

Synthesis and antibacterial activity of 1-[1,2,4-triazol-3-yl] and 1-[1,3,4-thiadiazol-2-yl]-3-methylthio-6,7-dihydrobenzo[c]thiophen-4(5H)ones

Sara Tehranchian,^a Tahmineh Akbarzadeh,^a Mohammad Reza Fazeli,^b
Hossein Jamalifar^b and Abbas Shafiee^{a,*}

^aDepartment of Medicinal Chemistry, Faculty of Pharmacy and Pharmaceutical Sciences Research Center, Tehran University of Medical Sciences, Tehran, Iran

^bDepartment of Biotechnology, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran

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Abstract—A series of 1-[1,2,4-triazol-3-yl] and 1-[1,3,4-thiadiazol-2-yl]-3-methylthio-6,7-dihydrobenzo[c]thiophen-4(5H)ones were synthesized and tested to demonstrate in vitro antimicrobial activity. Some of these compounds exhibited a good activity against *Staphylococcus aureus*, *S. epidermidis* and *Bacillus subtilis*.

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A dramatic increase in antibiotic resistance specially among Gram positive bacteria triggered a clear need for the discovery of new antimicrobials rather than analogs of the existing ones.¹ Traditionally, small molecules have been a reliable source for discovering novel biologically active compounds. Here, we focused mainly on benzo[c]thiophene as our basic structure and investigation of its combination with other heterocycles. Studies on thiophene-like compounds have served as a feasible field of research in the perusal for biologically active compounds.^{2–5} In this regard structures similar to benzo[c]thiophene had interesting antibacterial and antifungal properties. The importance of sulfur in fused ring system, as well as the significance of the ketone function group in 4-position has been determined,⁶ hence we were to define the effect of 1-substitution in benzo[c]thiophene ring on the antibacterial and antifungal effects of these compounds.

Substituted 1,2,4-triazoles and 1,3,4-thiadiazoles are associated with immense biological activities.^{7–10} Antibacterial activity data of these structures showed their

considerable activity against Gram negative and Gram positive bacteria as well as some strains of fungi.^{11–14}

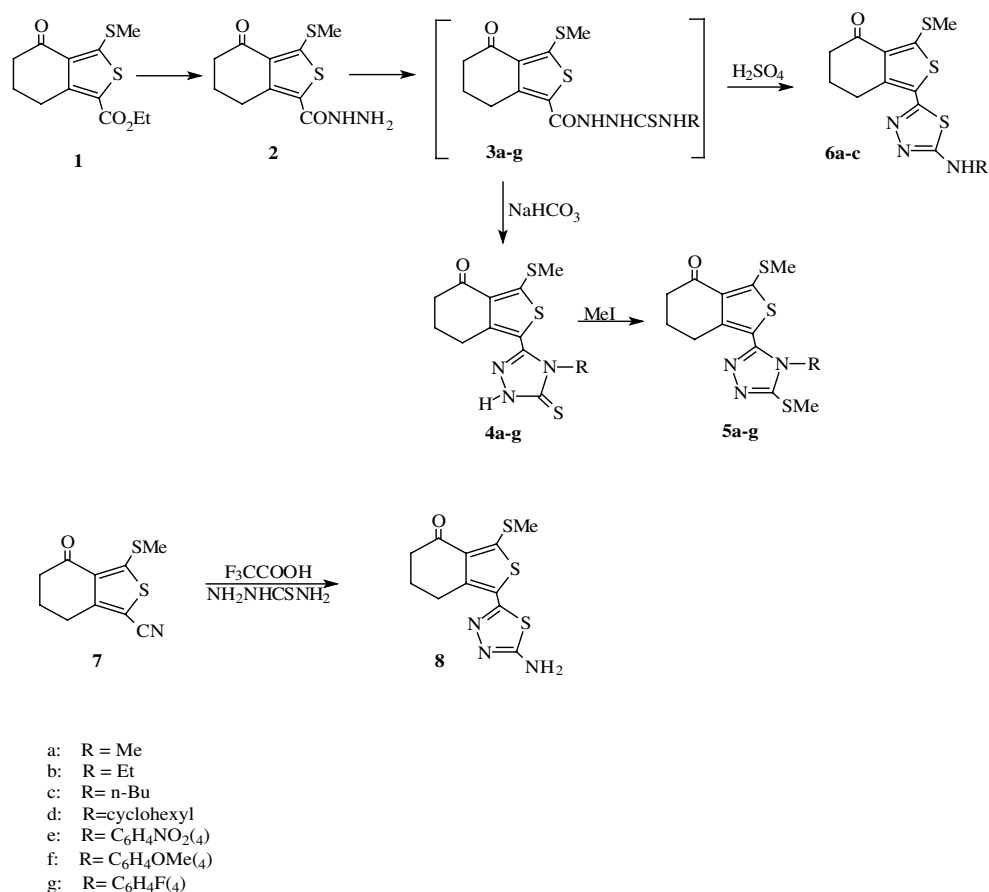
By considering these active heterocycles with potential antimicrobial effects, a new series of 1-[1,2,4-triazol-3-yl] and 1-[1,3,4-thiadiazol-2-yl]-6,7-dihydrobenzo[c]thiophen-4(5H)ones were synthesized and their antimicrobial properties was evaluated.

