetic anhydride (10ml) was added slowly to compounds (4, 5) (0.001 mol). The mixture was heated under reflux for 6 hr. The reaction mixture was cooled, poured onto water and allowed to stand at room temperature for 3 hr. The solid product formed was collected and recrystallized from petroleum ether/ ethyl acetate mixture.

2-[(1,3-benzothiazol-2-ylthio)acetyl]hydrazinecarbothioamide (10)[8]

The hydrazide (2) (0.01 mol) was added to ammonium thiocyanate (0.01 mol) in dry benzene (10ml) and the mixture was heated under reflux for 6hr.The solid material obtained on cooling was filtered and recrystallized from methanol.

5-[(1,3-benzothiazol-2-ylthio)methyl]-4H-1,2,4-triazole-3-thiol (11)[8]

The compound [10] (0.001 mol) was treated with 2N-NaOH in absolute

ethanol under reflux for 5 hr, after cooling , the solution was made acidic with conc.HCl and the precipitate was then recrystallized from chloroform .

2-{[2-(3,5-dimethyl-1*H*-pyrazol-1-yl)-2-oxoethyl]thio}-1,3-benzothiazole (12) [9]

The hydrazide (2) (0.002 mol) and acetyl acetone (1ml, 0.1 mol) was heated under reflux for 1 hr, then ethanol (10ml) was added and the mixture was refluxed for additional 3 hr. The reaction mixture was allowed to cool .The solid product was collected and recrystallized from ethanol.

2-[(1,3-benzothiazol-2-ylthio)acetyl]-5-methyl-2,4-dihydro-3H-pyrrol-3-one (13)[10]

A mixture of (0.01mol) of compound (2) and (0.01mol) (13ml) of ethyl acetoacetate was heated on water bath for 2 hr. with stirring. The resultant heavy reddish syrup was allowed to cool to room temperature it was washed thoroughly with ether to remove colored impurities. The solid thus separated out was filtered, dried and purified by recrystallization from ethanol.

4-(arylmethyl)-2-[(1,3-benzothiazol-2-ylthio)acetyl]-5-methyl-2,4-dihydro-3*H*-pyrazol-3-one (14-17) [11]

2-[(1,3-benzothiazol-2-ylthio)acetyl]-5-methyl-4-{[2-arylhydrazino]methyl}-2,4-dihydro-3*H*-pyrazol-3-one (18-20) [11]

A Mixture of (0.005mol) of (13), 5ml of formaldehyde and (0.005mol) of primary amine derivatives (14-17) or hydrazine derivatives (18-20) was refluxed with 25ml of 98% ethanol for 2 hr. The resultant mixture was concentrated. The resultant solid was dried and purified by recrystallization from appropriate solvents Table 1.

2-[(1,3-benzothiazol-2-ylthio)acetyl]-2,3-dihydrophthalazine-1,4-dione (21)[2]

A mixture of hydrazide (2) (0.01mol), phthalic anhydride (0.01mol) in 5ml absolute ethanol and glacial acetic acid (0.005mol) was refluxed for 3 hr,cooled . The reaction mixture was poured into crush ice. The solid obtained was filtered, washed with dilute sodium bicarbonate solution and recrystallized from ethanol.

Biological Screening

Agar well-diffusion method [13,14] using Mueller Hinton agar medium were screened for their antibacterial activity of synthesized compounds (4,5, 8, 9, 11, 12, 15, 17, 20 and 21) against test organism *S. aureus, S.epidesmidis, K.peneumoniae, Enterobacter SPP, P.aerugenosa and E.coli* . The drug Amikacim was tested under similar conditions for comparison.

