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Synthesis and biological screening of thiosemicarbazones of substituted 3-acetylcoumarins having D-glucose moiety

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Abstract

Thiosemicarbazones **5a-j** were synthesized with yields of 45−68% by condensation of 3-acetylcoumarins **3a-j** and tetra-*O*-acetyl-β-D-thiosemicarbazide **4**. All obtained thiosemicarbazones were screened for anti-microorganic activities against bacteria (*B. subtilis*, *S. aureus*, *S. epidermidis*, *E. coli*, *P. aeruginosa*, *K. pneumoniae*, *S. typhimurium*) and fungi (*A. niger*, *C. albicans*, *S. cerevisiae*, and *A. flavus*). Some compounds had significant inhibitory activity with MICs of 0.78−3.125 μM in comparison with **5a**, including **5e**,**h**,**i** for *S. aureus*, and **5c**,**f**,**i** for *S. epidermidis* (Gram-(+) bacteria), **5c**,**f**,**g** for *E.coli*, **5f** for *K. pneumoniae*, **5b**,**c**,**g** for *P. aeruginosa*, and **5i** for *S. typhimurium* (Gram-(−) bacteria), **5d**,**h**,**i** for *A. niger*, **5i** for *A. flavus*, **5b**,**d**,**e**,**h** for *C. albicans*, and **5i** for *S. cerevisiae*. Compounds exhibited excellent activity against tested microorganism with MIC = 0.78 μM, including **5h,i** (against *S. aureus*), **5h** (against *C. albicans*), and **5i** (against *S. cerevisiae*).

Keywords: 3-Acetylcoumarins; Antibacterial; Antifungal; D-Glucose; Thiosemicarbazides; Thiosemicarbazones

Thiosemicarbazides and thiosemicarbazone derivatives had occupied important roles in organic and medicinal chemistry. These classes of compounds presented chelating properties by using C=S and NH groups for coordination with metal center.[1-3] They could be used as versatile intermediates for preparing various heterocyclic compounds.[4, 5] They exhibited a broad spectrum of potential pharmacological activities, such as antibacterial,[6] antifungal,[7] anticancer,[8] antimycobacterial,[9] and antidiabetic[10] activity. For example, nopinone-based thiosemicarbazone **A** displayed potent *in vitro* antitumor activity against three human cancer cell lines (MDA-MB-231, SMMC-7721 and Hela) with the IC_{50} values of 2.79 ± 0.38, 2.64 ± 0.17 and 3.64 ± 0.13 μM, respectively.[8] Thiosemicarbazone **B** exhibited antimycobacterial activity against *Mycobacterium tuberculosis* H37Ra with MIC value of 0.031 μg/mL and MBC (minimum bactericidal concentration) value of 0.063 μg/mL.[9] Compounds **C** were found to be the most active ALR2 inhibitors with IC50 values of 0.52 ± 0.04 μM (with R = Br) and 0.19 ± 0.03 μM (with R = F), respectively, and these compounds were more effective inhibitors as compared to the ALR2 (standard aldose reductase 2) inhibitor, sorbinil, which has an IC_{50} value of 3.14 ± 0.02 μM.[10]

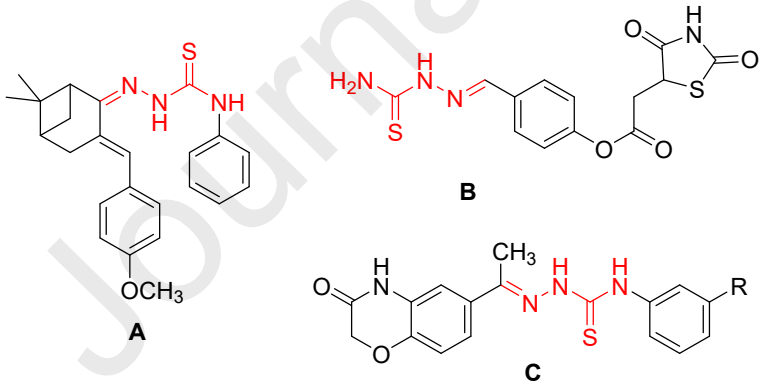


Figure 1. Various bioactive thiosemicarbazones.

