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SYNTHESIS AND INVESTIGATION OF THE ANTIBACTERIAL ACTIVITY OF NEW TRIS-THIOUREA DERIVATIVES

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An efficient procedure for the preparation of symmetrical *tris*-thiourea derivatives (**5a – 5h**) by means of one-pot condensation reaction between available benzoyl chlorides (**1a –1h**) with potassium thiocyanate (**2**) and melamine (**4**) under reflux conditions is presented. All the synthesized tris-thioureas were evaluated for their biological activities against a group of Gram-positive (*Staphylococcus aureus* and *Bacillus cereus*) and Gram-negative (*Escherichia coli*) bacteria. The synthesized compounds showed no activity against *P. aeruginosa*. All compounds exhibited excellent antibacterial activity against indicated bacterial strains. The new products were characterized using FT-IR, ^{1}H and ^{13}C NMR spectra, and elemental analysis.

Keywords: symmetrical *tris*-thioureas, benzoyl chlorides, potassium thiocyanate, melamine, antibacterial activity.

1. INTRODUCTION

The identification of heterocyclic rings as effective structures in drug exploration is, undoubtedly, one of the attractive fields in pharmaceutical chemistry. These special structures represent a group of compounds that act as ligands for various biological receptors with a vast degree of binding affinity. Infections caused by multi-drug resistant microorganisms pose a profound challenge to the medical community and the need for a serious therapy has led to a search for new antimicrobial agents. Utilization of these compounds should allow us to quickly discover new biologically active molecules possessing a wide range of therapeutic activities on a shorter time scale [1].

In this article, we report the synthesis and biological activity of some tris-thiourea derivatives containing triazine core as a class of privileged molecules that have a broad range of biological properties. Among the structures having high antimicrobial activities, triazine derivatives constitute a valuable group of heterocycles possessing various pharmacological properties including broadly active as antimicrobial [2] and herbicidal [3]. Some triazine derivatives showed anti-oxidant [4], anticoccidial [5], and herbicidal [6] activities. They were also used as potential therapeutic agents for diseases related to HIV infection [7], bacteria [8, 9], tumors [10, 11], cancer [12], and malaria [13, 14]. Furthermore, thiourea and its derivatives are the topic of significant interest because of their productivity in medicinal chemistry due to their biological activity as herbicides, fungicides [15], phosphodiesterase enzyme inhibitor [16], and antiproliferative agents [17]. Thiourea derivatives exhibit antimicrobial [18], anti-inflammatory [19], anti-hepatitis [20], and anticancer [21] activities. These compounds are noteworthy building blocks for the synthesis of guanidines, amides, and some types of heterocycles [22]. For these reasons, several methods have been reported for the preparation of thioureas. Among these procedures, condensation of amines with isothiocyanate or its derivatives constitutes the most widely accepted general procedure [23]. Notwithstanding their toxicity, the use of these materials remains inevitable because of the importance of thioureas and its derivatives in medicinal field [24]. Thus, new nontoxic and safer methods to synthesize thioureas are yet to be developed. Consequently, combination of the two cores in one molecule may lead to increase in all useful biological properties.

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2. EXPERIMENTAL

2.1. Materials and Methods

All materials used for the preparation of thioureas were obtained from Merck and Fluka Company, and used without purification. The product structures were identified by their FT-IR, ^{1}H and ^{13}C NMR, and elemental analyses. The melting points were measured on Electrothermal Type 9100 melting points apparatus and remained uncorrected. FT-IR spectra (ν, cm^{-1}) were recorded on Shimadzu IR-470 spectrophotometer using KBr pellets. The ^{1}H and ^{13}C NMR spectra were recorded on Bruker DRX 250 MHz spectrometer using DMSO-d_6 as a solvent and TMS as an internal standard, and the chemical shifts were expressed as *ä*, ppm. Elemental analyses were obtained using Carlo–Erba EA1110 CHNO-S analyzer and agreed with the calculated values.

2.2. General Procedure for the Synthesis of tris-Thioureas (5a –5h)

Benzoyl chlorides (15 mmol) in dry acetone (10 mL) was added dropwise into a stirred solution of potassium thiocyanate (15 mmol) in dry acetone (5 mL). The mixture was stirred under reflux conditions for 1 h to form compound **3**. The solvent was evaporated in vacuum to form a yellowish powder. The compound **3** was added to melamine (5 mmol) in DMSO (15 mL) and heated under reflux conditions for 16 h, the progress of reaction was monitored by TLC ($CHCl_3$:MeOH (4:1)). After completion of the reaction, the reaction mixture was evaporated slowly and the product powder were obtained. The white powder was filtered, washed with EtOH 96%, and dried to afford the pure compounds **5a – 5h**.

