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Synthesis and antimicrobial activities of some thieno[3,2-*d*][1,3]thiazine nucleosides derivatives

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ABSTRACT

New thieno[3,2-*d*][1,3]thiazine nucleosides derivatives were synthesized and structures of the new compounds were confirmed on the basis of elemental and spectral data. Some of the synthesized compounds were screened for antibacterial and antifungal activity.

1. Introduction

Much attention has been focused on the heterocyclic drugs agents includes sulfur-containing compounds have broad-spectrum activities, such as antimalarial [1], HIV-1 inhibitors [2], and antimicrobial [3]. 5,6-Dihydro-4*H*-1,3-thiazines were synthesized as cholecystokinin antagonists [4] or antimycobacterial [5]. Heterocyclic compounds containing on the thiazine includes carbon and nitrogen atoms and one sulfur atom in different locations on the six-membered ring in there is 1,2-; 1,3-; 1,4-thiazines [6-8] and include derivatives were synthesized NCS binding to use antibacterial, antimicrobial, insects, anti-tumor, fungal, and agents herbicides, and various colorants etc. [9-19]. 1,3-Thiazines derivatives are used in preparation of various organic [20]. Here, we report, researcher concentrates on the different synthetic procedures in addition to the biological activities of 1,3 thiazines and their derivatives.

2. Experimental

2.1. Instrumentation

Melting points were determined with an Electro Thermal Mel-Temp II apparatus and were uncorrected. IR spectra (KBr) were recorded on a FT IR-8201 PC spectrophotometer. ^{1}H NMR was measured with a Varian/Gemini 200 MHz spectrometer in DMSO-d_6 as a solvent and chemical shifts were recorded in (δ, ppm). Mass spectra were recorded on an instrument "VG-7035". Spectra were recorded at 70 or 15 eV. Elemental analysis was performed at the Micro Analytical Centre, Cairo University, Giza, Egypt.

2.2. Synthesis

2.2.1. Ethyl 2,6-diamino-4H-thieno[3,2-d][1,3]thiazine-7-carboxylate (2)

A mixture of compound **1** (0.01 mol), ethylcyanoacetate (0.01 mol), sulfur (0.01 mol) and diethylamine (0.01 mol) was heated (70 °C) with stirring in absolute ethanol for 4 h. According to Gewald *et al.* [21], then the mixture was leaved for 24 h at 0 °C. The solid was filtrated, washed with ethanol (20 mL), dried and crystallized from absolute ethanol to give yellow crystals (Scheme 1). Yield: 64%. M.p.: 267-269 °C. FT-IR (KBr, ν, cm^{-1}): 3420 (NH_2) (amine), 2917 (CH) (aliphatic), 1718 (CO) (ester). ^{1}H NMR (200 MHz, DMSO-d_6, δ, ppm): 1.58 (t, 3H, CH_3), 2.49 (q, 2H, CH_2CH_3), 4.08 (s, 2H, SCH_2), 4.52 (brs, 2H, NH_2), 7.73 (brs, 2H, NH_2). Anal. calcd. for $C_9H_{11}N_3O_2S_2$ (257.33): C, 42.01; H, 4.31; N, 16.33; S, 24.92. Found: C, 42.21; H, 4.33; N, 16.36; S, 24.95%.

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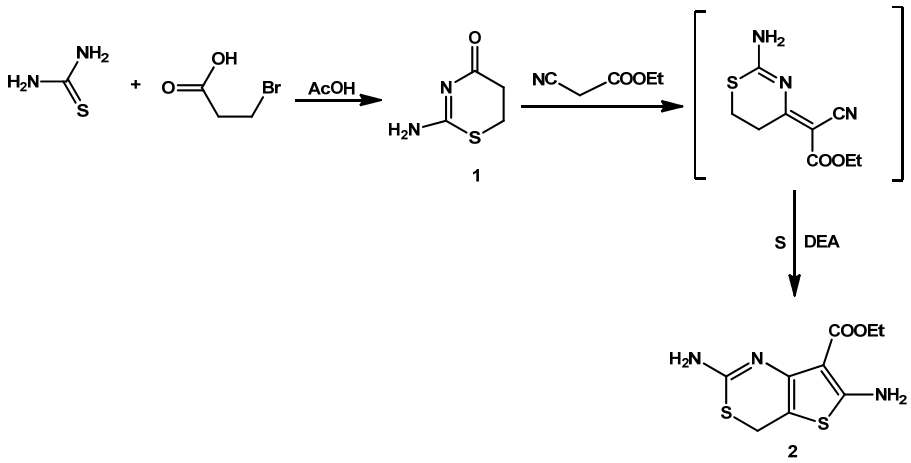


