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A facile synthesis of some novel thiazoles, arylazothiazoles, and pyrazole linked to thiazolyl coumarin as antibacterial agents

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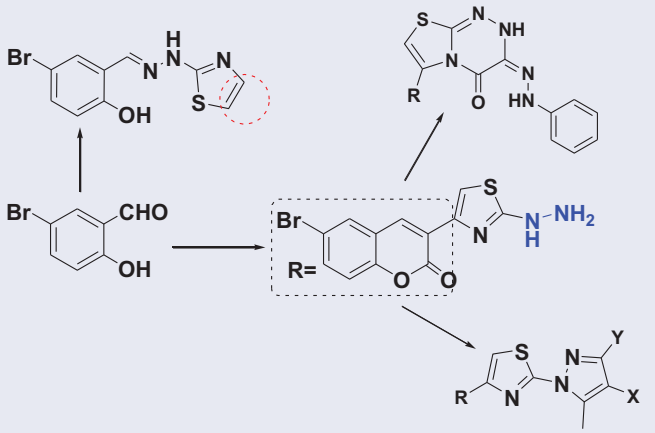
ABSTRACT

5-bromosalicylaldehyde (**1**) was reacted with thiosemicarbazide to afford thiosemicarbazone derivative **2**. The latter underwent cyclocondensation upon reaction with α-haloester, α-haloketone as well as hydrazonoyl halides affording 1,3-thiazoles and arylazothiazoles **3-6**, respectively. On the other hand, pyrazolyl thiazolyl coumarin derivatives **9a–c** and **11a–c** was obtained via reaction of hydrazinylthiazole **8** with acetylacetone, trifloroacetylacetone, ethyl acetoacetate and/or arylazoacetylacetone **10a–c**, respectively. Furthermore, thiazolotriazine derivative **12** was accomplished via reaction of **8** with ethyl 2-(2-phenylhydrazono)-2-chloroacetate. The structures of the newly prepared compounds were elucidated by spectral data. Eleven of the newly synthesized compounds were screened for their antibacterial activity. The results indicated that, compounds **5a**, **5b**, **9a, 9c, 11b** and **12** were strong active toward Gram-positive bacteria *Enterococcus faecalis*. Compound **5a** was strong active toward Gram-positive bacteria *Staphylococcus aureus*. Moreover, compounds **9b, 11b,** and **12** were strong active toward Gram-negative bacteria *Pseudomonas aeruginosa*.

GRAPHICAL ABSTRACT



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Introduction

Thiazoles are considered an important class of heterocyclic compounds both biologically and chemically. Previous studies have shown that thiazole based-compounds had effective pharmacological importance with antimicrobial,[1–8] anti-inflammatory,[9–11] anticonvulsant,[12,13] anti-diabetic,[14–16] anti-HIV[17,18] antitumor,[19–26] and antioxidant[27,28] activities. Moreover, a variety of natural products contain thiazole scaffold such as thiamin (vitamin B1) and thiamin pyrophosphate (TPP). Mycothiazole is isolated from sponge spongia mycofijiensis and shows a selective activity against lung cancer.[29] The antibiotic cystothiazole A was isolated from the myxobacterium culture by Sakagami et al. in 1998. In particular, thiazoles are found in many powerful biologically active synthetic drugs (Figure 1).

On the other hand, coumarins occur in the seeds, roots, and leaves of a large number of plants,[30] fungi, bacteria, and marine sources.[31] Coumarins exhibit diverse biological activities as antimicrobial[32] anticancer and anti-inflammatory,[33–35] antioxidant,[36] antiviral,[37] and anti-tubercular. [38] Warfarin is a coumarin derivative which possesses anticoagulant properties, used to treat or prevent blood clots in veins.[39] Furthermore, thiazolyl coumarin moiety has antimicrobial, anticancer, and antifibrotic activities.[40–44] Also, pyrazolyl thiazolyl coumarin is antimicrobial agents.[45] Based on the above facts, herein, we decided to prepare new thiazoles, molecular hybrids based on pyrazole-thiazole-coumarin (PTC), and study their antibacterial activities.

