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Synthesis and antimicrobial evaluation of 5-aryl-1, 2, 4-triazole-3-thione derivatives containing a rhodanine moiety

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Abstract

Three series of 5-aryl-1, 2, 4-triazole-3-thione derivatives containing a rhodanine moiety (**5a–k**, **6a–i**, and **7a–i**) have been synthesized, characterized and evaluated for their antibacterial activity. Some of these displayed potent antibacterial activity against several Gram-positive and Gram-negative bacterial strains (including multidrug-resistant clinical isolates) with minimum inhibitory concentration (MIC) values in the range of 4–64 μg/mL and minimum bactericidal concentration (MBC) values in the range of 8–256 μg/mL. Compared with previously reported rhodanine derivatives, these compounds exhibited a broad spectrum of antibacterial activity by means of introducing 4-amino-5-aryl-1,2,4-triazole-3-thione moiety. Notably, compound **5f** exhibited good antibacterial activity against *S.aureus* RN 4220, *S. aureus* 209, *S. aureus* 503, Gram-negative bacteria (*Escherichia coli* 1924), and *Candida albicans* 7535 with MBC values of 8 or 16μg/ml. All of the compounds

synthesized in the current paper were characterized by ^{1}H NMR, ^{13}C NMR, infrared and mass spectroscopy.

***Keywords*:** Rhodanine; 1, 2, 4-Triazole derivatives; Antibacterial activity; Minimum inhibitory concentration; Minimum bactericidal concentration.

Antibiotic resistance is becoming a serious threat to public healthcare and there is an urgent need for novel antimicrobial agents.[1-5] Heterocyclic compounds have antifungal and anticancer properties and are currently used therapeutically.[6-8] 4-Amino-5-aryl-1,2,4-triazole-3-thione derived compounds have attracted considerable attention because of their antimicrobial activity against several strains of bacteria.[9-10]

In previous work, we identified a series of rhodanine-3-acetic acid derivatives[11-14] which showed remarkable bacteriostatic activity against Gram-positive bacteria. An example is compound A with a minimum inhibitory concentration (MIC) value of 2 µg/mL (Fig. 1).[15] Unfortunately, none of the compounds were active against Gram-negative bacteria, even at 64 µg/mL. In contrast, compound B exhibited a good antibacterial activity against *Escherichia.coli* with an MIC value of 6.25 µg/mL (Fig. 1).[16] Thus, as a part of our ongoing studies towards the development of novel antibacterial agents, compounds A and B were used as leads to design novel compounds. Here, we reported the synthesis, characterization, and antimicrobial assessment of three series of 5-aryl-1,2,4-triazole-3-thione derivatives containing a rhodanine moiety (**5a–k**, **6a–i** and **7a–i**).

Compounds **5a-k**, **6a-i**, and **7a-i** were synthesized according to the synthetic route depicted in Scheme 1. Esterification between the R-substituted aromatic acid and ethanol in the presence of concentrated sulfuric acid afforded the corresponding ester which was further reacted with 85% hydrazine monohydrate in ethanol to get hydrazide **1**. The intermediate **2** was obtained by the reaction of hydrazide **1** and carbon disulfide (CS_2) in the presence of KOH in absolute methanol. The rhodanine intermediates **3** were prepared according to a method previously described in the

literature.[17-18] Compounds **4** were prepared by the Knoevenagel condensation reaction of terephthaldicarboxaldehyde with intermediates **3** in ethanol in the presence of glacial acid and piperidine.[19] The target compounds **5a-k**, **6a-i**, and **7a-i** were synthesized by reacting R-substituted 4-amino-5-aryl-1, 2, 4-triazole-3-thione **2** with the appropriate *N*-substituted rhodanine **4** in glacial acetic acid. The structures of the synthesized compounds were confirmed by IR, ^{1}H NMR, ^{13}C NMR, and mass spectroscopy.[20]

Twenty-nine synthesized compounds were screened for their *in vitro* antibacterial activities with a minimum inhibitory concentration (MIC) method. Their MBC values were also determined (only for the compounds with MIC values of $\leqslant$64μg/mL). The results are summarized in Table 1, Table 2, Table 3 and Table 4.