The synthesis of substituted aromatic or heterocyclic aromatic aldehyde/ketone thiosemicarbazones with sugar moieties were reported.[1, 4, 11-13] The series of aldehyde 4-(β-D-

glucopyranosyl)thiosemicarbazones[12-14] were prepared from per-*O*-acetylated β-D-glucopyranosyl isothiocyanate and several of them showed micromolar inhibitions against typical Gram-positive (*Bacillus subtilis*, *Staphylococcus aureus*, *Staphylococcus epidermidis*), Gram-negative bacteria (*Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Salmonella typhimurium*) and fungi (*Aspergillus niger*, *Candida albicans*, *Aspergillus flavus*). These such compounds also had shown various biological properties, such as antibacterial,[13] antifungal,[13] antioxidant,[11] anti-dyslipidemic,[11] and anticancer activities.[15] Figure 2 displayed some examples of bioactive thiosemicarbazones bearing sugar moiety. Compound **D** of D-glucose significantly decreased cancer cell growth with IC_{50} value of 1.60 μM on breast cancer cell line MDA-MB-231 and IC_{50} value of 2.8 μM on prostate cancer cell line PC-3, which was lower than that of cells treated with the well-known anticancer drug 5-fluorouracil with IC_{50} = 4.75 ± 1.41 and 2.88 ± 1.39 μM, respectively).[15] Sugar-based thiosemicarbazone of peracetylated galactoside (**E**) was discovered to be a potent rhodesain inhibitor with IC_{50} = 1.2 ± 1.0 μM.[16] Thiosemicarbazone **F** with *para*-F group had inhibitory efficiency for rabbit muscle glycogen phosphorylase b with IC_{50} = 5.7 μM.[17] Compound **G** containing simultaneously monosaccharide and isatin moieties exhibited *in vitro* antibacterial and *in vivo* antioxidant activities. When R′ = Br, R = H the compound showed selective cytotoxic effects against some cancer (LU-1, HepG2, MCF7, P338, SW480, KB) cell lines and normal fibroblast cell line NIH/3T3. This compound had good inhibitory activity with MIC of 1.56 μM against *B. subtilis*, *S. aureus*, and *S. epidermidis*.[13]

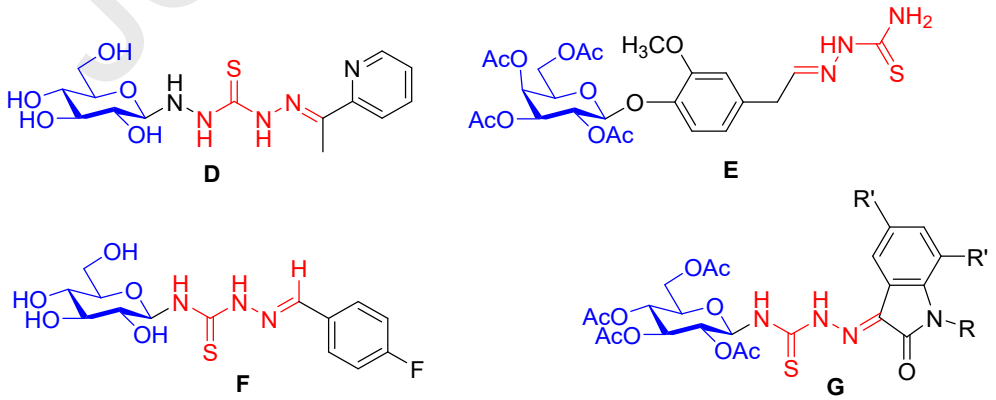


Figure 2. Some bioactive thiosemicarbazones bearing sugar moiety.

Coumarin (2*H*-chromen-2-one) was a compound of cinnamon. This heterocycle possessed remarkably pharmacological activities, such as antibacterial,[18] antioxidant,[19] anti-inflammatory,[20] anticancer[21] activity, and widely distributed in nature in many plants.[22, 23] Compound **H** and **I** (Fig. 3) were potential anti-tubercular agents with MIC of 0.09 μg/mL and 3.9 μmol/mL, respectively.[24, 25] Hydroxycoumarin **J** was used as selective MAO-B inhibitor with IC_{50} = 2.79 ± 0.19 μM.[26]