Results and discussion

Thiazoles can be synthesized by Hantzsch thiazole synthesis which involves the interaction between α-haloketones or α-haloesters and thioamide. Herein, synthesis of thiazole was accomplished by condensation of 5-bromosalicylaldehyde (**1**) with thiosemicarbazide in ethanol under reflux to furnish 1-(5-bromo-2-hydroxybenzylidene)thiosemicarbazide (**2**).[46] The latter underwent Hantzsch reaction via cyclocondensation with ethyl chloroacetate in ethanol containing triethylamine under reflux affording thiazolinone (**3**). Moreover, treatment of **2** with 6-bromo-3-(2-bromoacetyl)coumarin under the same reaction conditions yielded thiazole derivative **4** (Scheme 1). The spectral data for the synthesized compounds proved their chemical structures. The infrared spectrum lakes the absorption peaks for NH_2 and C=S groups which indicate cyclization reaction. ^{1}H NMR spectrum of compound **4** (DMSO-d_6) as an example, revealed signals at δ 6.84 (d,1H, $J = 8$ Hz), 7.33–7.45 (m, 2H), 7.72–7.78 (m, 2H), 8.08 (s, 1H), 8.25 (s, 1H), 8.46 (s, 1H), 8.52 (s, 1H, CH=N), 10.49 (s, 1H, NH) and 12.25 ppm (s, 1H, OH). Besides, the aryl azothiazoles were obtained by the reaction of thiosemicarbazone **2** with hydrazonoyl halides. Thus, compound **2** was reacted with 2-oxo-*N*-phenylpropanehydrazonoyl chloride and 2-(2-phenylhydrazono)-2-chloro-1-phenyl ethanone in ethanol containing triehylamine to give compounds **5a** and **5b**, correspondingly. The IR spectrum of compound **5a** displayed absorption peaks at 3444 and 3182 cm^{-1} for OH and NH groups, respectively. ^{1}H NMR spectrum of compound **5a** (DMSO-d_6) displayed singlet signal at δ 2.23 ppm for methyl group and aromatic protons at 6.92–7.86 ppm, in addition to, three singlet signals at 8.64, 10.47 and 10.96 ppm attributed to CH=N, NH and OH, respectively. Similarly, treatment of compound **2** with ethyl 2-(2-substituted

