Synthesis and Antibacterial Activity of Some New Functionalized Derivatives of 4-amino-5-benzyl-4H-[1,2,4]-triazole-3-thiol

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Abstract: The use of 4-amino-5-benzyl-4H-[1,2,4]triazole-3-thiol (1), as a precursor to synthesize some new biologically active heterocycles has been found to be effective. Condensation of 1 with appropriate aldehydes gave the new Schiff bases 2a, b, which either by cyclization with thioglycolic acid gave 3a, b, or by Mannich reaction using morpholine gave 4a, b. Reaction of 1 with different heterocycles has been found to be effective. Condensation of 1 with appropriate aldehydes gave the new Schiff bases 2a, b, which either of 4-Amino-5-benzyl-4H-[1,2,4]triazoles, it is of interest to synthesize new derivatives of 1,2,4-triazoles, antibacterial activity. 1H and 13C NMR spectra were determined in DMSO-d6 and recorded on a Shimadzu FT-IR 8101 PC spectrometer. The IR spectra were obtained at 70 eV using a GCMS-QP 1000 EX standard and are given in δ units. Electron impact mass spectra were obtained at 70 eV using a GCMS-QP 1000 EX standard and are given in m/z units. Electron impact mass spectra were obtained at 70 eV using a GCMS-QP 1000 EX standard and are given in m/z units.

Key words: Schiff bases, Mannich reaction, halogen compounds, 1,2,4-triazoles, antibacterial activity.

1. Introduction

A huge volume of published literature about 1,2,4-triazoles and their derivatives plays an important role among the classes of heterocycles and have received much attention due to their versatile biological and therapeutical activities including antibacterial activity [1]-[4], antifungal activity [5]-[7], antiviral activity [8]-[9], antitubercular activity [10]-[11], anticonvulsant activity [12]-[14], antioxidant activity [15], anti-inflammatory activity [16]-[18], antitumor activity [19], [20], analgesic activity [21]-[23], antidepressant activity [24], and antihelmintic activity [25]. Owing to the above significance and the existing biological activity of 1,2,4-triazoles, it is of interest to synthesize the new derivatives of 4-Amino-5-benzyl-4H-[1,2,4]triazole-3-thiol (1) as well as the investigation of their antibacterial activities.

2. Materials and Methods

Melting points (uncorrected) were recorded on an Electrothermal melting apparatus. The IR spectra were recorded on a Shimadzu FT-IR 8101 PC spectrometer. The 1H and 13C NMR spectra were determined in DMSO-d6 at 300 MHz on a Varian Mercury VX 300 NMR spectrometer; Chemical shifts are reported in ppm with TMS as an internal standard and are given in δ units. Electron impact mass spectra were obtained at 70 eV using a GCMS-QP 1000 EX spectrometer. Elemental analyses, mass and IR spectra were carried out at the Microanalytical Center of Cairo University.

2.1 Synthesis of 5-Benzyl-4-[(4-benzyloxy-benzylidene)-amino]-2,4-dihydro-[1,2,4]triazole -3-thione (2a) and 5-Benzyl-4-[(2,4-dimethoxy-benzylidene)-amino]-2,4-dihydro-[1,2,4]triazole-3-thione (2b): General procedure: A mixture of compound 1 (2 gm, 10 mmol) and 2,4-benzoxylbenzaldehyde and/or 2,4-dimethoxybenzaldehyde (10 mmol) in 50 ml absolute ethanol in presence of few drops of hydrochloric acid was refluxed for 1 h. After cooling, the solid crystals were filtered off and crystallized from ethanol to give the Schiff bases 2a and/or 2b respectively.