***N,N′,N″*-(((1,3,5-triazine-2,4,6-triyl)*tris*(azanediyl))*tris*-(carbonothioyl))tribenzamid (5a)**. Yield: 79%; M.P. 218 – 220°C; FT-IR (KBr): ν 3466, 3289 (N-H, str.), 3026 (C-H_{arom} str.), 1670 (C=O str.), 1594 (C=N str.), 1556, 1533 (C=C str.), 1313 (C=S str.), 1159 (C-N str.) cm^{-1}. ^{1}H NMR (250 MHz, DMSO-d_6): δ 7.08 (3H, s, 3NH), 7.47 – 7.64 (9H, m, 9CH), 7.89 (6H, d, J = 8.0 Hz, 6CH), 11.31 (3H, s, 3NH) ppm. ^{13}C NMR (63 MHz, DMSO-d_6): δ 174.1, 168.1, 162.7, 134.2, 133.0, 129.0, 128.8 ppm. Anal. calcd. for $C_{27}H_{18}F_3N_9O_3S_3$: C, 52.67; H, 3.44; N, 20.47. Found: C, 52.69; H, 3.42; N, 20.44.

***N,N′,N″*-(((1,3,5-triazine-2,4,6-triyl)*tris*(azanediyl))*tris*-(carbonothioyl))tris(4-chlorobenzamide) (5b)**. Yield: 87%; M.P. 269 – 270°C; FT-IR (KBr): ν 3492, 3420 (N-H, str.), 3118 (C-H_{arom} str.), 1728 (C=O str.), 1663 (C=N str.), 1633, 1541 (C=C str.), 1239 (C=S str.), 1131 (C-N str.) cm^{-1}. ^{1}H NMR (250 MHz, DMSO-d_6): δ 6.87 (3H, s, 3NH), 7.57 (6H, d, J = 8.4 Hz, 6CH), 7.90 (6H, d, J = 8.4 Hz, 6CH), 11.43 (3H, s, 3NH) ppm. ^{13}C NMR (63 MHz, DMSO-d_6): δ 174.3, 167.2, 163.6, 137.9, 132.9, 131.0, 128.9 ppm. Anal. calcd. for $C_{27}H_{18}Cl_3N_9O_3S_3$: C, 45.10; H, 2.52; Cl, 14.79; N, 17.53. Found: C, 45.14; H, 2.50; Cl, 14.77; N, 17.56.

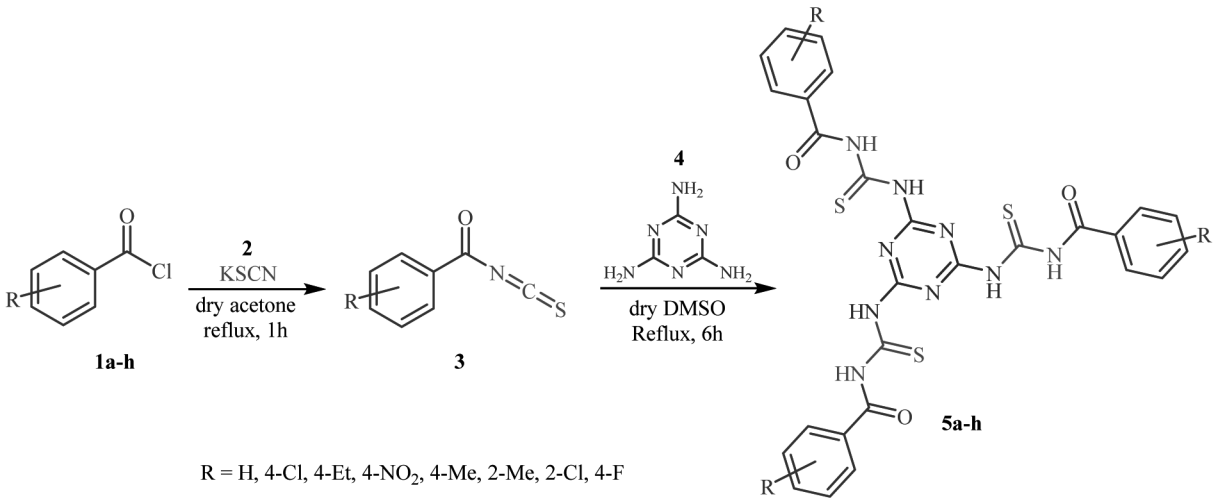
***N,N′,N″*-(((1,3,5-triazine-2,4,6-triyl)*tris*(azanediyl))*tris*-(carbonothioyl))*tris*(4-ethylbenzamide) (5c)**. Yield: 89%; M.P. 241 – 243°C; FT-IR (KBr): ν 3431, 3325 (N-H, str.), 3093 (C-H_{arom} str.), 2982 (C-H_{aliph} str.), 1668 (C=O str.), 1604 (C=N str.), 1555, 1527 (C=C str.), 1309 (C=S str.), 1151 (C-N Str.) cm^{-1}. ^{1}H NMR (250 MHz, DMSO-d_6): δ 1.24 (3H, t, J = 8.0 Hz, CH_3), 2.30 (2H, q, J = 6.7 Hz, CH_2), 7.30 (6H, d, J = 8.0 Hz, 6CH), 7.39 (3H, s, 3NH), 7.78 (6H, d, J = 8.0 Hz, 6CH), 11.09 (3H, s, 3NH) ppm. ^{13}C NMR (63 MHz, DMSO-d_6): δ 173.5, 167.9, 162.3, 143.3, 131.4, 129.3, 129.1, 23.0, 12.9 ppm. Anal. calcd. for $C_{33}H_{33}N_9O_3S_3$: C, 56.63; H, 4.75; N, 18.01. Found: C, 56.65; H, 4.72; N, 18.04.