Scheme 1

2.2.2. 2-Amino-7-thioxo-7,8-dihydro-4H-pyrimido[5',4':4,5] thieno[3,2-d][1,3]thiazin-9(6H)-one (3)

Compound **2** (10 mmol) fusion with thiourea (10 mmol) at 180 °C in oil bath for 5 h, added the ethanol to solidify and then filtration the solid, dried, and recrystallized from ethanol as the solvent to give compound **3** (Scheme 2). Yield: 75%. M.p.: 290-292 °C. FT-IR (KBr, ν, cm^{-1}): 3340 (NH), 1665 (C=O), 1260 (C=S). ^{1}H NMR (200 MHz, DMSO-d_6, δ, ppm): 3.44 (s, 2H, CH_2), 6.83 (brs, 2H, NH_2), 9.30 (s, 1H, NH, exchangeable with D_2O), 10.0 (s, 1H, NH, exchangeable with D_2O). Anal. calcd. for $C_8H_6N_4OS_3$ (270.35): C, 35.54; H, 2.24; N, 20.72; S, 35.58. Found: C, 35.38; H, 2.36; N, 20.68; S, 35.62%.

2.2.3. 6-Amino-2-(2`,3`,4`-tri-O-acetyl-β-L-rhamnopyranosyl thio)-9-thia-1H-7-thia-1,3,5-triazafluoren-4-one (4)

To solution of compound **3** (1 mmole) in KOH (0.73 g in 10 mL of distilled water), was added to 2,3,4-tri-*o*-acetyl-α-L-rhamnopyranosyl bromide (1 mmole) in acetone (30 mL). After the mixture was stirred for 72 hr at room temperature, then the reaction complete and monitored by TLC. The mixture was filtered and the residue washed with water to remove the potassium bromide. The residue was purified by silica gel column chromatography using eluent ethanol/ethyl acetate to afford a pale yellow crystal (Scheme 2). Yield: 80%. M.p.: 246-248 °C. FT-IR (KBr, ν, cm^{-1}): 3344 (NH), 1736 (C= O), 1604 (C=N), 523 (C-S). ^{1}H NMR (200 MHz, DMSO-d_6, δ, ppm): 6.52 (brs, 2H, NH_2), 5.82 (d, 1H, H-1`), 5.12 (m, 2H, H-5`,H-5``), 4.32-4.47 (m, 3H, H-2`,3`,4`), 3.17 (s, 2H, CH_2), 2.03 (s, 3H, CH_3), 1.90-2.13 (3s, 9H, 3OAc). Anal. calcd. for $C_{20}H_{22}N_4O_8S_3$ (542.61): C, 44.07; H, 4.09; N, 10.33; S, 17.73. Found: C, 44.27; H, 4.34; N, 10.52; S, 17.81%.

2.2.4. General procedure for preparation of compounds 5 and 9

Compounds **4** and **8** were dissolved in dry methanol and dry ammonia gaseous was passed through the stirred solution for 1-2 hrs. The solutions were concentrated and the residue was recrystallization from methanol-petroleum ether (Scheme 2).