5-Benzyl-4-[(4-benzyloxy-benzylidene)-amino]-2,4-dihydro-[1,2,4]triazole-3-thione (2a). This compound was obtained as yellow crystals, 3.3 g (82%); mp 130- 132 °C; IR (KBr): 3329 (NH), 2968 (CH-aromatic), 2886 (CH2's), 1594 (C=N) cm-1; 1H NMR (CDCl3): δ 10.08 (s, 1H, NH), 9.9 (s, 1H, N-C-H), 7.86-7.05 (m, 14H, Ar'H), 5.16 (s, 2H, O-CH2Ph), 4.16 (s, 2H, CH2Ph), 3.16 (s, 3H, OCH3); Ms: m/z 400 (M+), 380, 333, 290, 227, 168, 132; Anal. Calcd. for C23H20N4O2S: C, 68.98; H, 5.03; N, 13.99; S, 8.01. Found: C, 68.87, H, 5.11; N, 13.91; S, 8.12.

5-Benzyl-4-[(2,4-dimethoxy-benzylidene)-amino]-2,4-dihydro-[1,2,4]triazole-3-thione (2b). This compound was obtained as yellow crystals, 2.8 g (79%); mp 170- 172 °C; IR (KBr): 3212 (NH), 3004 (CH-aromatic), 2825 (CH2Ph), 1504 (C=N) cm-1; 1H NMR (CDCl3): δ 10.42 (s, 1H, NH), 9.72 (s, 1H, N-C-H), 7.55-6.95 (m, 8H, Ar'H), 4.16 (s, 2H, CH2Ph), 3.87 and 3.84 two (s, 3H, OCH3); Ms: m/z 354 (M+), 326, 291, 267, 191, 163, 132; Anal. Calcd. for C23H20N4O2S: C, 61.00; H, 5.12; N, 13.91; S, 8.01. Found: C, 61.07; H, 5.21; N, 15.59; S, 9.10.
3-(3-Benzyl-5-mercapto-[1,2,4]triazolo-4-yl)-2-(4-benzyloxophenyl)-thiazolidin-4-one (3a). This compound was obtained as white crystals, 3 g (63%); mp 100-102 °C; IR (KBr): 3200 (NH), 2950 (CH-aromatic), 1671 (C=O) cm$^{-1}$; $^1$H NMR (DMSO-d$_6$): $\delta$ 7.91 (s, 1H, N=CH-), 7.88-7.17 (m, 14H, Ar'H), 5.47 (s, 1H, thiazolidin-H), 4.16 (s, 2H, O-CH$_2$Ph), 3.81 and 3.77 two (s, 3H, OCH$_3$), 55.48 (N-CH$_2$, morpholine), 56.45 (O-CH$_2$, morpholine), 66.05 (N=CH-N), 88.98, 109.37, 113.88, 120.52, 121.00, 126.86, 128.47 and 135.05 (Ar-C), 149.17 (N=C-N, triazole), 153.18 and 153.84 (2 Ar-C=OMe), 157.84 (N=CH-) and 162.25 (C=S); Ms: m/z 453 (M$^+$), 382, 323, 262, 220, 147, 132; Anal. Calcd. for C$_{25}$H$_{22}$N$_4$O$_2$S$_2$: C, 63.27; H, 4.67; N, 11.81; S, 13.26.

3-(3-Benzyl-5-mercapto-[1,2,4]triazolo-4-yl)-2-(2,4-dimethoxy-phenyl)-thiazolidin-4-one (3b). This compound was obtained as white crystals, 2.6 g (60%); mp 162-165 °C; IR (KBr): 3204 (NH), 3030 (CH-aromatic), 2870 (CH-aliphatic), 1589 (C=N) cm$^{-1}$; $^1$H NMR (DMSO-d$_6$): $\delta$ 9.71 (s, 1H, N=CH-), 7.88-7.17 (m, 14H, Ar'H), 5.47 (s, 1H, thiazolidin-H), 4.16 (s, 2H, O-CH$_2$Ph), 3.81 and 3.77 two (s, 3H, OCH$_3$), 2.45 (s, 2H, CH$_2$, thiazolidin); Ms: m/z 474 (M$^+$).

