Synthesis and antibacterial activity of new 1,2,3-triazolylmethyl-2H-1,4-benzothiazin-3(4H)-one derivatives

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Abstract

Background: A novel series of 1,2,3-triazole derivatives containing 1,4-benzothiazin-3-one ring (7a–9a, 7b–9b), (10a–12a, 10b–12b) and (13–15) were synthesized by 1,3-dipolar cycloaddition reactions of azides α-α-d-galactopyranoside azide F, 2,3,4,6-tetra-O-acetyl-(d)-glucopyranosyl azide G and methyl-N-benzoyl-α-azidoglycinate H with compounds 4–6.

Findings: Initially, the reactions were conducted under thermal conditions in ethanol. The reaction leads, each time, to the formation of two regioisomers: (Schemes 2, 3) with yields of 17 to 21% for 1,5-disubstituted 1,2,3-triazole-regioisomers (7b–12b) and yields ranging from 61 to 65% for the 1,4-disubstituted regioisomers (7a–12a). In order to report an unequivocal synthesis of the 1,4-regioisomers and confirm the structures of the two regioisomers obtained in thermal conditions (Huisgen reactions), the method click chemistry (Copper-Catalyzed Azide-Alkyne Cycloaddition) has been used.

Conclusions: The newly synthesized compounds using cycloaddition reactions were evaluated in vitro for their antibacterial activities against some Gram positive and Gram negative microbial strains. Among the compounds tested, the compound 8a showed excellent antibacterial activities against PA ATCC and Acin ESBL (MIC = 31.2 μg/ml).

Keywords: 1,2,3-Triazole, 1,4-Benzothiazine, Antimicrobial activity, Cycloaddition, Spectroscopic methods

Introduction

Compounds containing 1,4-benzothiazine backbone have been studied extensively both in academic and industrial laboratories. These molecules exhibit a wide range of biological applications indicating that 1,4-benzothiazine moiety is a template potentially useful in medicinal chemistry research and therapeutic applications such as anti-inflammatory [1, 2], antipyretic [3], anti-microbial [4–7], anti-viral [8], herbicide [9], anti-cancer [10–13], and anti-oxidant [14] areas. They have also been reported as precursors for the synthesis of compounds [15] possessing anti-diabetic [16] and anti-corrosion activities [17, 18]. Figure 1 gives some examples of bioactive molecules with 1,4-benzothiazine moieties.

In order to prepare new heterocyclic systems with biological applications, we report in the present work 1,3-dipolar cycloaddition reactions [19–21] between 4-propargyl-2-(substituted)-1,4-benzothiazin-3-ones 4–6 as dipolarophiles and α-α-d-galactopyranoside azide F or 2,3,4,6-tetra-O-acetyl-(p)-glucopyranosyl azide G or methyl-N-benzoyl-α-azidoglycinate H as dipoles. It is worthy to note that the integration of two or more active heterocyclic rings in the same molecule may lead to new hybrid with broad biological activities.

As a continuation of our previous works related to the synthesis of new heterocyclic systems with potent pharmacological properties we describe a novel 1,2,3-triazol-α-α-d-galactopyranoside-2-(substituted)-1,4-benzothiazin-3-one
The structures of compounds isolated have been identified on the basis of $^1$H NMR and $^{13}$C NMR spectral data. The $^1$H NMR spectrum of the compounds 4–6 in DMSO-$d_6$ shows signals for the propargyl group as a doublet at 4.74, 4.90 and 4.86 ppm, respectively and a triplet centered at 2.20 (2.21) and 3.31 ppm corresponding to methylene groups bonded to the nitrogen atom and acetylenic HCC=C-proton, respectively. The $^{13}$C NMR spectrum showed the signal of hydrogenated acetylenic carbon at 75.0, 75.5 and 75.47 ppm, respectively. The structures of compounds 5 and 6 were confirmed by a crystallographic studies [22, 23] (Fig. 2).

The crystallographic study confirms that compounds 5, 6 have Z configuration about the exocyclic double bond. This result will allow to assign the Z configuration to all compounds coming from the products 5, 6 in future ulterior cycloaddition reactions the dipolarophiles 4–6 are then involved in cycloaddition reactions with the dipoles given above leading to new benzothiazine derivatives containing various 1,2,3-triazole moieties able to modulate their biological activities [24, 25].

**Results and discussion**

**Synthesis of dipolarophiles 4–6**

Dipolarophiles 4–6 have been prepared with good yields (88–92%) via alkylation reactions of compounds 1–3 by propargyl bromide under phase transfer catalysis conditions using tetra-$n$-butylammonium bromide (TBAB) as catalyst and potassium carbonate as base in dimethylformamide at room temperature (Scheme 1).