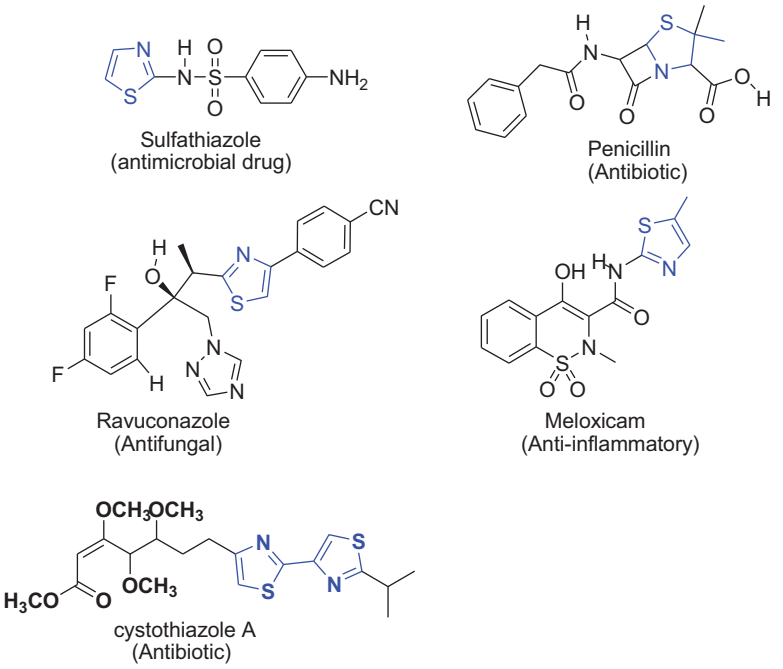
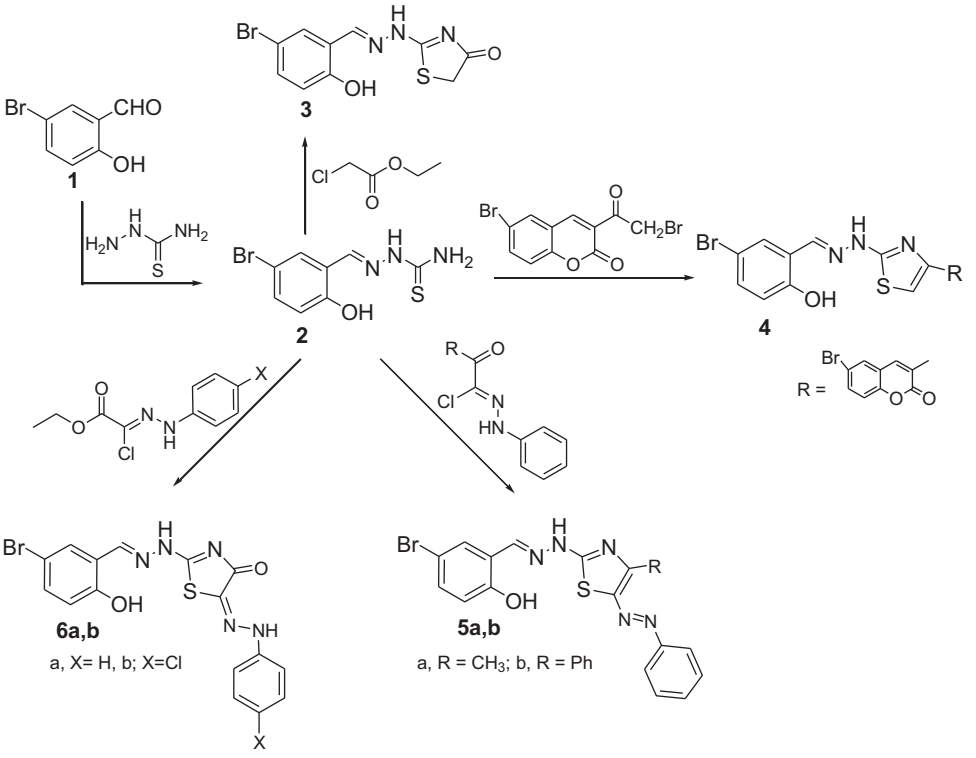
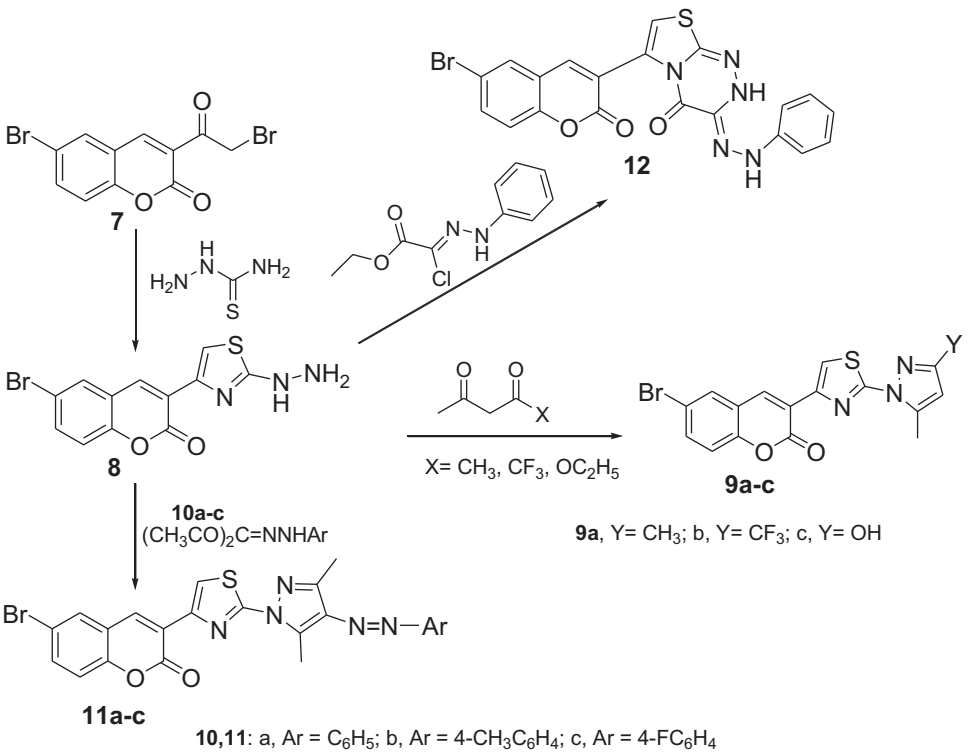


Figure 1. Biologically active drugs containing thiazole.



Scheme 1. Synthesis of thiazoles and arylazothiazoles **3–6**.