6-Amino-2-(β-L-rhamnopyranosylthio)-9-thia-1H-7-thia-1,3, 5-triazafluoren-4-one (**5**): Yield: 45%. M.p.: 259-263 °C. FT-IR (KBr, ν, cm^{-1}): 3324 (NH), 1604 (C=N), 523 (C-S). ^{1}H NMR (200 MHz, DMSO-d_6, δ, ppm): 7.26 (s, 1H, NH), 7.12 (brs, 2H, NH_2), 5.82 (d, 1H, H-1`), 4.28 (s, 1H, OH-4`), 4.65 (1s, 2H, OH-3`, 2`), 5.12 (m, 1H, H-5`), 4.32- 4.47 (m, 3H, H-2`,3`,4`), 3.17 (s, 2H, CH_2), 2.21 (s, 3H, CH_3). Anal. calcd. for $C_{14}H_{16}N_4O_5S_3$ (416.5): C, 40.37; H, 3.87; N, 13.45; S, 23.10. Found: C, 40.39; H, 3.97; N, 13.65; S, 23.23%.

7-(5-(β-L-rhamnopyranosylthio)-1,3,4-oxadiazol-2-yl)-4H-thieno[3,2-d][1,3] thiazine-2,6-diamine (**9**): Yield: 65%. M.p.: 239-242 °C. FT-IR (KBr, ν, cm^{-1}): 3324 (NH), 1624 (C=N), 525 (C-S). ^{1}H NMR (200 MHz, DMSO-d_6, δ, ppm): 7.12 (brs, 2H, NH_2), 6.34 (brs, 2H, NH_2), 5.70 (d, 1H, H-1`, $J_{1`,2`}$ = 8.2 Hz), 4.21 (s, 1H, OH-4`), 4.39 (s, 2H, OH-3`, 2`), 5.02 (m, 1H, H-5`), 4.22- 4.47 (m, 3H, H-2`,3`,4`), 3.09 (s, 2H, CH_2), 2.05 (s, 3H, CH_3). Anal. calcd. for $C_{14}H_{17}N_5O_5S_3$ (431.51): C, 38.97; H, 3.97; N, 16.23; S, 22.29. Found: C, 39.07; H, 3.87; N, 16.45; S, 22.10%.

2.2.5. 2,6-Diamino-4H-thieno[3,2-d][1,3]thiazine-7-carbohydrazide (6)

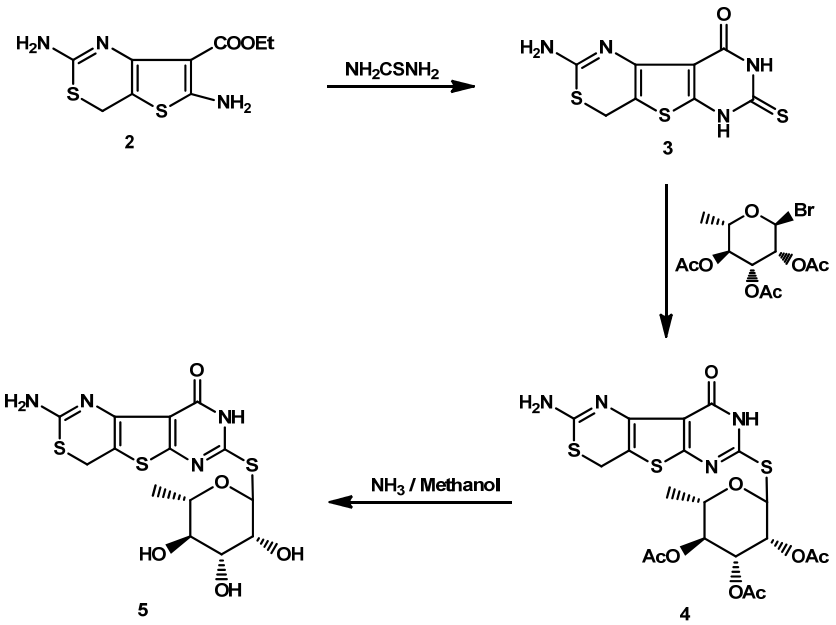
A solution of the ester **2** (2.6 g, 10 mmol) and hydrazine hydrate (0.6 mL, 99%) was refluxed in 50 mL of absolute ethanol for 5 hr. Then the solid was filtered off and recrystallized from EtOH/DMF to give the compound **6** as white powder (Scheme 3). Yield: 76%. M.p.: 235-237 °C. FT-IR (KBr, ν, cm^{-1}): 3310, 3222, 3145 (NH, NH_2), 1631 (C=O), 1588 (C=N). ^{1}H NMR (200 MHz, DMSO-d_6, δ, ppm): 9.02 (brs, 2H, NH_2, D_2O-exchangeable), 9.85 (brs, 1H, NH, D_2O-exchangeable), 7.45 (brs, 2H, NH_2), 6.45 (brs, 2H, NH_2), 3.15 (s, 2H, CH_2). Anal. calcd. for $C_7H_9N_5OS_2$ (243.31): C, 34.55; H, 3.73; N, 28.78; S, 26.36. Found: C, 34.96; H, 3.52; N, 28.76; S, 26.15%.