The literature reports several studies concerning the synthesis of 1,4 or 1,5-disubstituted 1,2,3-triazoles according to the Huisgen method under thermal conditions [26]. Due to the importance of the 1,2,3-triazole moiety in the biological and therapeutic areas, it seems interesting to include this backbone in the 1,4-benzothiazine derivatives. Thus, we have studied the reaction between azides F, G and H and compounds 4–6. The reaction was conducted in hot ethanol leading to the formation of products 7–12 related in each case to two regioisomers (7a–12a and 7b–12b) using azides F, G and H and compounds 4–6. The reaction was conducted in hot ethanol leading to the formation of products 7–12 related in each case to two regioisomers (7a–12a and 7b–12b) using azides F, G and H. The yields are between 17 and 21% for 1,5-disubstituted 1,2,3-triazole-regioisomers (7b–12b) and between 61 and 65% for 1,4-disubstituted regioisomers (7a–12a). These results are in agreement with those described in the literature [27–30]. The two 1,4 and 1,5 disubstituted 1,2,3-triazole isomers have been separated by chromatography.

**Synthesis of new 1,2,3-triazolymethyl-2H-1,4-benzothiazin-3(4H)-one derivatives**

The literature reports several studies concerning the synthesis of 1,4 or 1,5-disubstituted 1,2,3-triazoles according to the Huisgen method under thermal conditions [26]. Due to the importance of the 1,2,3-triazole moiety in the biological and therapeutic areas, it seems interesting to include this backbone in the 1,4-benzothiazine derivatives. Thus, we have studied the reaction between azides F, G and H and compounds 4–6. The reaction was conducted in hot ethanol leading to the formation of products 7–12 related in each case to two regioisomers (7a–12a and 7b–12b) using azides F, G and H. The yields are between 17 and 21% for 1,5-disubstituted 1,2,3-triazole-regioisomers (7b–12b) and between 61 and 65% for 1,4-disubstituted regioisomers (7a–12a). These results are in agreement with those described in the literature [27–30]. The two 1,4 and 1,5 disubstituted 1,2,3-triazole isomers have been separated by chromatography.
on silica gel column [eluent: ethyl acetate/hexane (1/9)] (Scheme 2).

In order to report an unequivocal synthesis of the 1,4-regioisomers 7a–12a and confirm the structures of the two regioisomers obtained previously in thermal conditions (Huisgen reactions), the method click chemistry [Copper-Catalyzed Azide-Alkyne Cycloaddition (CuAAC)] described in the literature [31–34] has been used in the condensation of dipolarophiles 4–6 with azides F and G in the presence of copper (II) sulfate (CuSO4), sodium ascorbate as a reducing agent in water and ethanol mixture (1:1). Thus the 1,4-disubstituted 1,2,3-triazole derivatives 7a–12a have been obtained exclusively in 86 to 90% yields. All the products are fully characterized by 1H and 13C NMR (see “Experimental part”). 1H NMR spectra in DMSO d6 of compounds 7a–12a present in particular signals: as singlets at 4.33(7a), 4.49(8a), 4.55(9a), 4.37(10a), 4.34(11a) and 4.37(12a) ppm related to the two protons of the methylene group linked to the nitrogen atom of 1,4-benzothiazine moiety and a signals as singlets at 7.93(7a), 8.01(8a), 7.99(9a), 8.35(10a), 8.37(11a) and 8.39(12a) ppm corresponding to the proton in position 5 of the 1,2,3-triazole ring. The 1H NMR spectra of 1,5-disubstituted regioisomers 7b–12b exhibit particularly signals as singlets at 4.54(7b), 4.39(8b), 4.42(9b), 4.37(10b), 4.34(11b) and 4.34(12b) ppm due to the two protons of the methylene groups linked to the nitrogen atom in position 1 of the 1,4-benzothiazine ring and signals as singlets at 8.31(7b), 8.29(8b), 8.25(9b), 7.63(10b), 7.62(11b) and 7.61(12b) ppm related to the proton in position 4 of the 1,2,3-triazole moiety. The 13C NMR spectra of compounds 7a–12a highlight in particular the signals of the two methylene groups linked to the nitrogen atom in position 3 of the bicyclic system at 40.78(7a), 41.57(8a), 41.42(9a), 41.84(10a), 41.51(11a) and 40.99 (12a) ppm, and for compounds 7b–12b the signals at 41.00(7b), 39.77(8b), 39.23(9b), 41.84(10b), 41.84(11b) and 41.74(12b) ppm. These results are in good agreement with those observed in the literature which show that the proton signal at position 5 of the 1,2,3-triazole ring is more deshielded than the one for the proton at position 4 of 1,2,3-triazole for compounds 7b–12b [27–30].

It should be noted that when compounds 4–6 reacted with azide H it has allowed us to isolate in each case only one isomer 13–15 (Scheme 3) with yields between 77 and 83%. For compounds 13–15 the 1H NMR in DMSO d6 exhibit in particular signals as singlets at 5.16(13), 4.86(14) and 4.85(15) ppm related to the two protons of methylene group linked to the nitrogen atom at position 4 and a singlets at 7.40(13), 7.54(14) and 7.53(15) ppm corresponding to the proton in position 5 of the 1,2,3-triazole moiety. The 13C NMR spectra highlight in particular the presence of signals related to the methylene groups at 40.32(13), 35.47(14) and 35.01(15) ppm.