Scheme 2. Synthesis of pyrazoles **9a-c** and aryalazopyrazoles **11a–c.**

phenylhydrazono)-2-chloroacetate under the same reaction conditions afforded phenylazothiazolinone derivatives **6a** and **6 b** (Scheme 1). ^{1}H NMR specrum of **6b** (DMSO-d_6) displayed signals at δ 6.92-6.97 (m, 2H), 7.25-7.33 (m, 3H + NH), 7.47-7.50 (dd, 1H, J = 8Hz), 7.87 (s, 1H), 8.65(s, 1H, CH=N), 10.48 (s,1H, NH), 12.25 (s, 1H, OH).

In view of our aim of building bioactive pyrazole-thiazole-coumarin (PTC) based molecular hybrids, 6-bromo-3-acetylcoumarin[42] was prepared from the reaction of 5-bromosalicylaldehyde with ethyl acetoacetate in the presence of piperidine as a catalyst. It was subjected to bromination using Br_2/AcOH to yield 6-bromo-3-(2-bromoacetyl)coumarin (**7**).[42,47] The latter underwent Hantzsch reaction with thiosemicarbazide in ethanol under stirring at room temperature afforded 6-bromo-3-(2-hydrazinylthiazol-4-yl)-2*H*-chromen-2-one (**8**). The target compounds **9a–c** were accomplished via cyclocondensation of **8** with dicarbonyl compounds such as acetylacetone, trifloroacetylacetone and/or ethyl acetoacetate in ethanol under reflux (Scheme 2). The spectroscopic analysis of the prepared compounds indicated the absence of signals attributed to $NHNH_2$ moiety, which confirm the cyclization reaction. For example, ^{1}H NMR spectrum of compound **9a** (DMSO-d_6) revealed signals at δ 2.19 (s, 3H, CH_3), 2.72 (s, 3H, CH_3), 6.21 (s, 1H, CH-pyrazole), 6.98 (d, 1H, J = 8 Hz), 7.69 (d, 1H, J = 8 Hz), 8.10 (s, 1H), 8.14 (s, 1H), 8.63 (s, 1H). Similarly, compound **8** was reacted with arylazoacetylacetone **10a-c** to give pyrazoles **11a–c**, respectively. Finally, thiazolotriazine derivative **12** was accomplished via the reaction of **8** with ethyl 2-(2-substituted phenylhydrazono)-2-chloroacetate.

Table 1. Response of various microorganisms to some synthesized compounds *in vitro* culture.

	Mean* of zone diameter, nearest whole mm.			
	Gram-positive bacteria		Gram-negative bacteria	
Organism Conc. sample	*Enterococcus faecalis* 1 mg/mL	*Staphylococcus aureus* 1 mg/mL	*Escherichia coli* 1 mg/mL	*Pseudomonas aeruginosa* 1 mg/mL
3	I	I	I	I
4	I	I	I	I
5a	H	H	I	I
5b	H	I	L	I
6a	I	L	I	L
6b	I	I	L	I
9a	H	L	I	I
9b	I	I	I	H
9c	H	I	I	I
11b	H	I	L	H
12	H	L	I	H
Control #	H	H	H	H

*Calculate from 3 values. L: Low activity = Mean of zone diameter ≤1/3 of mean zone diameter of control; I: Intermediate activity = Mean of zone diameter ≤2/3 of mean zone diameter of control; H: High activity = Mean of zone diameter >2/3 of mean zone diameter of control; #: Chloramphenicol in the case of Gram-positive bacteria, Cephalothin in the case of Gram-negative bacteria.

Antibacterial activity

All the tested microorganisms were chosen based on their pathogenicity. The organisms were tested against the activity of solutions with one concentration; 100 mg/ml and then 10 µl of preparation was dropped on disk of 6 mm in diameter and the concentrations became 1 mg/disk. In the case of insoluble compounds, the compounds were suspended in DMF and vortexed then processed. Chloramphencol was used as standard reference in the case of Gram-negative bacteria, Cephalothin was used as standard reference in the case of Gram-positive bacteria. The results were depicted in Table 1. The investigation of antibacterial screening data revealed that, compounds **5a**, **5b**, **9a, 9c, 11b,** and **12** were strong active towards Gram-positive bacteria *Enterococcus faecalis*, while compounds **3, 4, 6a, 6b,** and **9b** were intermediate active. All the tested compounds showed intermediate activity towards *Staphylococcus aureus* except compound **5a** which was strongly active and compounds **6a**, **9a,** and **12** which was low active. For Gram-negative bacteria, all the tested compounds showed intermediate to low activity except compounds **9b, 11b,** and **12** were strong active towards *Pseudomonas aeruginosa*.