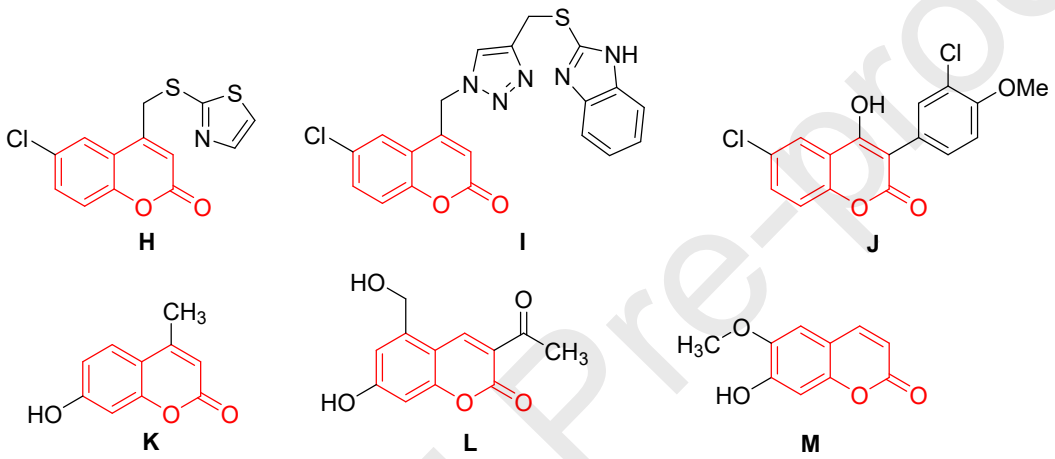
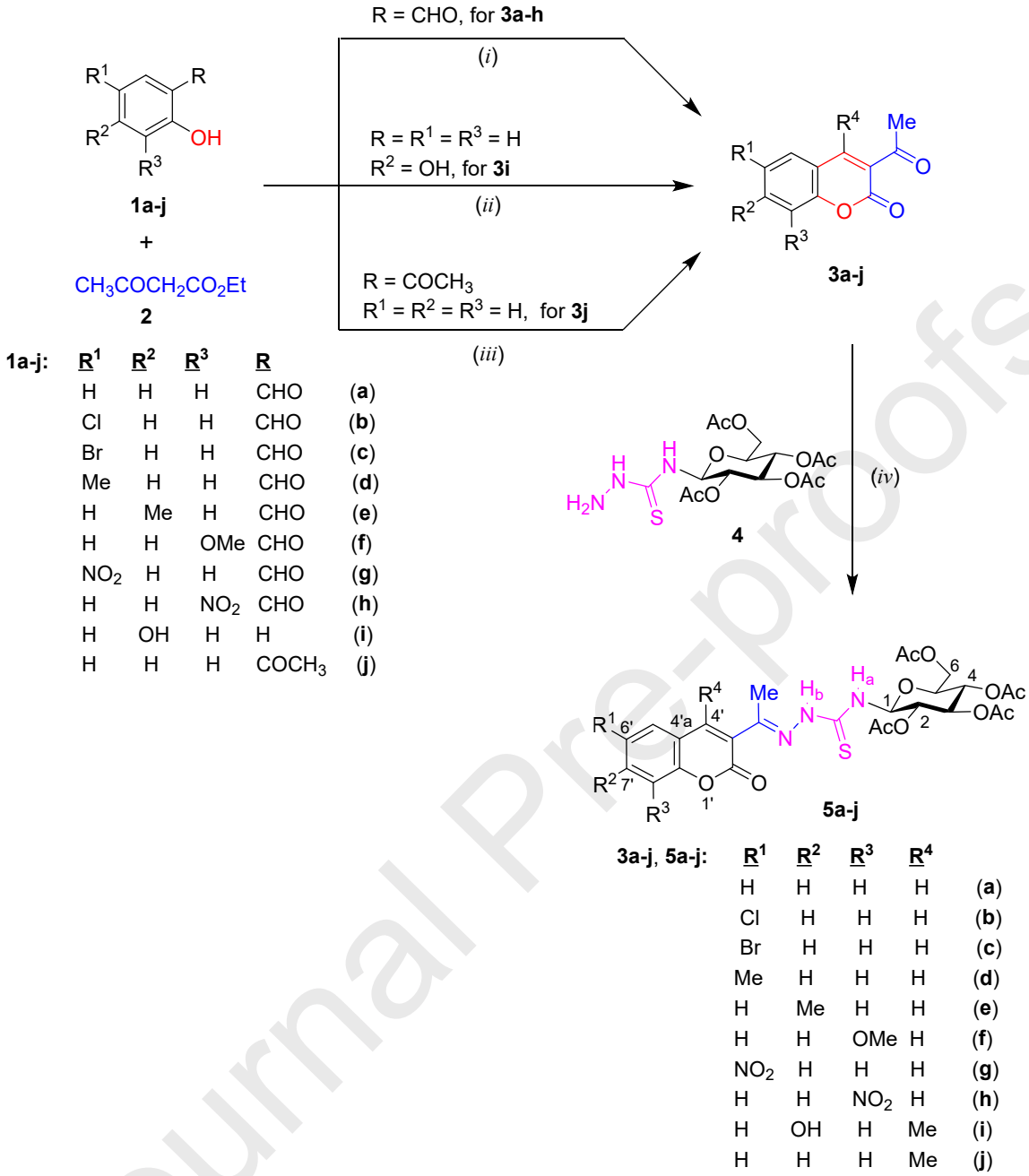