13C NMR (DMSO-d$_6$): 120.52, 121.00, 126.86, 128.47 and 135.05 (Ar-C), 149.17 (N=C-N, triazole), 153.18 and 153.84 (2 Ar-C=OMe), 157.84 (N=CH-) and 162.25 (C=S); Ms: m/z 453 (M$^+$), 382, 323, 262, 220, 147, 132; Anal. Calcd. for C$_{23}$H$_{22}$N$_4$O$_3$S$_2$: C, 60.91; H, 6.00; N, 15.44; S, 7.07. Found: C, 60.84; H, 6.07; N, 15.40; S, 7.11.

2.4 Synthesis of N-(3-Benzyl-5-mercapto-[1,2,4]triazolo-4-yl)benzenesulfonyl amine (5): Benzenesulfonyl chloride (ml, 10 mmol) was added dropwisely with stirring in ice bath to a solution of the triazole 1 (2 gm, 10 mmol) in 10 ml pyridine. The reaction mixture was vigorously stirred for 3hrs. The reaction mixture was poured on to crushed ice and the solid product was filtered off and recrystallized from ethanol/water (1:1) as white crystals. 2.4 g (69%); mp 158-160 °C; IR (KBr): 3287 (NH), 3085 (CH-aromatic), 2935 (CH$_3$), 2325 (NH), 1624 (C=O) cm$^{-1}$; $^1$H NMR (DMSO-d$_6$): 6.31.51 (s, 1H, SH), 10.15 (s, 1H, NH), 7.34-7.24 (m, 10H, Ar'H), 4.08 (s, 2H, CH$_2$Ph); Ms: m/z 346 (M$^+$), 255, 205, 190, 189, 161, 132; Anal. Calcd. for C$_{12}$H$_8$N$_2$O$_2$S: C, 52.01; H, 4.07; N, 16.17; S, 18.51. Found: C, 52.12; H, 4.01; N, 16.24; S, 18.39.

2.5 Synthesis of 2-(4-Amino-5-benzyl-4H-[1,2,4]triazolo-3-ylsulfanyl)-acetamide (6): To a solution of the triazole 1 (2 gm, 10 mmol) in dil. ethanolic KOH (30 mL, 10%), chloroacetamide (0.93 gm, 10 mmol) was added, and the reaction mixture was stirred at RT for 6 hrs. The reaction mixture was poured on to crushed ice and HCl. The solid formed was filtered off and crystallized from ethanol to give compound 4a and/or 4b respectively.

5-Benzyl-4-[4-benzyloxy-benzylidene]-amino]-2-morpholin-4-ylmethyl-2,4-dihydro-[1,2,4]triazole-3-thione (4a) and 5-Benzyl-4-[ (4-benzyloxy-benzylidene)-amino]-2-morpholin-4-ylmethyl-2,4-dihydro-[1,2,4]triazole-3-thione (4b): General procedure: The Schiff base 2a and/or 2b (10 mmol) was dissolved in 20 ml dioxane at RT. Then, a solution of formaldehyde (37%, 1ml) and morpholine (0.87 ml, 10 mmol) in 20 ml dioxane was added dropwisely with stirring. The reaction mixture was stirred at RT for 3 hours and left overnight in a freeze. Then the resulting mixture was poured on to crushed ice and the solid product was filtered off and recrystallized from ethanol/water to give compound 4a and/or 4b respectively.

2.6 Synthesis of 3-Benzyl-6-methyl-5H-[1,2,4]triazolo[3,4-bf]-1,3,4thiadiazine (7), Phenyl-thioacetic acid S-(4-amino-5-benzyl-4H-[1,2,4]triazol-3-yl) ester (8) and 3-Benzyl-[1,2,4]triazolo[3,4-bf]-1,3,4thiadiazin-6-one (9): General procedure: A mixture of compound 1 (2 gm, 10 mmol) and chloroacetone, phenyl acetyl chloride, and/or chloroacetic acid (10 mmol) in 20 ml methanol in presence of sodium acetate (0.82 gm, 10 mmol) was refluxed for 6 hrs. After cooling, the reaction mixture was poured onto crushed ice and kept overnight, the precipitate formed separated by filtration and crystallized from a proper solvent to give compound 7, 8 and/or 9 respectively.