***N,N′,N″*-(((1,3,5-triazine-2,4,6-triyl)*tris*(azanediyl))*tris*-(carbonothioyl))*tris*(4-nitrobenzamide) (5d)**. Yield: 88%; M. M. 196 – 198°C; FT-IR (KBr): ν 3451, 3301 (N-H, str.), 3118 (C-H_{arom} str.), 1713 (C=O str.), 1665 (C=N str.), 1593, 1568 (C=C str.), 1533, 1328 (NO_2 str.), 1243 (C=S str.), 1097 (C-N str.) cm^{-1}. ^{1}H NMR (250 MHz, DMSO-d_6): δ 7.10 (3H, s, 3NH), 8.26 (6H, d, J = 8.2 Hz, 6CH), 8.13 (6H, d, J = 8.2 Hz, 6CH), 11.11 (3H, s, 3NH) ppm. ^{13}C NMR (63 MHz, DMSO-d_6): δ 174.6, 167.0, 163.7, 150.0, 138.6, 131.0, 123.9 ppm. Anal. calcd. for $C_{27}H_{18}N_{12}O_9S_3$: C, 43.20; H, 2.42; N, 22.39. Found: C, 43.23; H, 2.45; N, 22.36.

***N,N′,N″*-(((1,3,5-triazine-2,4,6-triyl)*tris*(azanediyl))*tris*-(carbonothioyl))*tris*(4-methylbenzamide) (5e).** Yield: 83%; M. P. 177 – 179°C; FT-IR (KBr): ν 3435, 3256 (N-H, str.), 3131 (C-H_{arom} str.), 1717 (C=O str.), 1668 (C=N str.), 1610, 1515 (C=C str.), 1230 (C=S str.), 1117 (C-N str.) cm^{-1}. ^{1}H NMR (250 MHz, DMSO-d_6): δ 2.35 (3H, s, CH_3), 7.10 (3H, s, 3NH), 7.29 (6H, d, J = 7.5 Hz, 6CH), 7.79 (6H, d, J = 7.5 Hz, 6CH), 11.15 (3H, s, 3NH) ppm. ^{13}C NMR (63 MHz, DMSO-d_6): δ 173.8, 167.9, 163.2, 143.3, 131.4, 129.3, 129.1, 21.5 ppm. Anal. calcd. for $C_{30}H_{27}N_9O_3S_3$: C, 54.78; H, 4.14; N, 19.16. Found: C, 54.75; H, 4.16; N, 19.13.