2.2.6. 5-(2,6-Diamino-4H-thieno[3,2-d][1,3]thiazin-7-yl)-1,3,4-oxadiazole-2-thiol (7)

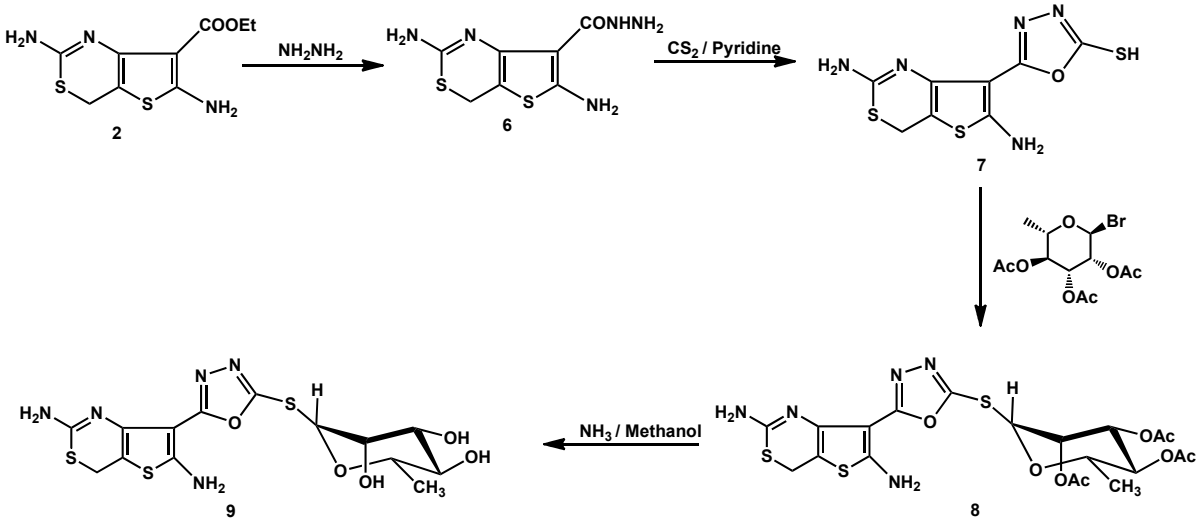
A mixture of compound **6** (0.01 mol) and carbon disulfide (5 mL) was refluxed in pyridine (25 mL) for 8 h, then allowed to cool. The product was formed and recrystallized from ethanol as yellow crystals (Scheme 3). Yield: 63%. M.p.: 195-197 °C. FT-IR (KBr, ν, cm^{-1}): 3222, 3145 (NH_2), 2860-2760 (S-H), 1588 (C=N). ^{1}H NMR (200 MHz, DMSO-d_6, δ, ppm): 9.02 (br. s, 2H, NH_2, D_2O-exchangeable), 6.89 (brs, 2H, NH_2), 3.27 (s, 2H, CH_2), 3.05 (s, 1H, C-SH). Anal. calcd. for $C_8H_7N_5OS_3$: (285.37): C, 33.67; H, 2.47; N, 24.54; S, 33.71. Found: C, 33.96; H, 2.52; N, 24.76; S, 33.55%.