3-Benzyl-6-methyl-5H-[1,2,4]triazolo[3,4-bf][1,3,4]thiadiazine (7). This compound was obtained as brown crystals, 1.7 g (69%); mp 220-222 °C; IR (KBr): 3198 (NH), 2935 (CH-aromatic), 2870 (CH-aliphatic), 1589 (C=N) cm$^{-1}$; $^1$H NMR (DMSO-d$_6$): $\delta$ 7.61 (b, 2H, CONH$_2$), 7.33-7.20 (m, 5H, Ar'H), 5.91 (s, 2H, NH$_2$), 4.08 (s, 2H, CH$_2$CO), 2.79 (s, 2H, CH$_2$Ph), 1.32 (s, 3H, CH$_3$); Ms: m/z 263 (M$^+$), 248, 232, 188, 176, 144, 132; Anal. Calcd. for C$_{13}$H$_{13}$N$_5$O$_2$S: C, 50.17; H, 4.98; N, 26.60; S, 12.18; Found: C, 50.36; H, 4.88; N, 26.53; S, 12.15.
Phenyl-thioacetic acid S-(4-amino-5-benzyl-4H-[1,2,4]triazol-3-yl) ester (8). This compound was obtained as brown crystals, 2.4 g (70%); mp 198–200 °C; [α]D +76.7° (CHCl3); IR (KBr): 3192 (NH), 3045 (CH-aromatic), 1695 (C=O) cm–1; 1H NMR (DMSO-d6): δ 7.38-7.08 (m, 10H, Ar'H), 4.34 (s, 1H, S-CH-S), 3.78 and 3.64 two (s, 2H, CH 2Ph), 3.20 (b, 2H, NH 2); Ms: m/z 450 (M+). Refluxing of compound 8 with thioglycolic acid in ethanol afforded the corresponding Mannich base 9, 2.4 g (64%); mp 156–158 °C; IR (KBr): 3436-3249 (NH2, NH), 2926 (CH-aromatic), 2891 (CH 2's), 1670 (C=O) cm–1; 1H NMR (DMSO-d6): δ 10.19 (s, 1H, NH), 7.44-7.06 (m, 5H, Ar'H), 7.33-7.20 (m, 5H, Ar'H); 3.78 and 3.64 two (s, 2H, CH 2Ph), 3.36 (b, 2H, NH 2); Ms: m/z 450 (M+). Anal. Calcd for C20H18N8OS2: C, 58.36; H, 4.61; N, 25.69; S, 9.33. Found: C, 58.35; H, 4.62; N, 25.71; S, 9.35.

3-Benzyl-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-6-one (9). This compound was obtained as white crystals, 2 g (81%); mp 242–244 °C; IR (KBr): 3467 (NH), 3197 (NH), 3046 (CH-aromatic), 2288 (CH 2's), 1670 (C=O) cm–1; 1H NMR (DMSO-d6): δ 10.08 (s, 2H, NH), 7.31-7.20 (m, 5H, Ar'H), 7.30 (s, 2H, CH-CO), 3.62 (s, 2H, CH 2Ph), 2.71 (s, 3H, S-CH 3). Ms: m/z 324 (M+). Anal. Calcd for C17H16N4OS: C, 62.94; H, 4.97; N, 17.27; S, 9.88. Found: C, 62.81; H, 4.92; N, 17.55; S, 9.79.