The crystallographic analysis of compound 13 indicates that the triazole nitrogen atom is unsubstituted and confirms the structures of compounds 13–15 (Figs. 3 and 4). It is interesting to note that compound 13 crystallizes in monoclinic system (P21/c). The crystallographic data have been assigned to the deposition number. CCDC 1564624.

The formation of compounds 13–15 suggests that the reaction operates via a traditional mechanism of 1,3-dipolar cycloaddition of azide H with alkynes 4–6, followed by transesterification. The nucleophilic substitution of triazole unit by ethanol leads to compounds 13–15 next to the glycine derivative 16, Scheme 4.

**Biological evaluation in vitro antibacterial evaluation**

The compounds tested showed an average antibacterial activity and the results of the assessments are shown in Fig. 5 and Table 1.

The results are presented in the form of antibiograms below:

The newly synthesized compounds 7a(7b), 8a(8b), 10a(10b) and 11a(11b), have been tested for their antibacterial activity in vitro against two Gram-positive bacteria: *Staphylococcus aureus* ATCC 25923 and *Staphylococcus aureus* MLSB and six Gram-negative bacteria: *Escherichia coli* (E. coli) ATCC 25922, *Pseudomonas aeruginosa* (PA) ATCC 27853, *Acinetobacter* (Acin) ATCC 17978, *Escherichia coli* ESB, *Klebsiella pneumonia* (KP) ESB and *Acinetobacter ESB*. The compounds were tested at a concentration of 500 µg/ml, using disc
Scheme 2 Preparation of new 1,2,3-triazolymethyl-2H-1,4-benzothiazin-3-one derivatives
diffusion method [35], the minimum inhibitory concentration (MIC) was measured in µg/ml and compared with that of chloramphenicol as reference standard. The strains used in this work are widely encountered in various pathologies in humans, were obtained from the Department of Microbiology, National Institute of Hygiene, Rabat, Morocco.

The results obtained in the antibacterial activity of the compounds 1–2, 4–5, 7a(7b), 8a(8b), 10a(10b) and 11a(11b) showed better activity vis-a-vis the eight tested bacteria (Table 1). This study determined the MIC of some synthesized derivatives of 1,4-benzothiazine. The results of the antibacterial activity of the products tested showed the absence of growth inhibition for compound 1 in the three bacterial strains: *Escherichia coli* (ATCC), *Pseudomonas aeruginosa* (ATCC) and *Staphylococcus aureus* (ATCC) and an activity MIC = 31.25 µg/ml for *Acinetobacter* (BLSE), MIC = 62.5 µg/ml for *Acinetobacter* (ATCC) and MIC = 250 µg/ml for *Escherichia coli* (BLSE), *Staphylococcus aureus* (MLSb) and *Klebsiella pneumoniae* (BLSE). By against the compound 2 obtained by substituting the compound 1 by the benzylidene group in position 2 has caused an activity MIC = 125 µg/ml for *Pseudomonas aeruginosa* (ATCC), *Staphylococcus aureus* (ATCC) and a MIC = 250 µg/ml *Escherichia coli* (ATCC) and *Acinetobacter* (BLSE) with absence of growth inhibition for compound 2 in four bacterial strains *Acinetobacter* (ATCC), *Escherichia coli* (ESBL), *Staphylococcus aureus* (MLSb) and *Klebsiella pneumoniae* (BLSE). In order to increase the inhibitory activity of compounds 1 and 2 we alkylated those compounds with propargyl bromide. It is deducible that the presence of a prop-1-yn hydrogen bonds (blue dotted lines) and their association through C–H–O hydrogen bonds (black dotted lines) of compound 13

![Scheme 3](image)

Scheme 3 Preparation of new 1,2,3-triazoles monosubstituted 13–15

![Fig. 3](image)

Fig. 3 Molecular structure of the compound 13 with the atom-labelling scheme. Displacement ellipsoids are drawn at the 50% probability ellipsoids (CCDC 1564624)

![Fig. 4](image)

Fig. 4 Packing showing portions of the chains formed by N–H–N hydrogen bonds (blue dotted lines) and their association through C–H–O hydrogen bonds (black dotted lines) of compound 13.
Acinetobacter (ESBL), with lack of growth inhibition in the two bacterial strains tested: Pseudomonas aeruginosa (ATCC), Acinetobacter (ATCC), Escherichia coli (ESBL), Staphylococcus aureus (MLSB) and Klebsiella pneumoniae (BLSE). On the other hand, the compound 5 has no activity against four bacterial strains tested: Acinetobacter (ATCC), Escherichia coli (ESBL), Staphylococcus aureus (MLSB) and Klebsiella pneumoniae (BLSE). However, the compound 5 also presents activity with MIC of the order of 125 μg/ml for Escherichia coli (ATCC) and 250 μg/ml for Pseudomonas aeruginosa (ATCC), Staphylococcus aureus (ATCC) and Acinetobacter (BLSE).