***N,N′,N″*-(((1,3,5-triazine-2,4,6-triyl)*tris*(azanediyl))*tris*-(carbonothioyl))*tris*(2-methylbenzamide) (5f).** Yield: 71%; M. P. 193 – 195°C; FT-IR (KBr): ν 3435, 3288 (N-H, str.), 1726 (C=O str.), 1665 (C=N str.), 1591, 1560 (C=C str.), 1261 (C=S str.), 1112 (C-N str.) cm^{-1}. ^{1}H NMR (250 MHz, DMSO-d_6): δ 2.34 (3H, s, CH_3), 7.08 – 7.70 (15H, m, 12CH, 3NH), 11.41 (3H, s, 3NH) ppm. ^{13}C NMR (63 MHz, DMSO-d_6): δ 174.0, 167.7, 162.7, 145.6, 135.8, 131.0, 130.8, 128.1, 127.2, 20.5 ppm. Anal. calcd. for $C_{30}H_{27}N_9O_3S_3$: C, 54.78; H, 4.14; N, 19.16. Found: C, 54.75; H, 4.11; N, 19.19.

***N,N′,N″*-(((1,3,5-triazine-2,4,6-triyl)*tris*(azanediyl))*tris*-(carbonothioyl))*tris*(2-chlorobenzamide) (5g).** Yield: 75%; M. P. 212 – 214°C; FT-IR (KBr): ν 3470, 3300 (N-H, str.), 1713 (C=O str.), 1665 (C=N str.), 1593, 1559 (C=C str.), 1308 (C=S str.), 1096 (C-N str.) cm^{-1}. ^{1}H NMR (250 MHz, DMSO-d_6): δ 6.95 (3H, s, 3NH), 7.08 (3H, d, J = 7.7 Hz, 3CH), 7.51 (3H, d, J = 7.5 Hz, 6CH), 7.62 – 7.84 (6H, m, 6CH), 11.28 (3H, s, 3NH) ppm. ^{13}C NMR (63 MHz,



Scheme 1. Synthesis of tris-thiourea derivatives from melamine.

DMSO-d_6): δ 173.3, 167.0, 163.1, 145.8, 132.1, 130.0, 129.3, 127.1, 126.5 ppm. Anal. calcd. for $C_{27}H_{18}Cl_3N_9O_3S_3$: C, 45.10; H, 2.52; Cl, 14.79; N, 17.53. Found: C, 45.13; H, 2.54; Cl, 11.79; N, 17.55.

***N*,*N*′,*N*″-(((1,3,5-triazine-2,4,6-triyl)*tris*(azanediyl))*tris*-(carbonothioyl))*tris*(4-fluorobenzamide) (5h).** Yield: 73%; M. P. 189 – 191°C; FT-IR (KBr): ν 3454, 3278 (N-H, str.), 1732 (C=O str.), 1677 (C=N str.), 1591, 1503 (C=C str.), 1223 (C=S str.), 1090 (C-N str.) cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6): δ 7.09 (3H, s, 3NH), 7.27 (6H, t, J = 6.2 Hz, 6CH), 7.49 (6H, dd, J = 6.0, 4.0 Hz, 6CH), 11.42 (3H, s, 3NH) ppm. ^{13}C NMR (63 MHz, DMSO-d_6): δ 175.0, 169.7, 162.1, 147.4 (^1J = 227.0 Hz), 135.8, 127.2, 126.2 (^2J = 39.6 Hz) ppm. Anal. calcd. for $C_{27}H_{18}F_3N_9O_3S_3$: C, 48.43; H, 2.71; F, 8.51; N, 18.82. Found: C, 48.45; H, 2.73; F, 8.54; N, 18.85.

2.3. Antibacterial Activity Assay

Antibacterial activity was determined using the disc diffusion procedure and principles of the Clinical and Laboratory Standards Institute (CLSI 2017). The antibacterial properties of each compound were tested against standard bacterial strains including *S. aureus* (ATCC 25923), *B. cereus* (ATCC 14579) and *E. coli* (ATCC 25922). To perform the test, each strain was added into the sterile phosphate buffer saline and its turbidity was adjusted to 0.5 McFarland tube (1.5×10^8 cells mL-1). Then 100 µL of the suspension was full streaked on the Muller-Hinton agar medium (Merck-Germany) and each of the synthesized tris-thioureas was placed on a medium after being impregnated with a paper disk. Antibiotic discs (Padtan Teb-Iran), viz., nitrofurantoin (300 µg), penicillin (10 µg), imipenem (10 µg), cefalexin (30 µg), co-amoxyclav (20 µg), trimethoprim sulfamethoxazole (1.2 µg), gentamicin (10 µg), tetracycline (30 µg), azithromycin (15 µg) and chloramphenicol (30 µg) were used as references to anti-bacterial drugs and placed on the medium. All the plates incubated in 37°C for 24 h. The disc strengths and the zone size interpretation were determined in accordance with Clinical Laboratory Standard Institute (CLSI 2017) guidelines.