2.7 Synthesis of 3-Benzyl-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-6,7-dione (10). A mixture of 1 (2 gm, 10 mmol) and oxalyl chloride (1.2 ml, 10 mmol) in 15 ml DMF was refluxed for 4 hrs. After cooling, the reaction mixture was poured on to crushed ice, the solid formed was filtered off and crystallized from acetic acid as white crystals. 1.85 g (81%); mp 216-218 °C; [α]D +76.7° (CHCl 3); IR (KBr): 3192 (NH), 3045 (CH-aromatic), 1695 (C=O) cm–1; 1H NMR (DMSO-d6): δ 7.38-7.08 (m, 10H, Ar'H), 4.34 (s, 1H, S-CH-S), 3.78 and 3.64 two (s, 2H, CH 2Ph), 3.36 (b, 2H, NH 2); Ms: m/z 450 (M+). Anal. Calcd for C21H16N8S: C, 56.64; H, 4.09; N, 22.75; S, 13.02. Found: C, 56.77; H, 4.01; N, 22.53; S, 13.19.

Scheme 1

Scheme 1: Two methods for the preparation of compound 1

Thus, boiling of compound 1 in ethanolic solution of 4-benzoxo-benzaldehyde and/or 2,4-dimethoxy-benzaldehyde in presence of few drops of HCl afforded the corresponding new Schiff bases 2a and 2b, respectively. The 1H NMR spectra of 2a, b showed the absence of the amino group of compound 1 and the presence of the proton of azomethine linkage (N=CH) as a singlet downfield at 9.9 and 9.72 ppm, respectively. The 13C NMR spectrum of compound 4a showed seventeen different signals for seventeen different carbon atoms which gives great evidence for the proposed structure [Experimental part].

2.8 Synthesis of 7-(4-Amino-5-benzyl-4H-[1,2,4]triazol-3-ylsulfanyl)-3-benzyl-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-6-one (11). Compound 1 (2 gm, 10 mmol) and dichloroacetic acid (1.9 ml, 15 mmol) were added to an ethanolic KOH solution (30 mL, 10%) and the reaction mixture was refluxed for 3 hrs. The reaction mixture was poured onto crushed ice, a brown resin was formed and after decantation, the resin was trituration with petroleum ether until solidification. The solid formed was collected by filtration and crystallized from ethanol/ water (1:2) as brown crystals. 2.9 g (64%); mp 156–158 °C; IR (KBr): 3467-3249 (NH2, NH), 2926 (CH-aromatic), 2891 (CH 2's), 1670 (C=O) cm–1; 1H NMR (DMSO-d6): δ 10.19 (s, 1H, NH), 7.44-7.06 (m, 10H, Ar'H), 4.34 (s, 1H, S-CH-S), 3.78 and 3.64 two (s, 2H, CH 2Ph), 3.36 (b, 2H, NH 2); Ms: m/z 450 (M+). Anal. Calcd for C20H18N8OS2: C, 58.36; H, 4.61; N, 25.69; S, 9.35. Found: C, 58.35; H, 4.62; N, 25.71; S, 9.35.

3. Results and Discussion

In the literature, two methods have been reported for the preparation of 4-amino-5-benzyl-4H-[1,2,4]triazole-3-thiolo (1), either by treatment of phenylacetic acid hydrazide with carbon disulfide in ethanolic potassium hydroxide, followed by refluxing the resulted potassium salt with hydrazine hydrate (Method A, 53% yield) [26], [27], or by fusion of phenylacetic acid with thiocarboxyhydrate at 180° (Method B, 68% yield) [28]. In the present work, the method B was used for the preparation of compound 1 due to the higher yield reaction (Scheme 1).

Thus, boiling of both Schiff bases 2a, b with thioglycolic acid in dioxane gave 1,2,4-triazol-4-yl-thiazolidin-4-one derivatives 3a, b. Also, the Schiff bases 2a, b were reacted with formaldehyde in the presence of morpholine to obtain the corresponding Mannich bases 4a, b (Scheme 2). The elemental analyses and spectroscopic data are consistent with the assigned structures of 3a, b and 4a, b. The 13C NMR of compound 4b showed eighteen different signals for eighteen different carbon atoms which adds additional confirmation for the proposed structure [Experimental part].

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Scheme 2: Formation of Schiff bases 2a,b, thiazolidin-4-one derivatives 3a,b and Mannich bases 4a,b.