Also, for the eight products triazole 7a(7b), 8a(8b), 10a(10b) and 11a(11b) obtained by cycloaddition reactions, it is worthy to note that compound 8a obtained by cycloaddition with azide F possess a strong inhibitory activity during the treatment of different bacteria: CMI = 62.5 μg/ml for Escherichia coli (ESBL), Pseudomonas aeruginosa (ATCC), Acinetobacter (ESBL) and CMI = 125 μg/ml for Acinetobacter (ATCC), Escherichia coli (ESBL), Klebsiella pneumoniae (ESBL).

Finally, the compound 10b obtained by cycloaddition with azide G the results of the antibacterial activity of the products tested showed the absence of growth inhibition for compound 10b towards all tested bacteria. In general, the molecular specifications of the 1,2,3-triazoles can also be used as a linker and show bioisosteric effects on peptide linkage, aromatic ring, double bonds. Some unique features like hydrogen bond formation, dipole–dipole and π stacking interactions of triazole compounds have increased their importance in the field of medicinal chemistry as they bind with the biological target with high affinity due to their improved solubility. This study is expected to take anti-inflammatory tests, antifungal, antiparasitic and anti-cancer, because the literature gives a lot of interesting results on these topics. Also, other bacteria should be selected to expand the investigation [36–38]. The 1,2,3-triazole based heterocycles have been well exploited for the generation of many medicinal scaffolds exhibiting anti-HIV, anticancer, antibacterial activities.

**Conclusion**

In conclusion, in the development of this work, the synthesis of the new heterocyclic systems derived from 1,2,3-triazolyl-1,4-benzothiazin-3-one was carried out in satisfactory yields by cycloaddition reactions under thermal and catalytic conditions (Cu I). The results showed a periselectivity and regioselectivity as a function of the dipole (azides F, G and H) employed. In addition, the
Fig. 5 Results of the antibacterial activity of the synthesized compounds 1, 2, 4, 5, 7a, 7b, 8a, 8b, 10a, 10b, 11a and 11b vis-a-vis bacteria tested (Escherichia coli ATCC, Pseudomonas aeruginosa ATCC, Staphylococcus aureus ATCC, Acinetobacter ATCC, Escherichia coli BLSE, Acinetobacter BLSE, Staphylococcus aureus MLSB and Klebsiella pneumonia BLSE). Chlor chloramphenicol (30 µg/ml), DMSO dimethylsulfoxide (1%)
obtained results highlight an original synthesis reaction of 1,2,3-triazoles monosubstituted by the action of azide-glycine (H) on dipolarophiles 4–6 under thermal conditions. The heterocyclic systems obtained were identified by 1H NMR, 13C NMR, and confirmed for product 13 by X-ray diffraction. The synthesized products were subjected to the evaluation of antibacterial activity. Several compounds tested showed significant activity.

**Experimental part**

**General:** Column chromatography was performed on silica gel 60 (Merck 230–400 mesh). Nuclear magnetic resonance spectra were recorded on a Varian Unity Plus spectrometer 1H NMR at 300 MHz; the chemical shifts (d) are expressed in parts per million (ppm) and the coupling constants (J) in Hertz (Hz). DMSO was used as the solvent and SiMe4 as the reference.

**General procedure of synthesis compounds 4, 5 and 6**

To a solution of (6.05 mmol) of 2-substituted)-1,4-benzothiazin-3-one 1 (2 or 3) in 15 ml of DMF, were added 11.3 mmol of potassium carbonate. The reaction mixture was stirred magnetically for 5 min then added 0.6 mmol of bromide tetra-n-butylammonium (BTBA) and 7.26 mmol of propargyl bromide, then the mixture was stirred magnetically for 24 h. After removal of salts by filtration, the solution was evaporated under reduced pressure, and the residue obtained is dissolved in dichloromethane. The remaining salts are extracted with distilled water, and the mixture obtained was chromatographed on silica gel column [eluent: ethyl acetate/hexane (1/9)].

### 4-(Prop-2-ynyl)-3,4-dihydro-2H-1,4-benzo-thiazin-3-one 4

Yield: 92%; mp = 492 K; 1H-NMR (DMSO-d6, 300 MHz) δ [ppm]: 7.42–7.04 (m, 4H, Harom), 4.74 (d, 2H, J = 1.9 Hz NCH2), 3.55 (s, 2H, S-CH2), 2.20 (t, 1H, J = 1.9 Hz ≡CH); 13C-NMR (DMSO-d6, 62.5 MHz) δ [ppm]: 165.2 (C=O), 139.0, 123.4, 79.8 (Cq), 128.6, 128.0, 124.1, 118.5 (CHarom), 75.0 (≡CH), 33.8 (NCH2), 30.6 (S-CH2).