2.2.7. 7-(5-(2',3',4'-Tri-O-acetyl-β-L-rhamnopyranosylthio)-1,3,4-oxadiazol-2-yl)-4H-thieno[3,2-d][1,3] thiazine-2,6-diamine (8)

A mixture of compound **7** (10 mmol) in dry DMF (20 mL), NaH (15 mmol) was added portion wise through 15 min. and the solution stirred at room temperature for 30 min.



Scheme 2

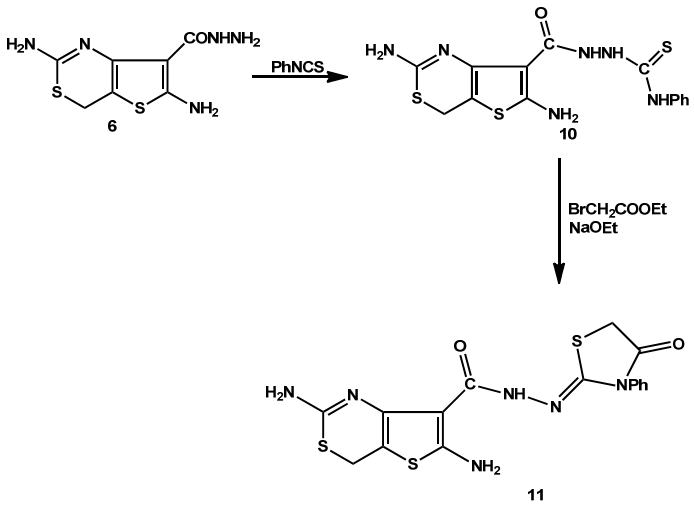


Scheme 3

Then, a solution of 2,3,4-tri-*o*-acetyl-α-L-rhamnopyranosyl bromide, in DMF (10 mL) was dropped within 30 min. and the mixture was stirred at room temperature for 12 h. After completion, the water was added to the reaction mixture and acidified with diluted acetic acid. The organic layer was extracted with ethyl acetate (20 mL), washed with water and dried over anhydrous sodium sulphate and evaporation the solvent to give a residue, which was purified by column chromatography using ethylacetate/ethanol as a solvent to give compound **8** (Scheme 3). Yield: 72%. M.p.: 210-212 °C. FT-IR (KBr, ν, cm^{-1}): 3410, 3222, 3145 (NH, NH_2), 1731 (C=O), 1568 (C=N). ^{1}H NMR (200MHz, *δ*, DMSO-d_6): 7.82 (brs, 2H, NH_2), 6.52 (brs, 2H, NH_2), 4.86 (d, 1H, H-1`, $J_{1',2'}$ = 9.5 Hz), 5.02 (m, 1H, H-5`), 4.02-4.23 (m, 3H, H-2`,3`,4`), 3.03 (s, 2H, CH_2), 2.23 (d, 3H, CH_3, $J_{5',6'}$ = 7.3 Hz), 1.90-2.01 (3s, 9H, 3×OAc). Anal. calcd. for $C_{20}H_{23}N_5O_8S_3$ (557.62): C, 43.08; H, 4.16; N, 12.56; S, 17.25. Found: C, 43.07; H, 4.37; N, 12.45; S, 17.10%.

2.2.8. 2,6-Diamino-4H-thieno[3,2-d][1,3]thiazine-7-phenyl hydrazinecarbothioamide (10)

A mixture of compound **6** (2.43 g, 10 mmol) and phenyl isothiocyanate (9 mmol) was refluxed in absolute ethanol (50 mL) for 5 h, cooled and filtration. The solid was dried and recrystallized from ethanol (Scheme 4). Yield: 84%. M.p.: 205-209 °C. FT-IR (KBr, ν, cm^{-1}): 3237-3121 (NH_2, NH), 1682 (C=O), 1598, 1548, 1495 (C=C, C=N), 1358-1385 (C=S), 1293 (S-CH_2), 1118 (C-O). ^{1}H NMR (200 MHz, DMSO-d_6, *δ*, ppm): 3.98 (s, 2H, SCH_2), 7.18-7.20 (dd, 2H, phenyl), 7.32-7.37 (m, 3H, phenyl), 9.50 (s br, 1H, NH-Ph), 9.75 (s, 1H, NHCS), 10.29 (s, 1H, CONH); 4.13 (s, 2H, NH_2), 3.45(s, 2H, NH_2). Anal. calcd. for $C_{14}H_{14}N_6OS_3$ (378.5): C, 44.43; H, 3.73; N, 22.20; S, 25.42. Found: C, 44.23; H, 3.70; N, 22.24; S, 25.21%.