Experimental section

All reagents and solvents were of commercial grade. Melting points were determined on the digital melting point apparatus and were uncorrected. ^{1}H and ^{13}C NMR spectra were measured with a Bruker Avance spectrometer (Bruker, Germany) at 400 and 101 MHz, respectively, using TMS as the internal standard. Hydrogen coupling patterns were described as singlet (s), doublet (d), triplet (t), quartet (q) and multiplet (m). Chemical shifts were defined as parts per million (ppm) relative to the solvent peak. Elemental analyses were performed on CHNS-O analyzer (Perkin-Elmer, USA). Hydrazonoyl halides[48–50] were prepared as previously reported.

Synthesis of thiazoles and arylazothiazoles 3-6

A mixture of thiosemicarbazone **2** (0.01 mol), ethyl chloroacetate, 6-bromo-3-(2-bromoacetyl)coumarin and/or hydrazonoyl halides (0.01 mole each) in ethanol containing triethylamine was heated under reflux for 2 h. The precipitate that separated on hot was filtered and recrystallized from dioxane yielding the desired products **3–6**, respectively.

2-{2-[(5-Bromo-2-hydroxyphenyl)methylidene]hydrazinyl}-1,3-thiazol-4(5H)-one (3)

White powder (dioxane); Yield 85%; m.p: 291–92 °C; IR (KBr) cm^{-1}: 3429 broad (OH, NH), 3028, 2962 (CH), 1716 (C=O), 1643 (C=N), 1593 (C=C). Anal. calcd. for $C_{10}H_8BrN_3O_2S$ (314.16): C, 38.23; H, 2.57; Br, 25.43; N, 13.38; S, 10.21. Found: C, 38. 30; H, 2.48; Br, 25.49; N, 13.43; S, 10.30%.

6-Bromo-3-(2-(2-(5-bromo-2-hydroxybenzylidene)hydrazinyl)-thiazole-4-yl)-2H-chromen-2-one (4)

Pale yellow powder (dioxane); Yield 89%; m.p: 275–76 °C; ^{1}H NMR: (400 MHz, DMSO-d_6, δ, ppm): 6.84 (d,1H, $J = 8$ Hz), 7.33–7.45 (m, 2H), 7.72–7.78 (m, 2H), 8.08 (s, 1H), 8.25 (s, 1H), 8.46 (s, 1H), 8.52 (s, 1H, CH=N), 10.49 (s, 1H, NH), 12.25 (s, 1H, OH). Anal. calcd. for $C_{19}H_{11}Br_2N_3O_3S$(521.18): C, 43.79; H, 2.13; Br, 30.66; N, 8.06; S, 6.15. Found**:** C, 43.72; H, 2.19; Br, 30.60; N, 8.12; S, 6.21%.

Biological screening

Antibacterial activity of the newly synthesized compounds was determined *in vitro* by standardized disk – agar diffusion method.[51] Cultures of four bacterial species, namely, Gram-positive bacteria: *Enterococcus faecalis* (ATCC 29212) and *Staphylococcus aureus* (*ATCC 25923*), Gram-negative bacteria: *Escherichia coli* (ATCC 25922) and *pseudomonas aeruginosa* (*ATCC 27853*), were used to investigate the antibacterial activity of the newly synthesized compounds.

Conclusions

In the present study, 1-(5-bromo-2-hydroxybenzylidene)thiosemicarbazide (**2**) was used as a starting material for the synthesis of thiazoles and arylazothiazoles via reaction with α-haloketones, α-haloesters and/or hydrazonoyl halides. Also, pyrazole-thiazole-coumarin (PTC) hybrid was prepared via reaction of 6-bromo-3-(2-hydrazinylthiazol-4-yl)-2*H*-chromen-2-one (**8**) with dicarbonyl compounds. Eleven of the newly synthesized compounds were screened for their antibacterial activity. The results revealed that compounds **5a**, **5b**, **9a, 9c, 11b,** and **12** were strong active towards Gram-positive bacteria *Enterococcus faecalis*. Compound **5a** was strongly active towards Gram-positive bacteria *Staphylococcus aureus*. Whereas, compounds **9b, 11b,** and **12** were strong active towards Gram-negative bacteria *Pseudomonas aeruginosa*.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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