3. RESULTS AND DISCUSSION

We have developed the synthesis of novel tris-thiourea derivatives (**5a – 5h**) using melamine as central core at suitable conditions (Scheme 1) and examined their biological activity against Gram-positive and Gram-negative bacteria (see Table 1 and Fig. 1 – 3). This report describes the synthesis, spectroscopic characterization, and antibacterial activity of several new tris-thiourea derivatives against *S. aureus*, *B. cereus*, and *E. coli* bacterial strains. For the preparation of the tris-thiourea derivatives, benzoyl chloride **1** was converted to isothiocyanate **3** through reaction with potassium thiocyanate **2** in dry acetone under reflux conditions. The last step was the reaction of isothiocyanate **3** with melamine **4**, generating tris-thiourea derivatives (**5a – 5h**) as shown in Scheme 1.

The target products were obtained via an efficient and simple synthetic route without minimal purification, with yields ranging from 71 to 89%. A noteworthy factor in the synthesis of tris-thiourea derivatives is the low solubility of melamine in acetone. To fix this problem, after completion of the reaction at the first stage, which is increases of benzoyl chlorides to potassium thiocyanate, acetone was evaporated and dimethyl sulfoxide was replaced.

The formation of all the synthesized compounds (**5a – 5h**) was fully characterized by FT-IR, ^1H and ^{13}C NMR spectroscopy. and elemental analysis. FT-IR spectroscopy data for compound **5b** reveal the presence of NH stretching at 3492 and 3420 cm^{-1}, C=O stretching at 1728 cm^{-1}, C=N

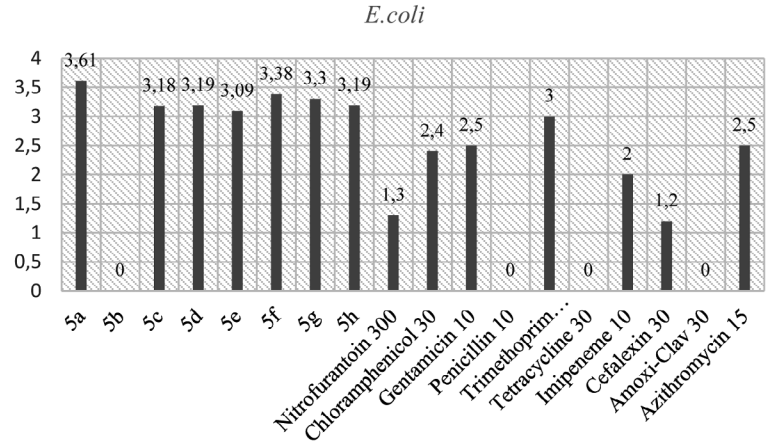


Fig. 1. Comparison of the germicidal effect of synthesized compounds and various antibiotics against *E. coli.*

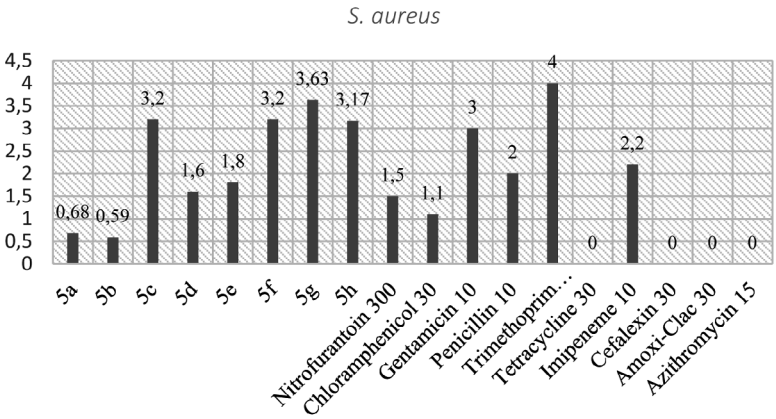


Fig. 2. Comparison of the germicidal effect of synthesized compounds and various antibiotics against *S. aureus.*

stretching at 1680 cm^{-1}, C=C stretching at 1633 and 1541 cm^{-1}, and C=S stretching at 1239 cm^{-1}. Furthermore, ^{1}H NMR spectra of compound **5b** in DMSO-d_6 showed two singlet at δ 6.87 and 11.43 ppm for –NH proton that confirmed the formation of this compound. Also, the ^{13}C NMR spectrum of compound **5b** in DMSO-d_6 showed seven signals in agreement with the proposed structure.