### (2Z)-2-Benzylidene-4-(prop-2-ynyl)-3,4-dihydro-2H-1,4-benzo-thiazin-3-one 5

Yield: 90%; mp = 403 K; 1H-NMR (DMSO-d6, 300 MHz) δ [ppm]: 7.84 (s, 1H, CHvinyl), 7.66–7.09 (m, 9H, Harom), 4.90 (d, 2H, J = 1.8 Hz, NCH2), 2.20 (t, 1H, J = 1.8 Hz ≡CH); 13C-NMR (DMSO-d6 62.5 MHz) δ [ppm]: 161.0 (C=O), 135.8, 134.4, 134.3, 118.4, 79.6 (Cq), 130.6, 129.8, 129.1, 128.1, 126.8, 124.5, 117.8 (CHarom), 75.0 (≡CH), 33.8 (NCH2), 30.6 (S-CH2).

### (Z)-2-(4-Chlorobenzylidene)-4-(prop-2-ynyl)-2H-1,4-benzo-thiazin-3-one 6

Yield: 88%; mp = 385 K; 1H-NMR (DMSO-d6 300 MHz) δ [ppm]: 7.83 (s, 1H, CHvinyl), 7.69–7.09 (m, 9H, Harom), 4.86 (d, 2H, J = 1.9 Hz, NCH2), 3.31 (t, 1H, J = 1.9 Hz ≡CH); 13C-NMR (DMSO-d6 62.5 MHz) δ [ppm]: 161.0 (C=O), 135.77, 134.4, 134.3, 118.4, 79.6 (Cq), 130.6, 129.8, 129.1, 128.1, 126.8, 124.5, 117.8 (CHarom), 75.0 (≡CH), 35.02 (NCH2).

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### Table 1 Results of the in vitro antibacterial activity (MIC values µg/ml) of the synthesized compounds 1, 2, 4, 5, 7a, 7b, 8a, 8b, 10a, 10b, 11a and 11b vis-à-vis bacteria tested (Escherichia coli ATCC, Pseudomonas aeruginosa ATCC, Staphylococcus aureus ATCC, Acinetobacter ATCC, Escherichia coli BLSE, Acinetobacter BLSE, Staphylococcus aureus MLSB and Klebsiella pneumonia BLSE)

| E. coli ATCC | PA ATCC | SA ATCC | Acin ATCC | E. coli ESBL | Acin ESBL | SA MLSB | KP ESBL |
|-------------|---------|---------|-----------|-------------|----------|--------|--------|
| 1           | –       | –       | 62.5      | 250         | 31.25    | 250    | 250    |
| 2           | 250     | 125     | 125       | –           | 250      | –      | –      |
| 4           | 125     | –       | 250       | –           | 250      | –      | –      |
| 5           | 125     | 250     | 250       | –           | 250      | –      | –      |
| 7a          | –       | –       | 250       | 125         | 62.5     | –      | 62.5   |
| 7b          | 125     | –       | 125       | 62.5        | –        | 62.5   | –      |
| 8a          | 62.5    | 62.5    | –         | 125         | 62.5     | –      | 125    |
| 8b          | –       | –       | –         | –           | –        | 125    | –      |
| 10a         | 125     | 125     | 125       | –           | 62.5     | –      | –      |
| 10b         | –       | –       | –         | –           | –        | –      | –      |
| 11a         | –       | 125     | 125       | 62.5        | –        | 62.5   | –      |
| 11b         | –       | –       | 250       | 62.5        | 125      | –      | 62.5   |
| DMSO        | –       | –       | –         | –           | –        | –      | –      |
| Chlor       | 4       | 7.5     | 2.5       | –           | 5        | –      | 3      |
General procedure for the synthesis of compounds 7a–12a, 7b–12b and 13–15 via Huisgen 1,3-dipolar cycloaddition reactions
To a solution of dipolarophile 4 (5 or 6) (8 mmol) in absolute ethanol (20 ml) was added azide F (G or H) (16 mmol). The reaction mixture was stirred at reflux and the reaction monitored by thin layer chromatography (TLC). After concentration under reduced pressure, the residue was purified by column chromatography on silica gel using a mixture [ethyl acetate/hexane (1:9)] as eluent.

General procedure for the synthesis of compounds 7a–12a by click chemistry: [Copper-Catalyzed Azide-Alkyne Cycloaddition (CuAAC)]
To a solution of 1 mmol of compound 4 (5 or 6) and 2 mmol of azide F (G) in 15 ml of ethanol were added 0.5 mmol of CuSO4 and 1 mmol of sodium ascorbate dissolved in 7 ml of distilled water. The reaction mixture was stirred for 24 h at room temperature. The reaction was monitored by TLC. After filtration and concentration of the solution under reduced pressure the residue obtained was chromatographed on silica gel column using as eluent ethyl acetate/hexane (1:9). The compounds have been obtained with yields ranging from 86 to 90%.