Scheme 4

2.2.9. 2,6-diamino-N'-(4-oxo-3-phenylthiazolidin-2-ylidene)-4H-thieno[3,2-d][1,3]thiazine-7-carbohydrazide (11)

A mixture of compound **10** (0.37 g, 1 mmol), sodium acetate (0.29 g, 4 mmol) and ethyl bromoacetate (0.16 g, 1.1 mmol) was refluxed in absolute ethanol (15 mL) for 3 h. the solvent was removed under reduced pressure, the residue was washed with water and extracted with chloroform. The white solid was crystallized from 2-propanol to give compound **11** (Scheme 4). Yield: 83%. M.p.: 190-189 °C. FT-IR (KBr, ν, cm^{-1}): 3229 (NH), 1669 (C=O), 1593, 1553, 1506 (C=C, C=N), 1295 (S-CH_2), 1119 (C-O-C). ^{1}H NMR (200 MHz, DMSO-d_6, δ, ppm): 4.15 (s, 2H, SCH_2), 4.07 (s, 2H, thiazolidine), 6.86 (d, 2H, phenyl), 7.15 (t, 1H, phenyl), 7.38 (t, 2H, phenyl), 8.32 (s, 1H, NH), 7.21 (s, 2H, NH_2), 7.21 (s, 2H, NH_2). Anal. calcd. for $C_{16}H_{14}N_6O_2S_3$ (418.52): C, 45.92; H, 3.37; N, 20.08; S, 22.98. Found: C, 45.72; H, 3.33; N, 20.28; S, 22.67%.

2.3. Antimicrobial activity

A loop full of the given bacterial strain was inoculated into 25 mL of N-broth (Nutrient Broth) and incubated for 24 hr, in an incubator at 30 °C in order to activate the bacterial strain. Petri-dish of 15 cm diameter was filled with 100 mL of nutrient agar media. Vaccination was carried out by the technique of molding panel. There has been made a full preparation of a hole in the plywood airflow to maintain the state-sterile and aseptic strict. After the consolidation of the media, the porosity in the media with the help of perforated cup (10 mm), and 0.1 mL of concentration (10 mg/1 mL) of the different compounds tested was transferred into the well. Dimethylforamide (DMF) was used as a control. The plates were incubated for 24 hours, at 30 °C. Inhibition zone formed by synthetic compounds the test bacterial strain, especially to determine the antibacterial activities of the compounds tested different [22].

Media Czepak Docs used to grow the types of fungi. The medium was seeded with different fungal species. After hardening of the media on the sheets, and make pores in the agar with a glass poorer (10 mm) diameter, then was transferred 0.1 mL of concentration (10 mg/1 mL) of various synthetic compounds in the well. It has been used DMF as a control. The plates were incubated for 5 days at 30 °C. Inhibition zone formed by the tested compounds to combat a certain strain experiments to determine the activities of anti-fungal as the vehicles tested different [23].

3. Results and discussion

3.1. Chemistry

2-Amino-5,6-dihydro-1,3-thiazin-4-one (**1**) was synthesized from the reaction of thiourea with 3-bromopropionic acid [24] (Scheme 1). Compound **1** was reacted with ethyl cyanoacetate in ethanol in the presence of diethylamine to yield ethyl 2,7-diamino-*4H*-thieno[3,2-d][1,3] thiazine-6-carboxylate, **2** (Scheme 1). The IR spectrum of compound **2** showed absorption bands at 3420 cm^{-1} due to NH_2.