The *in vitro* antibacterial activity was evaluated using a 96-well microtiter plate to obtain the MIC values for different strains (including multidrug-resistant clinical isolates). Gatifloxacin and moxifloxacin were used as positive controls. Four Gram-positive strains (*S. aureus* RN 4220, *S. aureus* KCTC 209, *S. aureus* KCTC 503, *Streptococcus mutans* 3065), five Gram-negative strains (*Escherichia coli* KCTC 1924, *Escherichia coli* CCARM 1356, *Pseudomonas aeruginosa* 2742, *Pseudomonas aeruginosa* 2004, *Salmonella typhimurium* 2421) and one fungus (*Candida albicans* 7535) were used to the evaluation. MBC were defined as the minimum bactericidal concentration that yielded no colonies for the corresponding agar subculture after the proper incubation interval. The MBC values of these compounds were determined against *S.aureus* RN 4220, *S. aureus* 209, *S. aureus* 503, *S.mutans* 3065, *Escherichia coli* 1924, *Candida albicans* 7535 and multidrug-resistant *S.aureus*. Gatifloxacin and moxifloxacin were used as positive controls and DMSO as a negative control.

The results indicated that most of the compounds strongly inhibited the Gram-positive bacteria with MIC values in the range of 4–64 μg/mL. Some of them also exhibited moderate to good levels of inhibition against the Gram-negative strain (*Escherichia coli* KCTC 1924) with MIC values in the range of 8–64 μg/mL. Especially, Compound **5f** exhibited good inhibitory activity against fungus (*Candida albicans* 7535) with MIC values of 4 or 8 μg/mL. Compounds **5a–k** displayed higher

inhibition against the three Gram-positive strains (*S. aureus* RN 4220, *S. aureus* KCTC 503, *Streptococcus mutans* 3065) than those in series **6a–i** and **7a–i**, as shown in Table 1. MBC values of several compounds were the same or 2-4-fold higher than their MICs. Among them, compounds **5a**, **5c–h** had identical or 2-fold higher MIC values than their MBCs against *S.aureus* RN 4220. Compound **5f** demonstrated an MBC value of 2-fold higher than its MIC against *S. aureus* 209 and an identical MIC and MBC values against *Candida albicans* 7535. The MBC/MIC ratio of the compounds **5a-f** and **5h-k** were ⩽4 for *S. aureus* 503,[21] and most of them displayed MBCs at 2-4 fold higher than their MICs against *S.mutans* 3065. Six compounds (**5b**, **5f**, **5i**, **6d**, **6g**, **7a**) showed good antibacterial activities (MBC/MIC ratio⩽4) against *Escherichia coli* 1924. Most derivatives, in general, exhibited high levels of antibacterial activity but were less active than the controles, as shown in Table 2.[22]

The MIC values against the clinical isolates of multidrug-resistant Gram-positive bacterial strains are reported in Table 3.[22] Most of the compounds exhibited inhibitory activity towards the multidrug-resistant Gram-positive bacterial strains (MRSA CCARM 3167 and 3506, QRSA CCARM 3505 and 3519) with MIC values in the range of 8–64 μg/mL. Especially, compound **5a** showed the most potent inhibitory effect with an MIC value of 8 μg/mL. The MBC values against the clinical isolates of multidrug-resistant *S.aureus*, as shown in Table 4, showed that compounds **5a**, **5b**, **5e**, **5f**, **5h** and **5i** exhibited good antibacierial activities against MRSA CCARM 3167 and 3506 with MBCs in the range of 8–64 μg/mL. Compounds **5a**, **5f** and **5h** displayed moderate antibacterial activity with MBC value of 32 μg/mL against QRSA CCARM 3505 and 3519. Although these compounds are less active than the controles, the results are encouraging and provide further clues towards the discovery of new antimicrobial agent.