4-[(1’4’,2’3’,3’’4’’-Di-O-isopropylidene-a-D-galactopyranosid-6-yl)-1’2,3’-triazol-4’-yl)methyl]-2H-1,4-benzothiazin-3-one 7a
Yield: 63%; brown oil; 1H-NMR (DMSO-d6, 300 MHz) δ [ppm]: 1.40, 1.31, 1.30, 1.23 (s, 12H, 4CH3), 3.52 (s, 2H, CH2–S), 4.69, 4.53, 4.39, 4.22 (m, 4H, 4CH2, H2, H3, H4), 4.35 (d, 2H, CH2–N), 5.32 (d, 2H, CH2–N, H6), 5.47 (d, 1H, CH, H1), 7.55–7.03 (m, 4H, H arom), 8.31 (s, 1H, CHtriazole); 13C-NMR (DMSO-d6 62.5 MHz) δ [ppm]: 164.04 (CO), 142.78, 140.17, 123.50, 109.62, 108.29 (Cq), 128.89 (CHtriazole), 127.93, 124.69, 124.23, 119.00 (CHarom), 97.01, 71.74, 70.75, 69.96, 66.97 (5CH, C1, C2, C3, C4, C5), 50.26, 41.00 (CH2–N), 31.23 (CH2–S), 26.34, 25.81, 25.27, 24.95 (4CH3); 161.44 (CO), 136.06, 134.68, 134.51, 132.47, 130.61, 129.72, 129.08, 128.95, 128.49, 118.06 (CHarom), 96.12, 70.90, 70.62, 70.22, 68.37 (5CH, C1, C2, C3, C4, C5), 48.56, 39.77 (CH2–N), 26.43, 26.13, 25.27, 24.85 (4CH3).

(2Z)-2-Benzylidene-4-[(1’1’,2’3’,3’’4’’-di-O-isopropylidene-a-D-galactopyranosid-6-yl)-1’2,3’-triazol-4’-yl)methyl]-2H-1,4-benzothiazin-3-one 8a
Yield: 65%; brown oil; 1H-NMR (DMSO-d6, 300 MHz) δ [ppm]: 1.41, 1.33, 1.31, 1.25 (s, 12H, 4CH3), 4.67, 4.39, 4.38, 4.36 (m, 4H, 4CH2, H2, H3, H4, H5), 4.39 (d, 2H, CH2–N), 5.47 (d, 2H, CH2–N, H6), 5.32 (d, 1H, CH, H1), 7.67–7.06 (m, 4H, H arom), 7.85 (s, 1H, CHvinyl), 8.29 (s, 1H, CHtriazole); 13C-NMR (DMSO-d6 62.5 MHz) δ [ppm]: 161.44 (CO), 136.06, 134.68, 134.51, 132.47, 130.61, 129.72, 129.08, 128.95, 128.49, 118.06 (CHarom), 96.12, 70.90, 70.62, 70.22, 68.37 (5CH, C1, C2, C3, C4, C5), 48.56, 39.77 (CH2–N), 26.43, 26.13, 25.27, 24.85 (4CH3).

4-[(1’1’,2’3’,3’’4’’-Di-O-isopropylidene-a-D-galactopyranosid-6-yl)-1’2,3’-triazol-5’-yl)methyl]-2H-1,4-benzothiazin-3-one 9a
Yield: 20%; brown oil; 1H-NMR (DMSO-d6, 300 MHz) δ [ppm]: 1.37, 1.27, 1.26, 1.17 (s, 12H, 4CH3), 4.63, 4.60, 4.49, 4.31 (m, 4H, 4CH2, H2, H3, H4, H5), 4.49 (d, 2H, CH2–N), 5.26 (d, 2H, CH2–N, H6), 5.37 (d, 1H, CH, H1), 7.49–7.06 (m, 4H, H arom), 7.81 (s, 1H, CHvinyl), 8.01 (s, 1H, CHtriazole); 13C-NMR (DMSO-d6 62.5 MHz) δ [ppm]: 161.10 (CO), 143.16, 136.53, 134.47, 120.63, 118.22, 109.33, 108.59 (Cq), 134.72 (CHvinyl), 130.47 (CHtriazole), 129.69, 129.12, 127.96, 126.68, 124.75, 124.29, 117.99 (CHarom), 95.94, 71.04, 70.56, 70.15, 67.26 (5CH, C1, C2, C3, C4, C5), 50.64, 41.57 (CH2–N), 26.34, 25.98, 25.26, 24.69 (4CH3).