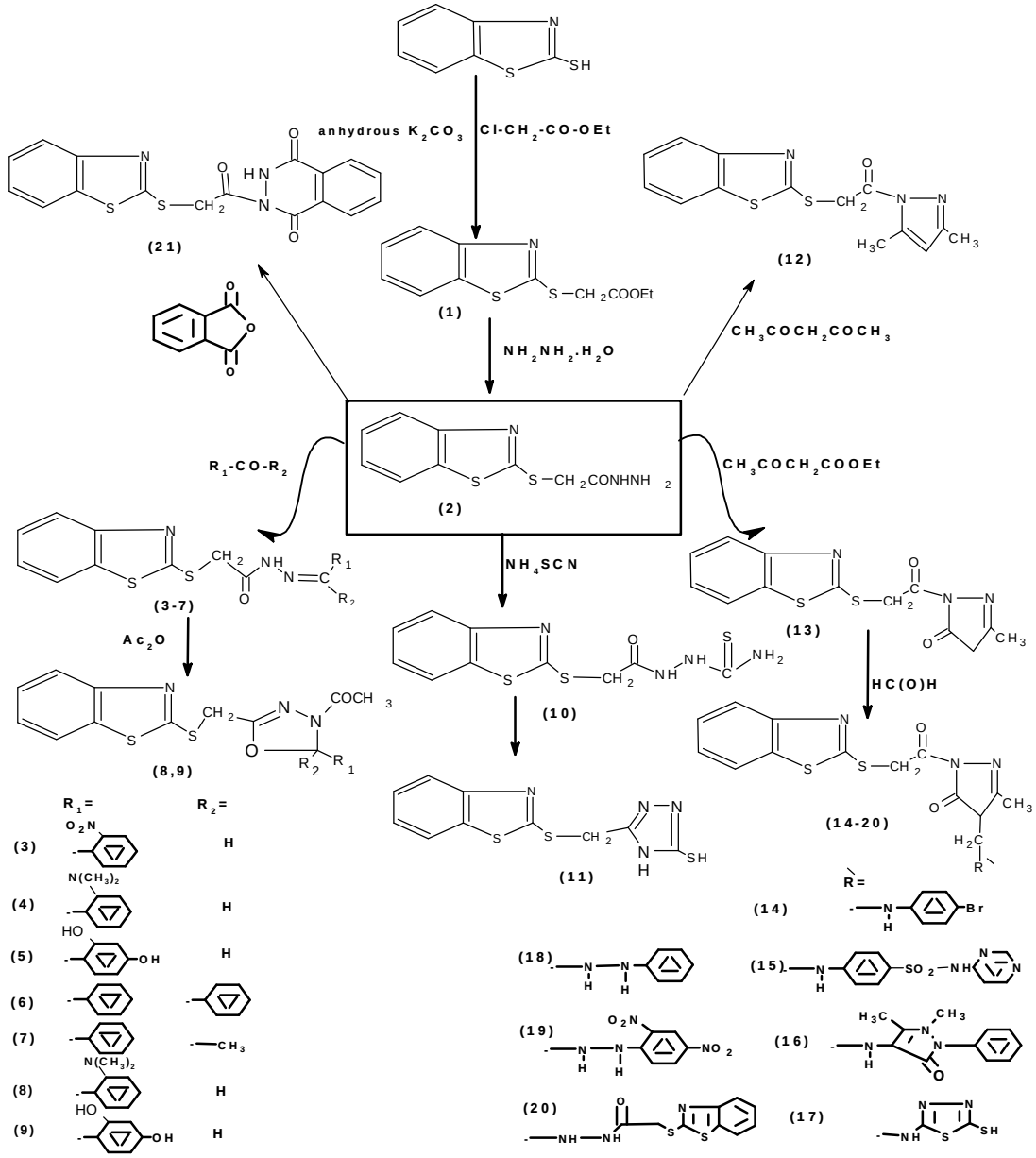
Wells were made (by scooping out medium with sterilized cork borer (6mm) in each plate which was streaked with test organisms. Uniform volume of different concentration 500µg/ml and 250 µg/ml of the test synthesized compounds were placed in each of the cavity, after over night incubation at 37 °C. The diameter of inhibition zone formed around the well was measured in mm DMSO was used as a solvent for all the compounds, which did not show any inhibition against test micro-organism.