Structure-activity relationships were observed from this study. First, the aforementioned results suggested that the antibacterial activity was not significantly affected by the position and physicochemical properties of the substituents on the phenyl ring. Second, a comparison of the activities across the three different series of compounds, a general antibacterial activity order of **5a-k** > **7a-i** > **6a-i** was obtained,

which indicated that a free carboxyl group on the rhodanine ring is not critical for the activity against Gram-positive bacteria and the introduction of phenylpropanoic acid is beneficial for the improvement of antibacterial activity. Third, none of the rhodanine derivatives previously reported by our group showed any activity against the Gram-negative strain. Nevertheless, the introduction of an 4-amino-5-aryl-1,2,4-triazole-3-thione moiety resulted in moderate antibacterial levels against the Gram-negative strain *E. coli* 1924, indicating that an 4-amino-5-aryl-1, 2, 4-triazole-3-thione moiety is critical for the improvement of the activities against the Gram-negative strain, which might be a hit for further optimization of 4-amino-5-aryl-1,2,4-triazole-3-thione derivatives.

In conclusion, based on our previous work, three novel series of 5-aryl-1,2,4-triazole-3-thione derivatives containing a rhodanine moiety (**5a–k**, **6a–i**, and **7a–i**) have been designed, synthesized and evaluated for their antibacterial activity against Gram-positive and Gram-negative bacteria. The results showed that most of the compounds have good levels of antibacterial activity against Gram-positive bacteria (including multidrug-resistant strains of clinical isolates). The results indicate that these hybrid compounds containing a phenylpropionic acid group at the *N*-3 position of the heterocycle ring play an important role and, compared to our previous work, the introduction of the 4-amino-5-aryl-1,2,4-triazole-3-thione moiety might be beneficial to increase the potency against Gram-negative strains. Further modification of these compounds including the study of possible mechanism of action is currently underway in our laboratories.

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Supplementary data

Supplementary data associated with this article can be found in the online version.

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20. Preparation of **5f**: Compound **2f** (1 mmol) and (*S*)-2-((*Z*)-5-(4-formylbenzylidene)-4-oxo-2-thioxothiazolidin-3-yl)-3-phenylpropanoic acid (1 mmol) were refluxed in glacial acetic acid (7 mL) at 100–110 °C for 4–6 h. The excess solvent was removed under reduced pressure. The resultant solid was washed with water and purified with silica gel column chromatography, eluting with DCM/methanol (100:1) to get a yellow solid. Yield 75%. m.p. 158–160 °C. IR (KBr) cm^{-1}: 1714 (C=O), 1604 (C=N). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm): δ 3.52 (s, 2H, CH_2), 5.88 (s, 1H, CH), 7.82 (s, 1H, CH=), 7.14-7.97 (m, 13H, Ar-H), 8.47 (s, 1H, CH=N), 12.10 (s, 1H, COOH). ^{13}C NMR (DMSO–d_6, 300 MHz, ppm): δ 193.11, 169.14, 166.92, 164.47, 162.28, 147.46, 136.98, 135.67, 134.47, 133.78, 133.51, 132.22, 131.84, 131.05, 129.46, 128.77, 128.46, 127.86, 127.23, 127.01, 121.78, 58.69, 33.48. EIMS *m/z* 606 (M+1).

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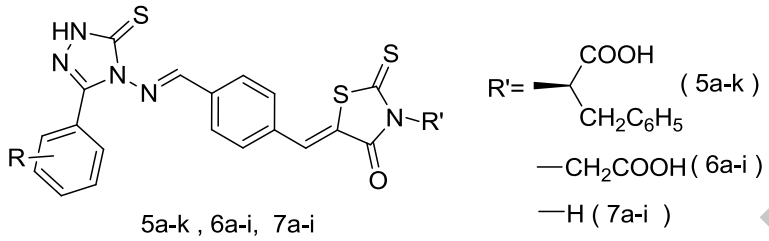
22. *Anti-bacterial activity assay:* The micro-organisms used in the present study were *S. aureus* RN 4220, *S. aureus* KCTC 209, *S. aureus* KCTC 503, *Streptococcus mutans* 3065, *Escherichia coli* KCTC 1924, *Escherichia coli* CCARM 1356, *Pseudomonas aeruginosa* 2742, *Pseudomonas aeruginosa* 2004, *Salmonella typhimurium* 2421 and one fungus (*Candida albicans* 7535). The strains of multidrug-resistant clinical isolates were methicillin-resistant *Staphylococcus aureus* (MRSA CCARM 3167 and MRSA CCARM 3506) and quinolone-resistant *Staphylococcus aureus* (QRSA CCARM 3505 and QRSA CCARM 3519). Clinical isolates were collected from various patients hospitalized in several clinics. The *in vitro* antimicrobial activity was evaluated using the minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) with different strains. Gatifloxacin and moxifloxacin were used as positive controls. The bacteria were grown to mid-log