(2Z)-2-Benzylidene-4-[(1’1’,2’3’,3’’4’’-di-O-isopropylidene-a-D-galactopyranosid-6-yl)-1’2,3’-triazol-4’-yl)methyl]-2H-1,4-benzothiazin-3-one 8b
Yield: 20%; brown oil; 1H-NMR (DMSO-d6, 300 MHz) δ [ppm]: 1.40, 1.31, 1.30, 1.23 (s, 12H, 4CH3), 4.69, 4.40, 4.34, 4.24 (m, 4H, 4CH2, H2, H3, H4, H5), 4.42 (d, 2H, CH2–N), 5.55 (d, 2H, CH2–N, H6), 5.26 (d, 1H, CH, H1), 7.50–7.00 (m, 4H, H arom), 7.93 (s, 1H, CHtriazole); 13C-NMR (DMSO-d6 62.5 MHz) δ [ppm]: 165.24 (CO), 143.56, 139.84, 123.27, 109.31, 108.60 (Cq), 128.46 (CHtriazole), 127.76, 124.49, 123.91, 118.63 (CHarom), 95.96, 71.04, 70.59, 70.16, 67.26 (5CH, C1, C2, C3, C4, C5), 50.58, 40.78 (CH2–N), 30.79 (CH2–S), 26.34, 26.05, 25.27, 24.70 (4CH3).
(2Z)-2-(4-Chlorobenzylidene)-4-[(1′,2′,3′,4′,6′-di-O-isopropylidene-a-D-galactopyranosid-6′-yl)-1’,2’,3’-tri-azol-5′-yl)methyl]-2H-1,4-benzo-thiazin-3-one 9b
Yield: 17%; brown oil; 1H-NMR (DMSO-d6, 300 MHz) δ [ppm]: 1.39, 1.30, 1.26, 1.18 (s, 12H, 4CH3), 4.62, 4.39, 4.28, 4.15 (m, 4H, 4CH, H2, H3, H4, H5), 4.55 (d, 2H, CH2−N), 5.37 (d, 2H, CH2−O, H6), 5.30 (d, 1H, CH, H1), 7.63−7.04 (m, 4H, Harom), 7.82 (s, 1H, CHvinyl), 7.99 (s, 1H, CHtriazole); 13C-NMR (DMSO-d6, 62.5 MHz) δ [ppm]: 160.82 (CO), 143.06, 136.80, 134.58, 125.30, 120.81, 117.99, 109.90, 108.09 (Cq), 135.03 (CHvinyl), 130.06 (CHtriazole), 129.91, 129.38, 128.50, 126.88, 124.43, 118.22 (Cq), 96.50, 71.42, 70.90, 70.15, 67.62 (5CH, C1, C2, C3, C4, C5), 50.93, 41.42 (CH2−N), 26.05, 25.71, 24.98 (4CH3).

(2Z)-2-Benzylidene-4-[(1′,2′,3′,4′,6′-tetro-O-acetyl-(o)-glucopyranos-1′-yl)-1’,2’,3’-tri-azol-5′-yl)methyl]-2H-1,4-benzo-thiazin-3-one 11b
Yield: 20%; brown oil; 1H-NMR (DMSO-d6, 300 MHz) δ [ppm]: 2.01, 1.97, 1.92, 1.72 (s, 12H, 4CH3), 5.64, 5.54, 5.21, 4.09 (m, 5H, 4CH, H2, H3, H4, H5), 4.37 (d, 2H, CH2−N), 5.30 (d, 2H, CH2−O, H6), 6.34 (d, 1H, CH, H1), 7.84 (s, 1H, CHvinyl), 7.65−7.03 (m, 4H, Harom), 7.62 (s, 1H, CHtriazole); 13C-NMR (DMSO-d6, 62.5 MHz) δ [ppm]: 170.52, 170.24, 169.88, 168.88, 161.52 (5C=O), 144.03, 136.66, 134.56, 120.78, 118.44 (Cq), 130.17 (CHtriazole), 134.73 (CHvinyl), 129.65, 129.29, 127.80, 126.66, 124.43, 123.67, 118.12 (CHarom), 84.40, 73.89, 72.59, 70.70, 68.21 (5CH, C1, C2, C3, C4, C5), 62.45 (CH2−O), 41.84 (CH2−N), 21.07, 20.82, 20.68, 20.40 (4CH3).

(2Z)-2-(4-Chlorobenzylidene)-4-[(1′,2′,3′,4′,6′-tetro-O-acetyl-(o)-glucopyranos-1′-yl)-1’,2’,3’-tri-azol-5′-yl)methyl]-2H-1,4-benzo-thiazin-3-one 12a
Yield: 63%; brown oil; 1H-NMR (DMSO-d6, 300 MHz) δ [ppm]: 2.01, 1.97, 1.95, 1.72 (s, 12H, 4CH3), 5.68, 5.55, 5.21, 4.09 (m, 5H, 4CH, H2, H3, H4, H5), 4.37 (d, 2H, CH2−N), 5.32 (d, 2H, CH2−O, H6), 6.37 (d, 1H, CH, H1), 7.51−7.03 (m, 4H, Harom), 7.63 (s, 1H, CHtriazole); 13C-NMR (DMSO-d6, 62.5 MHz) δ [ppm]: 170.24, 170.03, 169.75, 168.55, 161.13 (5C=O), 144.23, 136.66, 134.48, 120.78 (Cq), 130.61 (CHtriazole), 129.29, 128.07, 124.43, 118.13 (CHarom), 84.64, 73.81, 72.59, 70.70, 68.21 (5CH, C1, C2, C3, C4, C5), 62.45 (CH2−O), 41.84 (CH2−N), 30.50 (CH2−S), 21.10, 20.72, 20.68, 20.15 (4CH3).