Table 1 Physical and Analytical data of the synthesized compounds **(3-21)**

Com. No.	Molecular Formula	M.P °C	Color	Recrystalized Solvent	Yield (%)	Calc. (Found) %		
						C	H	N
3	$C_{16}H_{12}N_4O_3S_2$	159	Off-white	Ethanol	73	-----	-----	-----
4	$C_{18}H_{18}N_4OS_2$	191-192	Orange	Ethanol	70	58.38 (58.21)	4.86 (4.82)	15.16 (15.22)
5	$C_{16}H_{13}N_3O_3S_2$	186-188	Pale-Greenish-Yellow	Chloroform-Ethanol	58	53.48 (53.34)	3.62 (3.53)	11.70 (11.82)
6	$C_{22}H_{17}N_3OS_2$	150	brown	Chloroform-methanol	69	-----	-----	-----
7	$C_{17}H_{15}N_3OS_2$	165-167	brown	Ethanol	72	-----	-----	-----
8	$C_{20}H_{20}N_4O_2S_2$	203-205	Red	Petroleum ether-Ethyl acetate	61	58.25 (58.08)	4.85 (4.77)	13.59 (13.70)
9	$C_{18}H_{15}N_3O_4S_2$	102-103	Dark-Greenish-Yellow	Petroleum ether-Ethyl acetate	62	53.87 (53.93)	3.74 (3.81)	10.47 (10.61)
10	$C_{10}H_{10}N_4OS_3$	>220 dec.	Yellow	Methanol	54	40.27 (40.40)	3.36 (3.42)	18.79 ((18.88)
11	$C_{10}H_8N_4S_3$	195	Pale-brown	Chloroform	81	42.86 (42.77)	2.86 (2.79)	20.00 (20.14)
12	$C_{14}H_{13}N_3OS_2$	148-149	Pale-brown	Ethanol	71	55.26 (55.05)	4.61 (4.55)	13.82 (13.95)
13	$C_{13}H_{11}N_3O_2S_2$	250-251	Off-white	Ethanol	68	51.11 (51.23)	3.61 (3.75)	13.77 (13.90)
14	$C_{20}H_{17}N_4O_2S_2Br$	oily	Pale-brown	Benzene	51	-----	-----	-----
15	$C_{24}H_{21}N_7O_4S_3$	235-237	Yellow	Water: ethanol	55	50.79 (50.65)	3.70 (3.62)	17.28 (17.38)
16	$C_{25}H_{24}N_6O_3S_2$	264	Yellow	Ethanol	48	57.69 (57.51)	4.62 (4.55)	16.15 (16.29)
17	$C_{16}H_{14}N_6O_2S_4$	227	Pale-brown	Benzene	44	-----	-----	-----
18	$C_{20}H_{19}N_5O_2S_2$	271-272	orange	Chloroform	58	-----	-----	-----
19	$C_{20}H_{17}N_7O_6S_2$	266-268	Pale-brown	Water: ethanol	41	46.60 (46.71)	3.30 (3.38)	19.03 (19.15)
20	$C_{23}H_{20}N_6O_3S_4$	240-242	Pale-brown	Water: ethanol	40	-----	-----	-----
21	$C_{17}H_{11}N_3O_3S_2$	195-196	Off-white	Ethanol	66	55.28 (55.12)	2.98 (2.86)	11.38 (11.49)

Results and Discussion

Scheme (1) summarized the performed the synthesis of the target of benzothiazole heterocyclic derivatives in this work



Scheme 1

Accordingly reaction of 2-mercaptobenzothiazole with ethyl-chloroacetate in dry acetone in presence of K_2CO_3 afforded the Ethyl 2-(benzothiazolylthio) acetate **(1)**[6]. Compound **(1)** was treated with hydrazine hydrate in ethanol to afforded compound **(2)**. Compound **(2)** proved to be a versatile compound for synthesis of variety benzothiazole derivatives **(3-21)**.

Thus, reaction of the hydrazide **(2)** with various aromatic aldehydes and ketones in refluxing ethanol afforded

new Schiff bases **(3-7)**. The IR spectrum of compound **(3)**, showed a moderately strong band at 3348.79 cm^{-1} due to (NH) stretching vibrations, at 1678.13 cm^{-1} for (C=O of amide) and 1626.54 cm^{-1} for (C=N) stretching vibration. The U.V. spectrum for compound **(3)** has λ_{max} (MeOH) of 400 nm and 362.0 nm due to ($n-\pi^*$) and ($\pi-\pi^*$) transition respectively. Other IR bands of the synthesized Schiff's bases **(3-7)** are listed in Table 2. Refluxing the Schiff's bases **(4,5)** with acetic anhydride for 6 hr afforded good yield of oxadiazol derivatives **(8,9)**. The chqracteristic bands in IR spectrum of compounds **(8,9)** exhibited at regions 1660.22 – 1667.01 cm^{-1} (C=O, ketone),1614.41- 1623.03 cm^{-1} (C=N), 1271.13 cm^{-1} - 1235.84 cm^{-1} (C-O-C) and 1427.37 cm^{-1} (CH_3) stretching vibration [15].