phase in Mueller-Hinton broth and diluted 1000-fold in the same medium. Stock solutions of the test compounds in dimethyl sulfoxide were prepared and then poured into 96-well plates. The final concentration of 64±0.5 µg/mL underwent a two-fold serial dilution. The microbacteria were suspended and contained approximately 10^5 CFU/mL. These were applied to 96-well plates with a serial dilution and incubated at 37 °C for 24 h. The microbacterial growth was measured from the absorption at 630 nm. This was done using a microtiter, enzyme-linked immunosorbent assay (ELISA) reader. MBCs were determined by plating 5 µL of samples from each MIC assay tube which showed no visible growth of bacterial onto freshly prepared Mueller Hinton agar plates and plates were incubated at 37 ºC for additional 24 h. The MBC was defined as the lowest concentration of the test sample at which did not permit any visible bacterial colony growth on the agar plates during the period of incubation. All experiments were carried out in triplicate.

Table 1.

Inhibitory activity of compounds **5a-k**, **6a-i** and **7a-i** expressed as MIC (μg/mL) against strains of Gram-positive (*Staphylococcus aureus* and *Streptococcus mutans*) bacteria and Gram-negative (*Escherichia coli, Salmonela typhinurium* and *Pseudomonas aeruginosa*) bacteria and *Candida albicans* 7535.



Compound	R	Gram-positive strains				Gram-negative strains					Fungus
		S. aureus		*S. mutans*		*E.coli*		*P. aeruginosa*		*S. typhinurium*	*C.albicans*
		4220[a]	209[b]	503[c]	3065[d]	1924[e]	1356[f]	2742[g]	2004[h]	2421[i]	7535[j]
5a	H	8	>64	8	8	>128	>128	>128	>128	>128	>64
5b	2-CH_3	16	>64	16	8	64	>128	>128	>128	>128	>64
5c	3-CH_3	32	>64	64	64	>128	>128	>128	>128	>128	>64
5d	4-CH_3	8	>64	64	64	>128	>128	>128	>128	>128	>64
5e	2-Cl	16	>64	16	16	>128	>128	>128	>128	>128	>64
5f	3-Cl	8	8	8	4	8	>128	>128	>128	>128	8
5g	4-Cl	8	>64	16	16	>128	>128	>128	>128	>128	>64
5h	2-Br	8	>64	8	8	>128	>128	>128	>128	>128	>64
5i	3-Br	32	>64	64	64	64	>128	>128	>128	>128	>64
5j	4-Br	8	>64	8	16	>128	>128	>128	>128	>128	>64
5k	4-F	16	>64	32	64	>128	>128	>128	>128	>128	>64
6a	H	>64	>64	>64	>64	>128	>128	>128	>128	>128	>64
6b	3-CH_3	>64	>64	64	>64	32	>128	>128	>128	>128	>64
6c	4-CH_3	>64	>64	>64	>64	>128	>128	>128	>128	>128	>64
6d	2-Cl	64	>64	>64	>64	64	>128	>128	>128	>128	>64
6e	3-Cl	>64	>64	>64	>64	>128	>128	>128	>128	>128	>64
6f	4-Cl	>64	>64	>64	>64	>128	>128	>128	>128	>128	>64
6g	2-Br	64	>64	>64	>64	64	>128	>128	>128	>128	>64
6h	4-Br	>64	>64	>64	>64	>128	>128	>128	>128	>128	>64
6i	4-F	64	64	>64	>64	>128	>128	>128	>128	>128	>64
7a	H	32	64	32	16	32	>128	>128	>128	>128	>64
7b	3-CH_3	32	>64	32	>64	32	>128	>128	>128	>128	>64
7c	4-CH_3	>64	>64	>64	>64	>128	>128	>128	>128	>128	>64
7d	2-Cl	32	64	16	16	16	>128	>128	>128	>128	>64
7e	3-Cl	>64	>64	>64	>64	>128	>128	>128	>128	>128	>64
7f	4-Cl	>64	>64	>64	>64	>128	>128	>128	>128	>128	>64
7g	2-Br	16	64	16	16	16	>128	>128	>128	>128	>64
7h	4-Br	>64	>64	>64	>64	64	>128	>128	>128	>128	>64