(2Z)-2-(4-Chlorobenzylidene)-4-[(1′,2′,3′,4′,6′-tetro-O-acetyl-(o)-glucopyranos-1′-yl)-1’,2’,3’-tri-azol-5′-yl)methyl]-2H-1,4-benzo-thiazin-3-one 12b
Yield: 19%; brown oil; 1H-NMR (DMSO-d6, 300 MHz) δ [ppm]: 2.00, 1.95, 1.92, 1.73 (s, 12H, 4CH3), 5.62, 5.48, 5.14, 4.08 (m, 5H, 4CH, H2, H3, H4, H5), 4.34 (d, 2H, CH2−N), 5.27 (d, 2H, CH2−O, H6), 6.34 (d, 1H, CH, H1), 7.84 (s, 1H, CHvinyl), 7.65−7.05 (m, 4H, Harom), 7.61 (s, 1H, CHtriazole); 13C-NMR (DMSO-d6, 62.5 MHz) δ [ppm]: 170.24, 170.03, 169.46, 168.55, 161.13 (5C=O), 144.55,
Yield: 78%; mp = 352 K; 1H-NMR (DMSO-d6 300 MHz) δ [ppm]: 7.84 (s, 1H, CHtriazole), 7.37–7.00 (m, 4H, Harom), 5.16 (d, 2H, CH2–N), 3.56 (s, 2H, CH2–S); 13C-NMR (DMSO-d6 62.5 MHz); 160.79 (CO), 136.01, 134.38, 133.51, 121.18, 118.42 (Cq), 134.28 (CHvinyl), 128.40 (CHtriazole), 134.28, 132.55, 129.12, 128.40, 126.95, 124.73, 118.05 (CHarom), 35.47 (C–N).

(2Z)-2-Benzylidene-4-[1,2,3-triazolymethyl]-2H-1,4-benzothiazin-3-one 14

Yield: 81%; brown oil; 1H-NMR (DMSO-d6 300 MHz) δ [ppm]: 7.7–8.7 (m, 9H, Htriazole), 5.62 (d, 1H, CH2–O), 3.57 (q, 2H, CH2–O), 1.19, 1.13 (t, 6H, 2CH3); 13C-NMR (DMSO-d6 62.5 MHz); 165.49 (CO), 143.56, 139.75, 132.44 (Cq), 128.50 (CHtriazole), 129.11, 127.72, 123.93, 118.65 (CHarom), 40.32 (C–N), 30.76 (C–S).

(2Z)-2-[4-Chlorobenzylidene]-4-[1,2,3-triazolymethyl]-2H-1,4-benzothiazin-3-one 15

Yield: 77%; mp = 352 K; 1H-NMR (DMSO-d6 300 MHz) δ [ppm]: 7.83 (s, 1H, CHvinyl), 7.67–7.10 (m, 8H, Harom), 7.53 (s, 1H, CHtriazole), 4.85 (d, 2H, CH2–N); 13C-NMR (DMSO-d6 62.5 MHz); 160.68 (CO), 135.77, 134.28, 133.31, 132.29, 121.05, 118.05 (Cq), 134.15 (CHvinyl), 128.14 (CHtriazole) 132.30, 129.12, 128.40, 126.95, 124.73, 118.05 (CHarom), 35.47 (C–N).

Ethyl-N-(benzoyl)-2-ethoxylglycinate 16

Yield: 78%; mp = 369. 1H-NMR (DMSO-d6 300 MHz) δ [ppm]: 9.42 (d, 1H, N–H, J = 9.41), 7.92–7.44 (m, 5H, H arom), 5.62 (d, 1H, CH, J = 5.61), 4.13 (q, 2H, CH2–O), 3.57 (q, 2H, CH 2–O), 1.19, 1.13 (t, 6H, 2CH3); 13 C-NMR (DMSO-d6, 62.5 MHz); 168.47, 167.12 (2 CO), 133.54, 132.48, 128.87, 128.27 (CHarom), 77.94 (CH), 63.70, 61.62 (2CH3), 15.38, 14.46 (2CH3).

Authors’ contributions

The main idea for the work was thought up by NKS and EE. ME, IF and YO performed the synthesis. Antibacterial activities were performed by ZM and RC. X-ray analysis was performed by JTM. MU and EEE analyzed the results. All authors performed the synthesis. Antibacterial activities were performed by ZM and RC.

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Competing interests

The authors declare that they have no competing interests.

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