Figure 3. Some biologically active agents containing coumarin ring.

Some natural and synthetic coumarin-containing derivatives were used as biologically active agents. For example, hymecromone (4-methylumbelliferone or 4-methyl-7-hydroxycoumarin**, K**) was used as choleretic and antispasmodic agent.[27] Armillarisin A (3-acetyl-5-hydroxymethyl-7-hydroxycoumarin, **L**), extracted from the fungus *Armillariella tabescens* (Scop. ex Fr.) Sing.),[28] was used as an antibiotic agent. Scopoletin (6-methoxy-7-hydroxycoumarin, **M**), isolated from several plant species, exhibited antioxidant, hepatoprotective, anti-inflammatory and antifungal activity and inhibited *in vitro* against α-glucosidase enzyme.[29]

Based on the above-mentioned reviews on biological properties of coumarin- and sugar-containing compounds and continuing our previous studies on the synthesis and reactivity of *N*-(per-*O*-acetyl-

D-glycopyranosyl)thiosemicarbazides,[13, 30-32] we reported herein the synthesis and evaluation of biological activities of a series of substituted 3-acetylcoumarins *N*-(2,3,4,6-tetra-*O*-acetyl-β-D-glycopyranosyl)thiosemicarbazones having D-glucose moiety. The connection of monosaccharide moiety to coumarin ring through thiosemicarbazone linkage could induce novel activities. They were then evaluated by their antibacterial and antifungal activities against some Gram-positive bacteria (*S aureus*, *B subtilis*, *S epidermidis*), Gram-negative bacteria (*P aeruginosa*, *K pneumonia*, *S typhimurium*, and *E coli*), and some fungi (*A niger*, *C albicans*, *S cerevisiae*, and *A flavus*). Synthetic pathway for target thiosemicarbazones was displayed in Scheme 1. Substituted coumarins (**3a-j**) were prepared according to modified literature procedures by reaction of corresponding substituted salicylaldehydes (**1a-h**) with resorcinol (**1i**) or *o*-hydroxyacetophenone (**1j**), respectively (*see* Schema 1S-4S in Supplementary data in the online version of this article). Novel substituted 3′-acetylcoumarin *N*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)thiosemicarbazones (**5a-j**) were obtained by condensation of corresponding substituted 3-acetylcoumarins (**3a-j**) with *N*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)thiosemicarbazide (Scheme 1). Reactions were performed in absolute methanol in the presence of glacial acetic acid as catalyst using microwave-assisted heating method. We found that these thiosemicarbazides could be soluble in methanol at room temperature, and substituted 3-acetylcoumarins were dissolved with difficulty in this solvent with the same conditions, but they were dissoluble in this hot solvent. At the initial stage of reaction, the initial materials began dissolving when heated under the microwave-assisted conditions. Subsequently, the appearance of precipitate was used to identify the product formation.