According to Table 1 and Fig. 1 – 3, all bacteria showed a significant difference between the germicide rate under the action of various compounds ($P < 0.05$). For *E. coli*, the highest germicide rate was observed for compound **5a** and the lowest rate, for compound **5e**; for *S. aureus*, the highest microbicide rate was observed for compound **5g** and the lowest for compounds **5a** and **5b**; for *B. cereus*, the highest germicide rate was observed for compounds **5c**, **5d**, **5f**, **5g** and **5h** and the lowest, for compounds **5b** and **5e**.

In concluding, we reported an efficient protocol for synthesis of *tris*-thiourea derivatives (**5a** – **5h**) in good to excellent yields from one-pot condensation reaction between available benzoyl chlorides (**1a – 1h**) with potassium thiocyanate (**2**) and melamine (**4**) under reflux conditions. The chemical structure of all synthesized compounds was determined by examining the FT-IR, ^{1}H, ^{13}C NMR spectra and elemental analysis. The antibacterial activities of *tris*-thiourea derivatives were appraised against four bacterial

TABLE 1. Results of One-Way Analysis of Variance to Compare the Growth Rate of *E. coli*, *S. aureus* and *B. cereus* Bacteria in the Presence of Compounds Studied

Compound	*E. coli* (cm)	*S. aureus* (cm)	*B. cereus* (cm)
5a	$3.61^{a} \pm 0.110$	$0.68^{e} \pm 0.75$	$2.10^{b} \pm 0.235$
5b	0	$0.59^{e} \pm 0.085$	$1.50^{c} \pm 0.115$
5c	$3.18^{c} \pm 0.140$	$3.20^{b} \pm 0.070$	$3.41^{a} \pm 0.145$
5d	$3.19^{c} \pm 0.050$	$1.60^{d} \pm 0.125$	$3.40^{a} \pm 0.075$
5e	$3.09^{d} \pm 0.095$	$1.80^{c} \pm 0.140$	$1.28^{c} \pm 0.085$
5f	$3.38^{b} \pm 0.120$	$3.20^{b} \pm 0.060$	$3.59^{a} \pm 0.145$
5g	$3.30^{b} \pm 0.050$	$3.63^{a} \pm 0.098$	$3.40^{a} \pm 0.095$
5h	$3.19^{c} \pm 0.145$	$3.17^{b} \pm 0.085$	$3.41^{a} \pm 0.120$
One-way analysis of variance	$F = 404.763$ $P = 0.001$	$F = 483.274$ $P = 0.001$	$F = 152.961$ $P = 0.001$

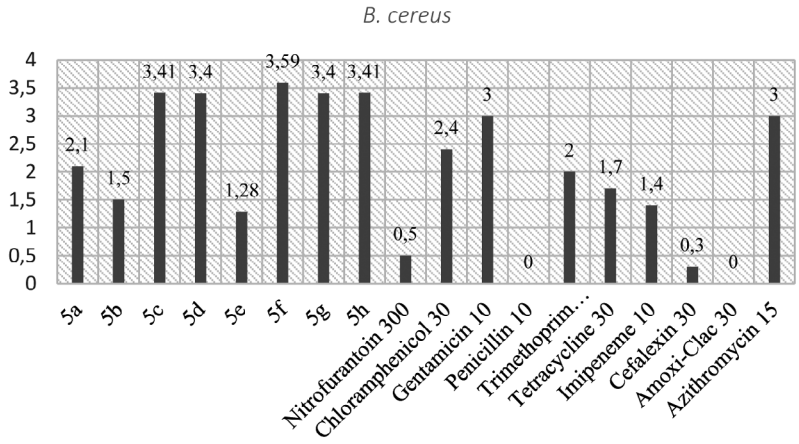


Fig. 3. Comparison the germicidal effect of synthesized compounds and various antibiotics against *B. cereus.*

strains, including *S. aureus*, *B. cereus*, *E. coli* and *P. aeruginosa*. The synthesized tris-thioureas showed excellent antibacterial activity against Gram-positive bacteria (*S. aureus* and *B. cereus*) as well as against some Gram-negative bacteria (*E. coli*). The synthesized compounds exhibited no activity against *P. aeruginosa.*

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