7i	4-F	>64	>64	>64	>64	>128	>128	>128	>128	>128	>64
Gatifloxacin		0.25	2	4	0.5	2	16	1	1	0.5	0.5
Moxifloxacin		0.25	2	2	0.25	2	128	1	2	0.5	0.5

[a] *S.aureus* RN 4220. [b] *S. aureus* 209. [c] *S. aureus* 503. [d] *S.mutans* 3065. [e] *E.coli* KCTC 1924. [f] *E.coli* CCARM 1356.
[g] *P.aeruginosa* 2742. [h] *P. aeruginosa* 2004. [i] *S. typhimurium* 2421. [j] *C.albicans* 7535

S.aureus RN 4220: A genotype of *S.aureus*. KCTC (Korean Collection for Type Cultures) CCARM (Culture Collection Antimicrobial Resistant Microbes)

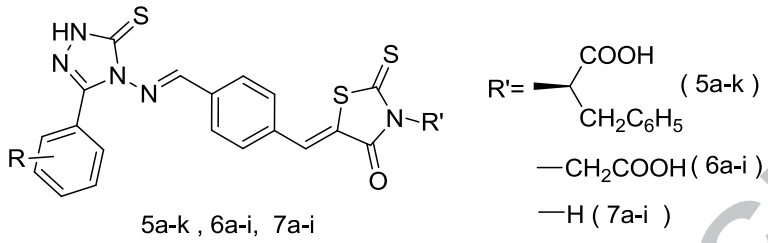
Table 2.

MICs and MBCs (minimum bactericidal concentrations) (both in μg/mL) of some compounds (MIC≤64μg/mL) against *S.aureus* RN 4220, *S. aureus* 209, *S. aureus* 503, *S.mutans* 3065, *Escherichia coli* 1924 and *Candida albicans* 7535.

Compound	R	4220 MIC/MBC	209 MIC/MBC	503 MIC/MBC	3065 MIC/MBC	1924 MIC/MBC	7535 MIC/MBC
5a	H	8/16		8/8	8/16		
5b	2-CH_3	16/64		16/32	8/16	64/64	
5c	3-CH_3	32/32		64/128	64/256		
5d	4-CH_3	8/8		64/64	64/>256		
5e	2-Cl	16/32		16/64	16/>128		
5f	3-Cl	8/8	8/16	8/16	4/>32	8/8	8/8
5g	4-Cl	8/16		16/128	16/32		
5h	2-Br	8/16		8/8	8/32		
5i	3-Br	32/256		64/128	64/>128	64/64	
5j	4-Br	8/64		8/32	16/64		
5k	4-F	16/128		32/128	64/256		
6b	3-CH_3			64/>256		32/>256	
6d	2-Cl	64/256				64/128	
6g	2-Br	64/>256				64/256	
6i	4-F	64/>256	64/>256				
7a	H	32/>256	64/>256	32/>256	16/>128	32/128	
7b	3-CH_3	32/>256		32>256		32/256	
7d	2-Cl	32/>256	64/>256	16>256	16/>128	16/>128	
7g	2-Br	16/128	64/>256	16/>128	16/>128	16/>128	
7h	4-Br					64/>256	
Gatifloxacin		0.25/0.25	2/2	4/4	0.5/0.5	2/2	0.5/0.5
Moxifloxacin		0.25/0.25	2/2	2/2	0.25/0.25	2/2	0.5/0.5

Blank: MIC > 64μg/mL, MBC not tested.