1a-j:	R1	R2	R3	R	
	H	H	H	CHO	(**a**)
	Cl	H	H	CHO	(**b**)
	Br	H	H	CHO	(**c**)
	Me	H	H	CHO	(**d**)
	H	Me	H	CHO	(**e**)
	H	H	OMe	CHO	(**f**)
	NO_2	H	H	CHO	(**g**)
	H	H	NO_2	CHO	(**h**)
	H	OH	H	H	(**i**)
	H	H	H	$COCH_3$	(**j**)

3a-j, 5a-j:	R1	R2	R3	R4	
	H	H	H	H	(**a**)
	Cl	H	H	H	(**b**)
	Br	H	H	H	(**c**)
	Me	H	H	H	(**d**)
	H	Me	H	H	(**e**)
	H	H	OMe	H	(**f**)
	NO_2	H	H	H	(**g**)
	H	H	NO_2	H	(**h**)
	H	OH	H	Me	(**i**)
	H	H	H	Me	(**j**)

Scheme 1. Synthetic route for final substituted 3-acetylcoumarin tetra-*O*-acetyl-β-D-glucopyranosyl)thiosemicarbazones **5a-j**. Reaction conditions: (*i*) Piperidine as catalyst, **Method A**: MW Irradiation; **Method B**: Ultrasound Irradiation; **Method C**: Solvent-free Ultrasound Irradiation. (*ii*) a) 70% Sulfuric acid, 0 °C then 25 °C, 24 h; b) Glacial acetic acid, $POCl_3$, under reflux, 90 min. (*iii*) Ethyl acetoacetate, CH_3COONa, under microwave-assisted conditions, 90 min. (*iv*) Glacial acetic acid (cat), MeOH (solvent), 30−45 min under MW-assisted conditions at 400W.

The end of reaction was monitored by thin chromatography. Irradiation times were 30−45 min at microwave power of 400 W. Glacial acetic acid as catalyst was used in order to activate the carbonyl group of 3-acetylcoumarins and to facilitate nucleophilic attack of thiosemicarbazide, and protonation of hydroxyl group in the dehydration stage. Strong inorganic acids, such as HCl, H_2SO_4, $HClO_4$, did not favor for this reaction because so the nucleophilic amino group of thiosemicarbazide was protonated, which loose unshared electron pair. Weak organic acids, such as acetic acid, was sufficient to activate the carbonyl group without protonation of amino-thiosemicarbazide group. The formation of thiosemicarbazone products **5a-j** could be preliminary confirmed by IR spectroscopy and compared to the IR spectra of corresponding substituted 3-acetylcoumarins **3a-j** and thiosemicarbazide **4**. On IR spectrum of thiosemicarbazones, characteristic absorption bands appeared for both components, coumarin and per-acetylated D-glucose, and stretching band for imine group >C=N−, whereas specific bands for amino group in thiosemicarbazide and for carbonyl group in substituted 3-acetylcoumarin were not present. These evidences initially indicated that the reaction had occurred, and we expected thiosemicarbazone was formed. IR spectra showed characteristic absorptions in the range of 3354−3447 and 3328−3234 cm^{-1} belonged stretching vibrations of N−H groups of thiosemicarbazone linkage group (−NHCSNHN=C<). Chemical shifts that appeared at 11.15−9.28 (singlet) and 9.05−8.66 ppm (doublet) in ^1H NMR spectra confirmed the presence of N−H groups in molecular structure of thiosemicarbazone **5a-j**. The former chemical shift was assigned to proton H_b and the latter one specified to proton H_a; this proton had coupling interaction to proton H-1 on pyranose ring with coupling constant J = 9.25−8.50 Hz. These values of coupling constants agreed with *trans*-axial H–H disposition and β-anomeric configuration. Resonance of carbon atom C-1 on pyranose ring was easily recognized at δ= 81.5 ppm, which was the signal lying in the weakest field in resonance region of pyranose's carbon. The cause of this phenomenon was that the carbon atom C-1 was influenced by electronegative oxygen atom of pyranose ring and of the adjacent nitrogen atom of thiosemicarbazone linkage. ^{13}C NMR spectra of compound **5a-j** showed resonance signals at δ=181.6−180.0 ppm (carbon atom in C=S group),

δ=170.5−168.8 ppm (carbon atoms in C=O bond of acetyl groups). Carbon atoms in coumarin ring had chemical shifts at δ=155.4−110.1 ppm, whereas resonance signals at δ=82.0−61.1 ppm belonged carbon atoms on D-glucopyranose ring, and chemical shifts were at δ=21.5−21.1 ppm belonged methyl carbons in acetyl groups. Carbon atom in lactone carbonyl group on coumarin ring had chemical shift at δ=159.6−158.7 ppm.

