Available online at www.sciencedirect.com
SCIENCE DIRECT®
Bioorganic & Medicinal Chemistry Letters 15 (2005) 1023–1025
Bioorganic & Medicinal Chemistry Letters

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(5*H*)ones

Sara Tehranchian,[a] Tahmineh Akbarzadeh,[a] Mohammad Reza Fazeli,[b] Hossein Jamalifar[b] and Abbas Shafiee[a,*]

[a]*Department of Medicinal Chemistry, Faculty of Pharmacy and Pharmaceutical Sciences Research Center, Tehran University of Medical Sciences, Tehran, Iran*
[b]*Department of Biotechnology, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran*

Received 20 September 2004; revised 12 December 2004; accepted 14 December 2004
Available online 12 January 2005

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(5*H*)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*.

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]

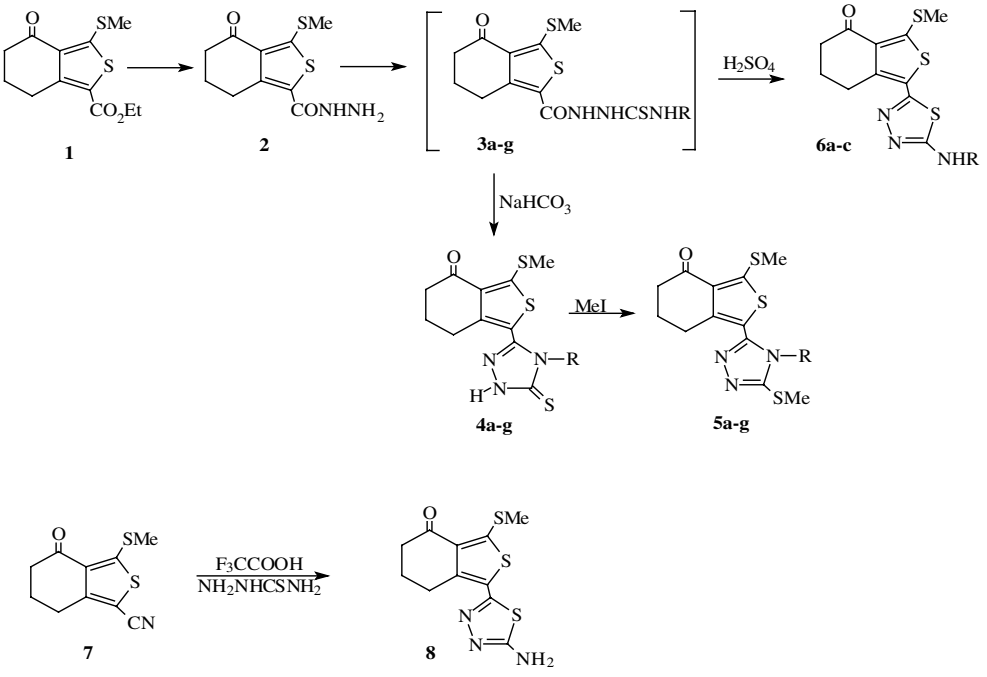
By considering these active heterocycles with potential antimicrobial effects, a new series of 1-[1,2,4-triazol-3-yl] and 1-[1,3,4-thiadiazol-2-yl]-6,7-dihydrobenzo[*c*]thiophen-4(5*H*)ones were synthesized and their antimicrobial properties was evaluated.

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(5*H*)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(5*H*)one (**7**)

Keywords: 1,2,4-Triazole; 1,3,4-Thiadiazole; 6,7-Dihydrobenzo[*c*]thiophen-4(5*H*)ones; Antibacterial activity.
* Corresponding author. Tel.: +98 21 6406757; fax: +98 21 6461178; e-mail: ashafiee@ams.ac.ir

0960-894X/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2004.12.039



a: R = Me
b: R = Et
c: R= n-Bu
d: R=cyclohexyl
e: R= $C_6H_4NO_2(_4)$
f: R= $C_6H_4OMe(_4)$
g: R= $C_6H_4F(_4)$

Scheme 1.