The synthesis of the compound **(11)** was achieved in two steps; the first step was the preparation of compound **[10]** by treatment the hydrazide **(2)** with ammonium thiocyanate in dry benzene under reflux for 6 hr, the resulting product after isolation showed an IR spectrum which exhibited bands at 3350,3378.38 cm^{-1} (NH_2), 3107.58 cm^{-1} (N-H), 1651.12 cm^{-1} (C=O, amide) and 1280.27cm^{-1} (C=S) . The second step involved the treatment of (**10)** with (2N) sodium hydroxide in absolute ethanol under reflux for 5hr to give compound **(11)**. The IR spectrum exhibited characteristic bands at 3195.9 cm^{-1} (N-H, 1, 2, 4- triazole), 2800.20 cm^{-1} (SH) and 1673.91 cm^{-1} (C=N).

Hydrazide **(2)** easily undergoing cyclocondensation reaction with acetyl acetone or ethylacetoacetate gives pyrazol-yl derivative **(12)** and pyrrol-one derivative **(13)** respectively. The IR spectrum of compounds **(12, 13)** showed the disappearance of the characteristic bands of ($NHNH_2$) group. The IR spectrum for compound **(13)** exhibited bands 1718.22 cm^{-1} (C=O, cyclic), 1672.14 cm^{-1} (C=O, amidyl) and strong band 1621.58 cm^{-1} (C=N), which give a good indication for the cyclization [16]. When Compound **(13)** was treated with different primary amines **(14-17)** or different hydrazide **(18-20)** in the presence of formaldehyde produced compounds (14-20). Thus, the IR spectrum of compound **(17)**, showed bands 3353.54 cm^{-1} attributed to the (NH) group, 2750.89cm^{-1} refer to (SH) and 1424.76 cm^{-1} (C-S-C). The IR spectrum of compound (18), showed band at 3369.64 cm^{-1} attributed to the (NH) group. Other IR bands of the synthesized compounds **(14-20)** are listed in Table 2.

Further compound **(21)** was obtained in good yield when the hydrazide **(2)** was allowed to condense with phthalic anhydride. The structure of this compound was confirmed by the presence of amidic carbonyl stretching vibration bands 1739.79 cm^{-1} (C=O, amide), 1668.48 (C=O, cyclic amide) and 3327.44 cm^{-1}(NH). The U.V. spectrum of compound **(21)** has λ_{max} (MeOH) of 464.0 nm and 312.0 nm due to ($n-\pi^*$) and ($\pi-\pi^*$) transition respectively.