Ethyl 2,7-diamino-4*H*-thieno[3,2-*d*][1,3]thiazine-6-carboxylate (**2**) was fused with thiourea in absent solvent at 180 °C to give the compound thiopyrimidine derivative **3**. Compound **3** was combined with 2,3,4-tri-*o*-acetyl-α-L-rhamnopyranosyl bromide [25] in the presence of potassium hydroxide and ethanol as the solvent to give the approved compound **4**. The subsequent removal of the protecting groups by treatment of compound **4** with ammonia gas in dry methanol, gave the final required *S*-glycoside, **5** (Scheme 2).

The reaction of compound **2** with hydrazine hydrate was refluxed with ethanol afforded the carbohydrazide derivative **6**. Its IR spectra showed the appearance of three absorption bands due to NH_2 and NH functions in addition to the carbonyl absorption band. Its mass spectrum showed a peak corresponding to its molecular ion at *m/z* 243 (M^+).

The carbohydrazide **6** was refluxed with carbon disulfide in the presence of pyridine yielded oxadiazoyltheinothiazine derivative **7,** which was combined with 2,3,4-tri-*o*-acetyl-*α*-L-rhamnopyranosyl bromide in the presence of sodium hydride and dimethylformamide to provide the corresponding S-glycoside, **8**. Deacetylation of the *S*-nucleoside **8** proceeded with methanolic ammonia to tolerate the free nucleoside **9** in good yields (Scheme 3). The structures of compounds **8** and **9** were created by IR and ^{1}H NMR.

Compound **6** was refluxed with phenyl isothiocyanate in absolute ethanol gave the compound hydrazinecarbothioamide **10** a good yields. The compound **10** has been confirmed by spectral data. The infrared spectrum of compound **10** appearance characteristic absorption bands in a region of 3237-3121 cm^{-1} for NH, at 1682 cm^{-1} for C=O and in the region of 1358-1385 cm^{-1} corresponding to C=S vibrations. Compound **10** was reacted with ethyl bromoacetic acid in existence absolute ethanol in the presence of anhydrous sodium acetate as a base to produce the compound of 4-thiazolidinones **11**.

Table 1. Screening for antimicrobial activity of the tested compounds.

Sample no	Inhibition zone diameter (mm/mg sample) *			
	***E. coli* (G–)**	***S. aureus* (G+)**	***A. flavus***	***C. albicans***
2	9	7	8	7
3	9	6	7	6
4	10	4	7	4
5	9	6	7	6
7	12	7	5	6
8	8	10	10	9
9	8	8	15	6
10	11	8	7	8
11	7	9	8	7
Chloramphenicol	2	23	-	-
Amphotericin B	-	-	18	10

* The concentration of the solution 20.0 mg/mL was tested. (G-): Gram negative bacteria; (G+): Gram positive bacteria; *E. coli*: *Esherichia coli*; *S. aureus*: *Staphylococcus aureus*; *A. flavus*: *Aspergillus flavus*; *C. albicans*: *Candida albicans.*

Thiazolidinones **11** show absorption bands for ring C=O in the region of 1760 cm^{-1} together with amide C=O absorption at 1670 cm^{-1}. The ^1H NMR spectrum revealed the presence of two singlets for thiomethylene protons (Scheme 4).

3.2. Antimicrobial activity

Compounds tested for their activities against bacteria Gram(+) (*Staphylcoccus aureus*) and Gram(-) bacteria (*Escherichia coli*) in addition to pathogenic fungi (*Aspergillus flavus* and *Candida albicans*). Measured results of the examination of antimicrobial average diameter of the inhibition zones, expressed in mm, and shown in Table 1. The results of the tests performed in all of the tested compounds show significant activities to combat *E. coli* and *S. aureus*, while the vehicles were only Compound **4** and **11** moderately active to fight *A. Flavus* and *C. albicans*. However, the activities of the tested compounds are much lower than those factors, anti-fungal and anti-bacterial standard used.

4. Conclusion

Newly synthesized thieno[3,2-*d*][1,3]thiazine nucleosides derivatives were thoroughly characterized and some of them exhibited antimicrobial activity.

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