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

Compound	*S. aureus*	*S. epidermidis*	*B. cereus*	*B. subtilis*	*P. aeruginosa*	*E. coli*	*C. albicans*	*A. niger*
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, μg/mL) of selected compounds against certain bacterial strains[a]

Compound	*S. aureus*	*S. epidermidis*	*B. subtilis*
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 trifluroacetic 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 μg/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, *Aspergilus 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 μg/mL), its activity was equal to nitrofurantion, compounds **4c** and **5c** were the most potent compounds against *S. epidermidis* and their activities were equal to gentamycin (MIC = 1 μg/mL). Derivatives **6a**, **6b** and **6e** showed significant activity against *B. subtilis* (MIC = 1–2 μg/mL) and compound **6e** had the same potency as nitrofurantoin against *B. subtilis*.

Acknowledgements

This work was supported by grants from the research council of Tehran University of Medical Sciences and Iran Chapter of TWAS.

References and notes

1. Service, R. F. *Science* **1995**, *270*, 724.
2. Van Rhee, A. M.; Diddiqi, S. M.; Melman, N.; Shi, D.; Padgett, W. L.; Daly, J. W.; Jacobson, K. A. *J. Med. Chem.* **1996**, *39*, 398.
3. Yasuma, T.; Oda, T.; Hazama, M.; Taketomi, S. WO 98 09,958, 1998; *Chem. Abstr*. **1998**, *128*, 217366v.
4. Mcmahon, G.; Hirth, K. P.; Tang, P. C. WO 96 40, 113, 1995; *Chem. Abstr*. **1997**, *126*, 126918u.
5. Broughton, H.; Chambers, M. S.; Hobbs, S. Ch.; Macleod, A. M.; Reeve, A. J. WO 98 18,792, 1998; *Chem. Abstr*. **1998**, *129*, 4573u.
6. Cagniant, P.; Kirsch, G.; Wierzbicki, M.; Lepage, F.; Cagniant, D., et al. *Eur. J. Med. Chem. Chim. Ther*. **1980**, *15*, 5439.
7. Kane, J. M.; Staeger, M. A.; Dalton, C. R.; Miller, F. P.; Dudley, M. W.; Ogden, A. M.; Kehne, J. H.; Ketteler, H. J.; McCloskey, T. C.; Senyah, Y. *J. Med. Chem.* **1994**, *37*, 125.
8. Mullican, M. D.; Wilson, M. W.; Connor, D. T.; Kostlan, C. R.; Schrier, D. J.; Dyer, R. D. *J. Med. Chem.* **1993**, *36*, 1090.
9. Boschelli, D. H.; Connor, D. T.; Bornemeier, D. A.; Dyer, R. D.; Kennedy, J. A.; Kuipers, P. J.; Okonkwo, G. C.; Schrier, D. J.; Wright, C. D. *J. Med. Chem.* **1993**, *36*, 1802.
10. Kane, J. M.; Dudley, M. W.; Sorensen, S. M.; Miller, F. P. *J. Med. Chem.* **1988**, *31*, 1253.
11. Hui, X.; Zhang, L.; Zhang, Z. *Indian J. Chem.* **1999**, *38B*, 1066.
12. Rollas, S.; Karakus, S.; Durgun, B. B.; Kiraz, M.; Erdeniz, H. *Farmaco* **1996**, *51*, 811.
13. Vashi, B. S.; Mehta, D. S.; Shah, V. H. *Indian J. Chem.* **1996**, *35B*, 111.
14. Ate, O.; Kocabalkanli, A.; Utuk-Sani, G.; Ekinci, A. C.; Vidin, A. *Drug Res.* **1997**, *47*, 1134.
15. Prim, D.; Kirsch, G. *Synth. Commun.* **1995**, *25*, 2449.
16. Barry, A. L. *The Antimicrobial Susceptibility Test: Practical and Practices*; Illus lea and Febiger: Philadelphia, 1976; p 180; *Biol. Abstr.* **1977**, *64*, 25183.
17. Chand, S.; Lusunzi, I.; Veal, D. A.; Williams, L. R. *J. Antibiot.* **1994**, *11*(47), 1295.