The synthesis of 1,2,4-triazole and 1,3,4-thiadiazole derivatives is outlined in Scheme 1. Compound **1** was prepared by a known procedure.¹⁵ Reaction of corresponding ester group of compound **1** with hydrazine hydrate gave 3-methylthio-6,7-dihydrobenzo[c]thiophen-4(5H)ones-1-carboxylic acid hydrazide (**2**), which was used as the key intermediate for the preparation of final compounds. Treatment of compound **2** with different isothiocyanates in alkaline aqueous phase gave corresponding thiosemicarbazides **3a–g**. Cyclizations of compounds **3a–g** were accomplished in aqueous media to give the corresponding 1,2,4-triazole-5-thiones **4a–g**. Reaction of compound **4** with methyl iodide in alkaline media under the ultrasonic condition produced S-methyl derivatives **5a–g**.

Cyclization of compounds **3a–g** with concd sulfuric acid afforded compounds **6a–e**. Refluxing of 1-cyano-3-methylthio-6,7-dihydrobenzo[c]thiophen-4(5H)one (**7**)

Keywords: 1,2,4-Triazole; 1,3,4-Thiadiazole; 6,7-Dihydrobenzo[c]thiophen-4(5H)ones; Antibacterial activity.

* Corresponding author. Tel.: +98 21 6406757; fax: +98 21 6461178; e-mail: ashafiee@ams.ac.ir



Scheme 1.

Table 1. Antimicrobial activities of compounds 4–6 and 8 (zone of inhibition in mm)

Compound	<i>S. aureus</i>	<i>S. epidermidis</i>	<i>B. cereus</i>	<i>B. subtilis</i>	<i>P. aeruginosa</i>	<i>E. coli</i>	<i>C. albicans</i>	<i>A. niger</i>
4a	—	—	—	—	—	—	—	—
4b	—	—	—	—	—	—	—	—
4c	17	26	—	14	—	—	—	—
4d	—	—	—	—	—	—	—	—
4e	18	25	—	23	14	—	—	—
4f	—	—	—	11	—	—	—	—
4g	—	—	—	—	—	—	—	—
5a	—	—	—	—	—	—	—	—
5b	—	—	—	—	—	—	—	—
5c	17	26	16	16	—	—	—	—
5d	—	—	—	—	—	—	—	—
5e	18	24	12	21	14	—	—	—
5f	—	—	—	—	—	—	—	—
5g	—	—	—	—	—	—	—	—
6a	—	—	—	28	—	—	12	11
6b	—	—	—	20	—	—	13	8
6c	—	—	—	22	—	—	11	9
6d	—	—	—	—	—	—	—	12
6e	—	—	—	33	—	—	14	10
8	—	—	—	—	—	—	—	—
Genta. ^a	23	20	28	30	27	23	NT ^d	NT
Nitrof. ^b	21	—	20	18	21	20	NT	NT
Amph. B ^c	NT	NT	NT	NT	NT	NT	22	22

^a Gentamycin.^b Nitrofurantoin.^c Amphotricin B.^d Not tested.

Table 2. Minimum inhibitory concentration (MIC, $\mu\text{g/mL}$) of selected compounds against certain bacterial strains^a

Compound	<i>S. aureus</i>	<i>S. epidermidis</i>	<i>B. subtilis</i>
4c	16	1	NT ^b
4e	2	4	NT
5c	32	1	NT
5e	4	8	NT
6a	NT	NT	2
6b	NT	NT	2
6c	NT	NT	4
6e	NT	NT	1
Nitrofurantoin	2	NT	1
Gentamycin	1	1	NT

^a Disc diffusion method used to determine the MICs.¹⁷^b Not tested.

in trifluoroacetic acid with thiosemicarbazide resulted in the formation of compound **8**.

Compounds **4–6** and **8** were screened for their antimicrobial activity by using cup–plate agar method at a concentration of 300 $\mu\text{g/disc}$ against *Staphylococcus aureus* ATCC 29737, *S. epidermidis* ATCC 12229, *Bacillus cereus* ATCC 1274, *B. subtilis* ATCC 12711, *Pseudomonas aeruginosa* ATCC 9027, *Escherichia coli* ATCC 8739, *Candida albicans* ATCC 10231, *Aspergillus niger* ATCC 16404 (Table 1).¹⁶ The preliminary results of antimicrobial activities indicated that some of the compounds exhibited a moderate to good activity against Gram positive strains, however none of the compounds exerted a significant effect against the Gram negative strains or fungi. Presence of bulky group of *n*-butyl or *p*-nitrophenyl at 4-position of 1,2,4-triazole in compounds **4** and **5** produced active compounds against Gram positive strains. Although, *S*-methylation of 1,2,4-triazole-3-thiones **4c,e** resulted in broader activity of the obtained compounds **5c,e** against more bacterial strains but it did not cause to make more potent derivatives. 5-Amino-1,3,4-thiadiazole **8** showed no antimicrobial activity.

In addition substitution of amino group of **8** resulted to compounds **6a–e** with antifungal activity and high potency against *B. subtilis*. Determination of the minimum inhibitory concentration (MIC) values of the potent derivatives against certain bacterial strains (Table 2) indicates that compound **4e** was the most active derivative against *S. aureus* (MIC = 2 $\mu\text{g/mL}$), its activity was equal to nitrofurantoin, compounds **4c** and **5c** were the most potent compounds against *S. epidermidis* and their activities were equal to gentamycin (MIC = 1 $\mu\text{g/mL}$).

Derivatives **6a**, **6b** and **6e** showed significant activity against *B. subtilis* (MIC = 1–2 $\mu\text{g/mL}$) and compound **6e** had the same potency as nitrofurantoin against *B. subtilis*.

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