Table 3. Inhibitory activity (MIC, μg/mL) of compounds **5a-k,6a-i** and **7a-i** against clinical isolates of multidrug-resistant *S.aureus*.



Compound	R	Multidrug-resistant *S.aureus*			
		MRSA		*QRSA*	
		3167[a]	3506[b]	3505[c]	3519[d]
5a	H	8	8	8	8
5b	2-CH_3	16	16	16	16
5c	3-CH_3	16	16	16	16
5d	4-CH_3	8	16	16	16
5e	2-Cl	16	16	16	16
5f	3-Cl	8	16	8	8
5g	4-Cl	8	16	16	16
5h	2-Br	8	16	8	8
5i	3-Br	32	16	16	32
5j	4-Br	8	16	8	8
5k	4-F	16	64	16	16
6a	H	>64	>64	>64	>64
6b	3-CH_3	64	>64	64	64
6c	4-CH_3	>64	>64	>64	16
6d	2-Cl	>64	>64	>64	>64
6e	3-Cl	>64	>64	>64	>64
6f	4-Cl	>64	>64	>64	>64
6g	2-Br	64	>64	>64	64
6h	4-Br	>64	>64	>64	>64
6i	4-F	16	>64	>64	32
7a	H	32	32	32	32
7b	3-CH_3	64	32	32	32
7c	4-CH_3	>64	>64	>64	>64
7d	2-Cl	16	16	16	16
7e	3-Cl	>64	>64	>64	>64

7f	4-Cl	>64	>64	>64	>64
7g	2-Br	16	16	16	16
7h	4-Br	>64	>64	>64	>64
7i	4-F	>64	>64	>64	>64
Gatifloxacin		2	2	8	4
Moxifloxacin		1	1	4	4

[a] *Methicillin-resistant S. aureus* CCARM 3167. [b] *Methicillin-resistant S. aureus* CCARM 3506.
[c] *Quinolone-resistant S. aureus* CCARM 3505. [d] *Quinolone-resistant S. aureus* CCARM 3519.

Table 4. MICs and MBCs (both in μg/mL) of some compounds (MIC≤64μg/mL) against clinical isolates of multidrug-resistant *S.aureus*.

Compound	R	3167 MIC/MBC	3506 MIC/MBC	3505 MIC/MBC	3519 MIC/MBC
5a	H	8/16	8/32	8/32	8/32
5b	2-CH_3	16/32	16/64	16/64	16/>128
5c	3-CH_3	16/128	16/64	16/64	16/128
5d	4-CH_3	8/64	16/128	16/128	16/>128
5e	2-Cl	16/32	16/64	16/>128	16/>128
5f	3-Cl	8/8	16/16	8/32	8/32
5g	4-Cl	8/64	16/128	16/64	16/128
5h	2-Br	8/16	16/32	8/32	8/32
5i	3-Br	32/128	16/64	16/128	32/256
5j	4-Br	8/32	16/128	8/32	8/64
5k	4-F	16/128	64/>256	16/128	16/128
6b	3-CH_3	64/>256		64/>256	64/>256
6c	4-CH_3				16/>128
6g	2-Br	64/256			64/>256
6i	4-F	16/>128			32/>256
7a	H	32/>256	32/>256	32/>256	32/>256
7b	3-CH_3	64/>256	32/>256	32/>256	32/>256
7d	2-Cl	16/>128	16/>128	16/>128	16/>128
7g	2-Br	16/>128	16/>128	16/>128	16/>128
Gatifloxacin		2/2	2/2	8/8	4/4
Moxifloxacin		1/1	1/1	4/4	4/4

Blank: MIC > 64μg/mL, MBC not tested.