All the synthesized thiosemicarbazones **5a-j** were screened for their *in vitro* antibacterial activity against three representative Gram-positive bacteria, which were *B. subtilis* (ATCC 11774), *S. aureus* (ATCC 11632), *S. epidermidis* (ATCC 12228), and four representative Gram-negative bacteria, which were *E. coli* (ATCC 25922), *P. aeruginosa* (ATCC 25923), *K. pneumoniae* (ATCC 4352), *S. typhimurium* (ATCC 14028). Some antibiotics were used as positive references for antibacterial activity, including ciprofloxacin and vancomycin. Vancomycin and ciprofloxacin are used to treat a number of bacterial infections, with the former used to treat serious, life-threatening infections by Gram-positive bacteria that are unresponsive to other antibiotics. The latter treated serious infections caused by Gram-negative bacteria, including *P. aeruginosa*. All the experiments were performed three times. Evaluated results for compounds **5a-j** were given in Table 1.

The results showed that almost all novel molecules exhibited antibacterial activity against the tested bacteria at their different concentrations. In general, it has been observed that almost all tested compounds showed mild to moderate activity against the tested bacteria in comparison with the MIC values of the reference compounds. MIC values of these reference drugs are as follows: Ciprofloxacin, 3.125 μM (for Gram-positive bacteria), 1.56 μM (for Gram-negative bacteria); Vancomycin, 0.78−3.125 μM (for Gram-positive bacteria). Some thiosemicarbazones **5a-j** had higher ability to inhibit to both Gram-positive bacteria (*B. subtilis*, *C. difficile, S. aureus*, and *S. epidermidis*) and Gram-negative bacteria (*E. Coli*, *K. pneumoniae*, *P. aeruginosa*, and *S. Typhimurium*), with MIC values of 1.56–3.125 μM. From obtained results of inhibitory activities in Table 1 for tested bacteria, some comments were discussed as follows. Almost all thiosemicarbazones **5a-j** series had remarkable inhibitory activity against Gram-positive bacteria *S.*

aureus, *S. epidermidis* (especially, compounds **5h** and **5i** with MIC = 0.78 and 1.56 μM), Gram-negative bacteria *E. coli* (especially, compound **5f** with 8-methoxy group, MIC = 1.56 μM) and *P. aeruginosa* (**5g**, MIC = 1.56 μM). Thiosemicarbazones **5a-j** exhibited similar inhibitory activities for both Gram-negative and Gram-positive bacteria. Almost all these compounds displayed significant inhibitory activity against all tested bacteria (with MIC were equal 3.125 μM or smaller), especially for *S. aureus* and *S. epidermidis*. In ranges of MIC = 0.78−3.125 μM, thiosemicarbazones **5a-j** series displayed better inhibitory activity against Gram-negative bacteria than against Gram-positive bacteria. In ranges of MIC = 0.78−3.125 μM. Compound **5i** and **5h** had strongest inhibitory activity against bacterium *S. aureus*. Both compounds had MIC values of 0.78 μM.

Based on the obtain results of the inhibitory activities in Table 1 for the tested bacteria, some SAR results were deduced as follows:

1. Thiosemicarbazone **5a** from unsubstituted 3-acetylcoumarin (**3a**) had unnoticeable inhibitory activity against all tested bacteria, with MIC values in the range from 50 μM to 400 μM, except against bacterium *S. epidermidis* with MIC = 12.5 μM
2. Electron-donating groups on benzene ring of coumarin (such as methyl, hydroxy, and methoxy): Compounds that had strong inhibitory activity with MIC values of 0.78−3.125 μM against Gram-positive bacteria were **5e** and **5i** (for *S. aureus*), **5f** and **5i** (for *S. epidermidis*). Compounds that exhibited notable inhibition against Gram-negative bacteria included **5f** (for *E. coli* and *K. pneumoniae*), **5i** (for *S. typhimurium*). The remaining compounds had unremarkably inhibitory activity for both tested bacterial types. Additionally, all of the tested compounds **5d**,**e**,**f**,**i**,**j** had unremarkably inhibitory activity against *B. subtilis*. The methyl group on position 4 led to decrease inhibition for almost all tested bacteria. The presence of 7-hydroxy group in compound **5i** strengthened inhibition against several tested bacteria, such as *S. aureus*, *S. epidermidis*, and *S. typhimurium*.
3. Electron-withdrawing groups on benzene ring of coumarin (including 6-chloro, 6-bromo, 6-nitro, and 8-nitro): In general, thiosemicarbazones **5b**,**c**,**g**,**h** had unremarkable inhibitory

activity against tested Gram-positive bacteria, except **5h** (for *S. aureus*) and **5c** (for *S. epidermidis*). For Gram-negative bacteria, compounds **5c** (bromo substituent) and **5g** (nitro substituent) had strong inhibition against *E. coli*, and *P. aeruginosa* with MICs of 1.56−3.125 μM. The presence of chloro substituent (compound **5b**) increased activity against only for *P. aeruginosa*.