Table 2 Spectral data for compounds **(3-21)**

Compound Number	UV λ_{max} (nm)	ν(C=O)	ν(C=N)	ν(C-H)al. ν(C-H)ar.	Others
3	400 362	1678.13	1626.54	(2970)asy (2850) sy 3050	1070 **(C-S)$_{st}$** 3348.79 **(N-H)$_{st}$**
4	434 292 220	1668.48	1620.76	2950 asy 2850 sy 3050	1463.36 **(N-CH$_3$)$_{st}$** 3343.36 **(N-H)$_{st}$**
5	563 296	1670.75	1622.99	(2950)asy (2800)sy 3070	interference with 3349.94 **(NH$_2$)$_{st}$** 680.37 **(p-sub.)**
6	311 283	1675.94	1636.81	(2900)asy (2800)sy 3050	3346.55 **(N-H)$_{st}$**
7	287	1662.12	1634.82	2830 3030	1481.44 **(C-CH$_3$)$_{st}$**
8	259 211	1660.22	1614.41	2950 asy 2800 sy 3075	3590.87-3583.54 **(OH)$_{st}$** 1271.13 **(C-O-C)$_{st}$** 1427.37 **(C-CH$_3$)$_{st}$**
9	347 230	1667.01	1623.03	(2920) asy (2850) sy 3090	1235.84 **(C-O-C)$_{st}$** 1389.34 **(C-CH$_3$)$_{st}$** 1437.66**(N-CH$_3$)$_{st}$**
10	379 277	1651.12	1600.02	(2950)asy (2800) sy 3055	3350,3378.38 **(NH$_2$)$_{st}$** 3107.58 **(NH)$_{st}$** 1280.27 **(C=S)$_{st}$**
11	318 222	-------	1673.91	(2970) asy (2820) sy 3085	3195.90 **(NH)$_{st}$** 2800.20 **(SH)$_{st}$**
12	384 705	1668.8	1595.6	(2995) asy (2850) sy 3044	1390.87 **(CH$_3$)$_{st}$**
13	300 269	1718.22 1672.14	1621.58	(2950) asy (2850) sy 3098	1250-1231 **(C-N)$_{st}$** 755.54 **(C-S)$_{st}$**
14	386 248	1720.04 1638.26	1622.23	(2950) asy (2820)sy	670 **(C-Br)$_{st}$** 3150.80 **(NH)$_{st}$**
15	371 268	1717.22 1673.83	1580.22	(2940) asy (2800) sy 3077	1300.90 **(SO$_2$)$_{st\ (as)}$** 1120.62 **(SO$_2$)$_{st\ (sy)}$** 810 **(S-O)$_{st}$**, 3356.81**(NH)$_{st}$**
16	328 200 251	1715.90 1677.99	1595.91	(2960)al 3020	1350.28 **(CH$_3$)$_{st}$** 3400.31 **(NH)$_{st}$** 1290.52 **(N-N)$_{st}$**
17	293 205	1715.20 1665.89	1630.05	(2950)al 3050	3353.54 **(NH)$_{st}$** 2750.89 **(SH)$_{st}$** 1424.76 **(C-S-C)$_{st}$**
18	223	1708.77 1656.71	1627.70	(2970)asy (2800)$_{sy}$ 3080	3369.64 **(NH)$_{st}$**
19	309 277	1724.84 1666.98(ring)	1610.00	(2950) asy (2820)sy 3087	3389.39 **(NH)$_{st}$** 1550.20 ;1354.01 **(aromatic NO$_2$)$_{st}$**
20	572 322	1700.23 1680.06 (ring)	1635.79	(2970) asy (2820) sy 3095	3400.03 **(NH)$_{st}$** 743.88 **(C-S)$_{st}$** 1400.07 **(C-S-C)$_{st}$**
21	464 312	1739.79 1668.48	1627.18	(2970) asy (2820) sy 3085	3327.44 **(NH)$_{st}$**

Antimicrobial Activity

Some of the newly synthesized compounds **(8,9,11,12,15,17,20 and 21)** were screened for their antimicrobial activity the results given in Table 3.

The antibacterial activity was carried out in vitro using the agar well-diffusion method [13,14] using Mueller Hinton agar medium against test bacteria *(S. aureus, S.epidesmidis, K.peneumoniae, Enterobacter SPP, P.aerugenosa and E.coli).*

From the table its clear that compounds **(8,9,11,12,15,17,20 and 21)** exhibited good antibacterial activity against *Stphylococcus aureus, Staphylococcus epideredis and Enterobacter SPP.* Moreover, compounds **(4)** and **(5)** showed good antibacterial activity against *Enterobacter SPP* only. All derivatives are devoid antibacterial activity against *K.Penumoniae, P,aeruginosa and E.coli.*

The drug Amikacim shows 100% inhibition with test bacteria.

Table 3: Antimicrobial activity of some compounds synthesized

Compound No.	Zone of Inhibition (diameter in mm)					
	S.aureus*	***S.epidesmidis****	***K.peneumoniae****	***Enterobacter SPP****	*P.aerugenosa**	***E.coli****
4	---	---	---	**9**	---	---
5	---	---	---	**10**	---	---
8	**11**	**11**	---	**10**	---	---
9	**12**	**11**	---	**11**	---	---
11	**10**	**10**	---	**11**	---	---
12	**11**	**10**	---	**11**	---	---
15	**15**	**14**	---	**13**	---	---
17	**15**	**15**	---	**12**	---	---
20	**14**	**13**	---	**13**	---	---
21	**12**	**12**	---	**11**	---	---
Amikacin**	**17**	**20**	**17**	**16**	**16**	**17**

*500µg/ml and 250 µg/ml, ** **30**µg/disc

References

1. R. El-Sayed, (2006) "Synthesis, *antibacterial and surface activity of 1,2,4-triazole derivatives"* Grasas Y Aceites , 57(2),180-188.