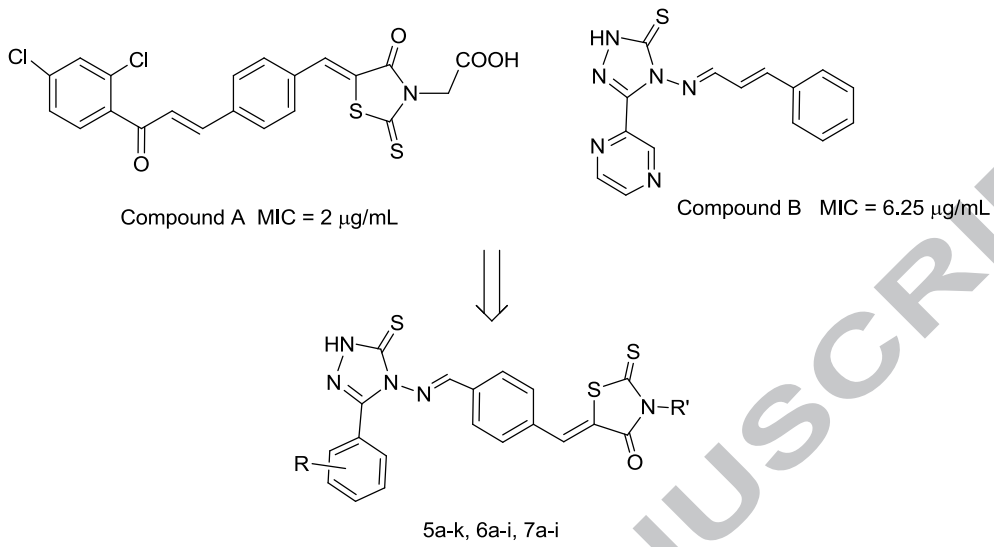
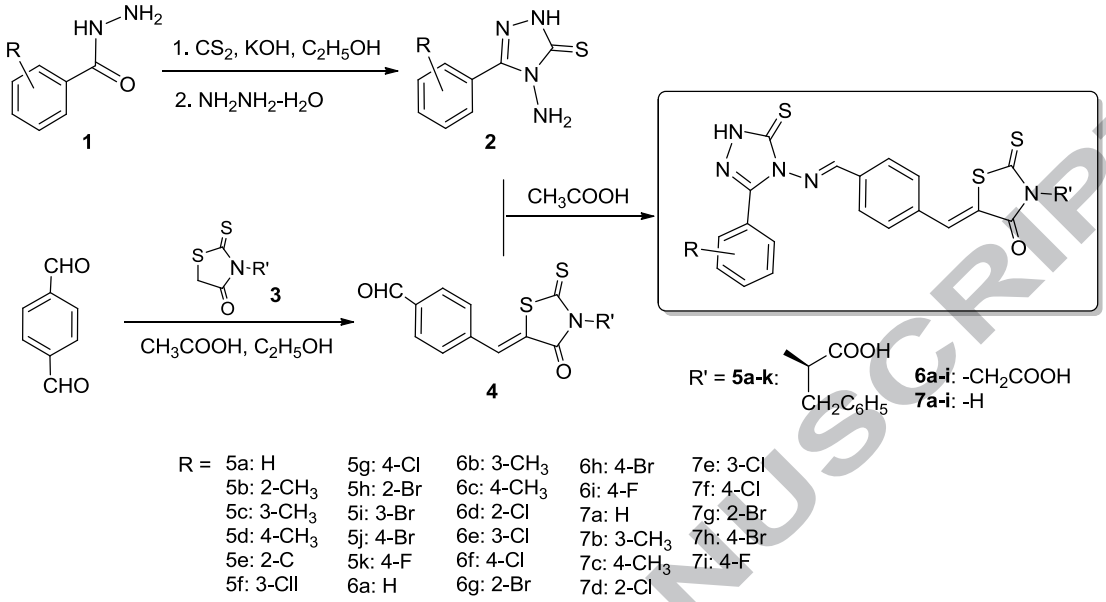


Figure 1. Previously reported compound A, B and the structure-based design of the target compounds.



Scheme 1. Synthetic scheme for the synthesis of compounds **5a-k**, **6a-i** and **7a-i**.

Synthesis and antimicrobial evaluation of 5-aryl-1, 2, 4-triazole-3-thione derivatives containing a rhodanine

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