The reactivity of the triazole 1 towards different halogen compounds has been investigated. Thus, stirring of compound 1 with benzenesulphonyl chloride in pyridine gave compound 5 via HCl elimination. The mass spectrum of compound 5 showed molecular ion peak at m/z = 346 (84%) and various characteristic peaks at 255 (15%), 205 (26%), 190 (28%), 189 (77%), 161 (38%) and 132 (40%). Scheme 3 shows the fragmentation pattern for compound 5, which confirms its structure.

Scheme 3: Mass fragmentation pattern of compound 5
When compound 1 was allowed to react with chloroacetamide in ethanolic KOH, compound 6 assigned as 2-(4-Amino-5-benzyl-4H-[1,2,4]triazol-3-ylsulfanyl)-acetamide was obtained (Scheme 4). The IR spectrum of 6 showed absorption bands at 3444, 3317 for (NH$_2$), 3085 (CH-aromatic), 2926 (CH$_2$'s) and 1673 for (C=O) cm$^{-1}$.

Hoping to expand the biological activity investigation of these derivatives, compound 1 was next reacted with chloroacetone, phenyl acetylchloride and chloroacetic acid in methanol/ sodium acetate to give the corresponding 7, 8 and 9, respectively (Scheme 4).

The structure of 7 was confirmed from its Mass and $^1$H NMR data. The Mass spectrum showed molecular ion peak at m/z= 244 and the $^1$H NMR showed signals at 10.07 corresponding to (NH), singlet at $\delta$ 7. 62 for the alkene proton (C=CH-S) and a singlet at 1.32 for the (CH$_3$) group. The IR of 8 showed bands at 3277 for (NH$_2$), 2876 for (CH$_2$'s) and 1698 cm$^{-1}$ for (C=O) and $^1$H NMR showed signals at $\delta$ 3.85 and 3.68 for the two methylene groups of (CH$_2$CO) and (CH$_2$Ph) and appearance (NH$_2$) at $\delta$ 3.20. The structure of compound 9 was confirmed from its full analysis [Experimental part].

In dimethylformamide, compound 1 was refluxed with oxalyl chloride to give the corresponding triazolo[3,4-b][1,3,4]thiadiazine-6,7-dione derivative 10. The structure of 10 was confirmed from its IR, $^1$H-NMR, MS and elemental analysis [Experimental part].

Compound 11 assigned as 7-(4-Amino-5-benzyl-4H-[1,2,4]triazol-3-ylsulfanyl)-3-benzyl-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazin-6-one was obtained from the reaction of compound 1 with dichloroacetic acid in ethanolic KOH (Scheme 4). The elemental analysis and spectroscopic data are in agreement with the assigned structure. Thus, the IR showed bands at 3436-3249 for (NH$_2$, NH) and at 1670 cm$^{-1}$ for (C=O), $^1$H NMR showed two singlets at 610.19 and 3.36 for NH and NH$_2$, respectively, presence of singlet proton at $\delta$ 4.34 for (S-CH-S) and two peaks at $\delta$ 3.78 and 3.64 for the two (CH$_2$Ph), and the mass spectrum showed molecular ion peak at m/z= 450 (54%) corresponding to the formula (C$_{20}$H$_{18}$N$_8$O$_4$S), and characteristic peaks at 407 (30%), 333 (28%), 268 (87%), 245 (23%), 202 (25%), 147 (30%) and 56 (39%). Scheme 5 shows the fragmentation pattern for compound 11, which supports the proposed structure.
Formation of compound 11 may proceed via reaction of two molecules of 1 with one molecule of dichloroacetic acid to give an unstable intermediate followed by cyclic condensation through losing of water according to the proposed mechanism (Scheme 6).

**Scheme 5**

**Scheme 6**

**Scheme 6**: The suggested reaction mechanism of 1 to give compound 11
3.1 Antimicrobial Activity

**Bacterial source and culture condition:**

The used Bacterial strains were Gram negative bacteria including *E. Coli* (ATCC 25922) and Gram positive bacteria *Enterococcus faecalis* (ATCC 29212). Mueller-Hinton Agar was used as culture media (gl-1) [29], Beef extract, 3.0; Peptone, 17.5; Starch, 1.5; Agar, 17, pH= 7.3 ± 0.1. The plates were incubated at 37ºC for 24 – 48 hrs.