We also evaluated the antifungal activities of the above thiosemicarbazones **5a-j** against some fungi, such as *Aspergillus niger* (ATCC 439), *Aspergillus flavus* (ATCC 204304), *Candida albicans* (ATCC 7754), and *Saccharomyces cerevisiae* (SH 20). Miconazole and fluconazole were used as references. Miconazole is mainly used externally for the treatment and prophylactic treatment of *Candida* infection in the oral cavity and the digestive tract. Fluconazole is a first-generation triazole antifungal medication. It has a spectrum of activity, which includes most *Candida* species but not *C. krusei* or *C. glabrata*, *Cryptococcus neoformans*, some dimorphic fungi, and dermatophytes. MIC values of miconazole were 1.56, 1.56, 3.125 and 3.125 μM for each fungus, respectively, and of fluconazole were 1.56, 0.78, 0.78 and 0.78 μM for each fungus, respectively. All the experiments were performed three times. The obtained results were given in Table 2. Some comments could deduce as follows. In range of MIC values of 0.78−3.125 μM, almost all the tested thiosemicarbazones **5a-j** were remarkably active against fungus *A. niger* and *C. albicans*, and were more resistant to *A. niger, A. flavus*, and *S. cerevisiae* than miconazole and fluconazole. Remarkably, compounds **5h** (against *C. albicans*) and **5i** (against *S. cerevisiae*) were more active (all MIC = 0.78 μM) than miconazole and comparably active with miconazole. Almost all compounds **5a-j** did not exhibit inhibitory activity against fungus *S. cerevisiae*, except compound **5i** (bearing 4-methyl and 7-hydroxy) that expressed the best inhibition with MIC = 0.78 μM that could be comparable with reference drug fluconazole (MIC = 0.78 μM). This compound had higher inhibition than miconazole (MIC = 3.125 μM) against *S. cerevisiae*.

Table 1. Antibacterial activity of thiosemicarbazones **5a-j**

Compounds	Micro-organisms/ MIC (μM)						
	Gram-positive bacteria			Gram-negative bacteria			
	B. subtilis	*S. aureus*	*S. epidermidis*	*E. coli*	*K. pneumoniae*	*P. aeruginosa*	*S. typhimurium*
5a	>100	N.E.	12.5 ± 0.65	50 ± 4.23	100 ± 12.35	50 ± 3.56	100 ± 12.35
5b	N.E.	>100	>100	25 ± 1.45	N.E.	3.125 ± 0.48	50 ± 3.75
5c	N.E.	100 ± 12.35	3.125 ± 0.32	3.125 ± 0.37	25 ± 1.45	3.125 ± 0.51	25 ± 1.12
5d	N.E.	12.5 ± 0.78	50 ± 3.51	50 ± 3.54	100 ± 12.35	12.5 ± 0.95	25 ± 1.18
5e	100 ± 11.45	1.56 ± 0.14	N.E.	25 ± 1.15	25 ± 1.14	25 ± 1.15	N.E.
5f	50 ± 3.43	50 ± 3.39	3.125 ± 0.36	1.56 ± 0.75	1.56 ± 0.71	N.E.	N.E.
5g	>100	12.5 ± 0.86	12.5 ± 0.75	3.125 ± 0.41	50 ± 3.46	1.56 ± 0.21	100 ± 12.35
5h	12.5 ± 0.79	0.78 ± 0.08	12.5 ± 0.72	25 ± 1.15	12.5 ± 0.71	N.E.	>100
5i	100 ± 11.35	0.78 ± 0.07	1.56 ± 0.15	100 ± 12.35	100 ± 12.35	12.5 ± 0.69	3.125 ± 0.32
5j	>100	25 ± 1.21	100 ± 12.35	N.E.	50 ± 4.35	N.E.	N.E.
Ciprofloxacin	3.125 ± 0.34	3.125 ± 0.36	3.125 ± 0.35	1.56 ± 0.23	1.56 ± 0.15	1.56 ± 0.16	1.56 ± 0.15
Vancomycin	1.56 ± 0.12	3.125 ± 0.25	0.78 ± 0.06	–	–	–	–