2. M. Vedavathi, B. Somashekar, G .M. Sreenivasa, E. Jayachandran, (2010)"*Synthesis, Characterization and Anti-microbial activity of fluoro benzothiazole incorporated with 1, 3, 4-thiadiazole"* J. Pharm. Sct. & Res.; 2(1), 53-63.

3. H. Kaur, S. Kumar, I. Singh, K. K. Saxena, A. Kumar, (march2010) *"Synthesis, Characterization and Biological activity of various substituted benzothiazole derivatives"* Digest J. Nanomaterials and Biostructures ,5(1), 67-76.

4. C. Franchini, M. Muraglia, F. Corbo, M. A. Florio, A. D. Mola, A. Rosato, R. Matucci, M. Nesi, F.V. Bambeke, C. Vitali, (2009) *"Synthsis and Biological evaluation of 2-Mercapto-1,3-benzothiazole derivatives with potential antimicrobial activity"* Arch. Pharm. Chem. Life Sci. 342, 605-613.

5. V. R. Solomon, H. Changkun and L. Hoyun, *" Hybrid pharmacophore design and synthesis of isatin – benzothiazole analogs for their anti-breast cancer activity"*

6. K.G. Desai a, J.P. Ravalb and K.R. Desaic, (2006*)" Neat Reaction Technology for the Synthesis of 4-Oxo-thiazolidines Derived from2-SH-Benzothiazole and Antimicrobial Screening of Some Synthesized 4-Thiazolidinones"* J. Iranian Chemical Society, 3(3), 233-241.

7. A. A. H. Farghaly, (2004) *" Synthesis, Reaction and Antimicrobial activity of some new Indolyl-1, 3, 4-Oxadiazole, Triazole and Pyrazole derivatives"*
J. Chin. Chem. SOC., 51(1), 147-156.

8. M. Belkadi and A.A.Othman, *(2006) "A common route to the synthesis of 1,3,4-oxadiazole-2-thione and 1,2,4-triazole-3-thiols derivatives of trioses and pentoses as models for acyclic C-nuclesides"* Arkivoc,183-195 .

9. A.M. Kamal El-Dean, R. Shaker,A. A. AboEl-Hassan and F. F. Abdel Latif , (2004) *"Synthesis of some thienotetrahydroquinoline derivatives*" J. Chin. Chem. Soc., 51 (2), 335-345.

10. B. S. Furniss , A. J. Hannaford, P. W. G. Smith ,and A. R. Tatchell, (1989)*"Vogel's Textbook of Practical Organic Chemistry*. 5th Ed.p1146, John Wiley & Sons, Inc., New York.

11. S.R.Pattan, P.A.Rabara, J.S.Pattan, A.A.Bukitagar, V.S.Wakale and D.S.Musmade, (2009) *"Synthesis and evaluation of novel substituted 1,3,4-oxadiazole and pyrazole derivatives for antitubercular activity"* Indian J. of chemistry vol.48B,1453-1456.

12. D. Shreenivas , G. Anant and P. Vasantakumar, (Jan-Mar, 010*) "Synthesis and biological evaluation of 2-(N-substituted)-3H-phthalazin-1,4-diones and 1-(N-substituted)2,4,5-trihydropyridazin-3,6-diones as potent vasodilators"* Indian J .Pharm .Educ .Ress. 44(1), 1-7.

13. E.J.Baron and S.M. Finegold, (1994) "*Diagnostic Microbiollogy"* 9th Ed., Th C.V.Mosby,USA

14. M.J. Mahmoud, A.J. Hussam, A.M. Al-Omeri and A. Al-Naib, (1989)*" Invitro antimicrobial activity of Salsola rosmarinus and Adiantum Capillusueneris"*
Int.J.Crude,Drug.Res. 27, 14-16

15. E. Pretsch, P. Buhlmann, M. Badertscher, (2009) *"Structure Determination of Organic Compounds"* 4th Ed. , 282 Springer-Verlag Berlin Heidelberg.

16. H. H. Fahmy, E.M. Kassem, W. A. Abdou and S. A. Mahmoud , (1997)*"Synthesis of some New Indole derivatives of possible antimicrobial activities"* Egypt .J. Pharm. Sci. 38, (1-3), 13-22.