**Paper disc technique:** Antibacterial activity was determined against the above strains using the paper disc assay method [30]. Whatman number 1 filter paper disc 6.0 mm diameter was sterilized by autoclaving for 20 min at 121 °C. The sterile discs were impregnated with the spaced samples at the center of the plates, and plates were incubated at 37°C for 24- 48 hrs [31]. Chloramphenicol 30 µg/disc was used as a positive control.

**Results:**

The assays were carried out in triplicate. Antibacterial activity was determined against the above strains using the paper disc assay method [30]. Whatman number 1 filter paper disc of 6.0 mm diameter was sterilized by autoclaving for 20 min at 121 °C. The sterile discs were impregnated with the spaced samples at the center of the plates, and plates were incubated at 37°C for 24- 48 hrs [31]. Chloramphenicol 30 µg/disc was used as a positive control. Diameter of the growth inhibition halos caused by the tested compounds were measured and expressed in millimeter. All the assays were carried out in triplicate.

**Table 1:** Effect of the synthesized compounds (1- 11) on bacterial growth (mm).

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<th>Sample No.</th>
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<td>Chloramphenicol (30 µg (Control))</td>
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**E. coli** (Escherichia coli) is the name of a germ, or bacterium that lives in the digestive tracts of humans and animals. Many types of *E. coli* can cause bloody diarrhea and urinary tract infections. Some strains of *E. coli* bacteria may also cause severe anemia or kidney failure [32]. Also, *Enterococci* are Gram-positive cocci that often occur in pairs (diplococci) or short chains. The important clinical infections caused by *Enterococcus* include urinary tract infections, bacteremia, bacterial endocarditis, diverticulitis, and meningitis [33].

The antibacterial activity of the synthesized compounds 1-11 were carried out on the growth of two pathogenic bacteria (*E. Coli* and *Enterococcus faecalis*). The data obtained in Table (1) indicate that 12/14 of these compounds have effects on *E. Coli* bacteria where the great inhibition (9 mm) was observed by the Mannich base 4a, benzensulfonylamine 5, acetamide 6 and the triazolothiadiazine 7, but the low inhibition (6 mm) was appeared by Schiff bases 2a, b and the thiazolidinone 3b. The triazole 1, thiazolidinone 3a, Phenyl-thioacetic acid ester 8, thiadiazinone 9 and thiadiazimedione 10 showed moderate inhibition (7- 8 mm), while the Mannich base 4b and the triazolothiadiazinone 11 showed no activity.

The inhibition effect was decreased on *Enterococcus faecalis* and also 7/14 only of the tested compounds showed moderate and low inhibition effect (5- 7 mm).

4. Conclusion

In summary, 4-amino-5-benzyl-4H-[1,2,4]triazole-3-thiol (1) has been utilized as a key starting material in the synthesis of many novel heterocyclic compounds 2- 11. The constitution of these compounds assigned on the basis of IR, 1H 13C NMR, mass spectra and elemental analyses were found to be in correlation with the desired structure. The antimicrobial activity screening revealed that the compounds 1-10 have significant antimicrobial activity. Compounds 4a, 5, 6 and 7 have high biological activity against gram (-ve) bacteria, and compounds 1, 3a, 8, 9 and 10 showed moderate inhibition effect.

On the other hand, compounds 1, 3a, 4a, 6, 8, 9 and 10 showed moderate inhibitions effect against gram (+ve) bacteria, while compounds 2a, 2b, 3b, 4b, 5, 7 and 11 showed no activity. The results are promising and show that the fine tuning of the structures 4a, 5, 6 and 7 can lead to some new antimicrobial agents in treating microbial infections.

5. Acknowledgements

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