Note: N.E. = not evaluated

Table 2. Antifungal activity of thiosemicarbazones **5a-j**

Compounds	Fungi/ MIC (μM)			
	A. niger	*A. flavus*	*C. albicans*	*S. cerevisiae*
5a	>100	25 ± 1.65	100 ± 15.09	50 ± 3.54
5b	100 ± 12.12	12.5 ± 1.10	1.56 ± 0.06	50 ± 3.35
5c	N.E.	6.25 ± 0.78	50 ± 3.34	25 ± 1.34
5d	1.56 ± 0.27	N.E.	3.125 ± 0.89	25 ± 1.65
5e	25 ± 1.64	>100	3.125 ± 0.96	>100
5f	6.25 ± 0.84	6.25 ± 0.82	25 ± 1.26	50 ± 3.46
5g	12.5 ± 0.89	100 ± 12.17	25 ± 1.52	25 ± 1.54
5h	3.125 ± 0.34	12.5 ± 1.04	0.78 ± 0.06	12.5 ± 0.96
5i	3.125 ± 0.23	1.56 ± 0.34	>100	0.78 ± 0.09
5j	12.5 ± 0.97	25 ± 1.54	12.5 ± 0.89	12.5 ± 0.89
Miconazole	1.56 ± 0.09	1.56 ± 0.21	3.125 ± 0.24	3.125 ± 0.22
Fluconazole	1.56 ± 0.12	0.78 ± 0.02	0.78 ± 0.03	0.78 ± 0.02

Some SAR results were deduced as follows, based on obtained results of inhibitory activities for all tested fungi:

1. Thiosemicarbazones from unsubstituted 3-acetylcoumarin (**5a**) had no activity against all tested fungi.
2. The electron-donating groups on benzene ring of coumarin, such as methyl, hydroxy, and methoxy: In general, these groups created strong to medium inhibitory activity against tested fungi in thiosemicarbazones **5d**,**e**,**f**,**i**,**j** with MIC = 0.78−12.5 μM when compared with thiosemicarbazone of unsubstituted 3-acetylcoumarin. Compound **5i** had remarkable inhibitory activity against three fungi, *A. niger*, *A. flavus* and *S. cerevisiae*.

3. The electron-withdrawing groups on benzene ring of coumarin (such as 6-chloro, 6-bromo, 6-nitro, and 8-nitro): These substituents also decreased the inhibitory activity against *A. niger* and *S. cerevisiae* of thiosemicarbazones **5b**,**c**,**g**,**h**, but greatly increased the inhibitory activity against *A. flavus* (**5g,h**) and *C. albicans* (**5b,h**). Compound **5h** exhibited strong activity against *A. niger* and *C. albicans*.

In summary, microwave-assisted heating method was an efficient and convenient method for synthesis of *N*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)thiosemicarbazones of substituted 3-acetylcoumarins. All synthesized thiosemicarbazones except for **5a** displayed significant inhibition in vitro against bacteria bacteria (*B. subtilis*, *S. aureus*, *S. epidermidis*, *E. coli*, *P. aeruginosa*, *K. pneumoniae*, *S. typhimurium*) and fungi (*A. niger*, *C. albicans*, *S. cerevisiae*, and *A. flavus*).

Appendix A. Supplementary data

Supplementary data (experimental section, IR, ^{1}H NMR, ^{13}C NMR, mass spectral data and elemental analysis for the synthesized compounds) can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl...

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Highlights

- Ten new thiosemicarbazones of substituted 3-acetylcoumarins with D-glucose moiety were synthesized in 45−68% yields.
- Several thiosemicarbazones were active against Gram-(+) and Gram-(−) bacteria with MICs of 1.56−3.125 μM.
- Some thiosemicarbazones had activity against fungi with MICs of 1.56−3.125 μM.

- Compounds **5h** and **5i** exhibited excellent activity against *S. aureus* with MIC of 0.78 μM.
- Compounds exhibited excellent activity with MIC of 0.78 μM, including **5h** (for *C. albicans*), and **5i** (for *S. cerevisiae*).