Bioorganic & Medicinal Chemistry Letters 23 (2013) 4358–4361

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Synthesis and biological evaluation of rhodanine derivatives bearing a quinoline moiety as potent antimicrobial agents

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ARTICLE INFO

Article history:
Received 5 March 2013
Revised 8 May 2013
Accepted 24 May 2013
Available online 4 June 2013

Keywords:
Rhodanine
Quinoline
Antibacterial activity
Methicillin-resistant *Staphylococcus aureus*
Quinolone-resistant *Staphylococcus aureus*

ABSTRACT

Three series of rhodanine derivatives bearing a quinoline moiety (**6a**–**h**, **7a**–**g**, and **8a**–**e**) have been synthesized, characterized, and evaluated as antibacterial agents. The majority of these compounds showed potent antibacterial activities against several different strains of Gram-positive bacteria, including multidrug-resistant clinical isolates. Of the compounds tested, **6g** and **8c** were identified as the most effective with minimum inhibitory concentration (MIC) values of 1 μg/mL against multidrug-resistant Gram-positive organisms, including methicillin-resistant and quinolone-resistant *Staphylococcus aureus* (MRSA and QRSA, respectively). None of the compounds exhibited any activity against the Gram-negative bacteria *Escherichia coli* 1356 at 64 μg/mL. The cytotoxic activity assay showed that compounds **6g**, **7g** and **8e** exhibited in vitro antibacterial activity at non-cytotoxic concentrations. Thus, these studies suggest that rhodanine derivatives bearing a quinoline moiety are interesting scaffolds for the development of novel Gram-positive antibacterial agents.

The treatment of bacterial infections capable of causing serious and widespread diseases still remains a significant and worldwide problem because of problems associated with the emergence of new infectious diseases and the increased number of pathogenic microorganisms that are developing resistance to the existing drugs.[1–5] So development of novel antimicrobical drugs with different mechanisms of action to the currently available antibacterial drugs is still in demand.[6,7]

A significant number of compounds bearing a quinoline moiety have been reported in the literature with a variety of different pharmacological activities, including antimicrobial,[8–10] antituberculosis,[11] anticancer,[12] anti-HIV,[13] antimalarial,[14] and anti-inflammatory activities.[15] Furthermore, rhodanine-based molecules have been reported to be associated with antibiotic activity.[16] In our previous work, we found that several rhodanine derivatives bearing chalcone,[17] 1,3-diarylpyrazole,[6] (2-oxo-2-phenylethoxy)benzylidene,[18] and (benzyloxy)benzylidene[19] moieties showed moderate to strong activities against several Gram-positive bacterial strains, including multidrug-resistant clinical isolates. Although, to date, there have been no reports in the literature providing a clear understanding of the mechanisms of action associated with these derivatives, the focus of the present work was to introduce a (quinolin-3-yl)methylidene moiety at the 5-positon of the rhodanine ring instead of the benzylidene moiety, with the aim of modulating the hydrophobicity of the resulting molecule and affecting its enzyme binding affinity. Moreover, the effects of different substituents at the 3-position of the rhodanine ring were simultaneously investigated using aromatic or aliphatic groups to observe their effects on the inhibitory activities of the compounds. Thus, as a part of our ongoing studies towards the development of novel antibacterial agents, herein we report the design, synthesis, and antimicrobial evaluation of three novel series of rhodanine derivatives containing a quinoline moiety as efficient antimicrobial agents.

Nineteen new rhodanine derivatives were synthesized according to the synthetic route depicted in Scheme 1. Williamson condensation reactions between 6-hydroxy-3,4-dihydroquinolin-2(1*H*)-one (**2**) and a variety of different substituted chloromethylbenzene compounds (**1a**–**1h**) afforded the corresponding 6-(substitutedbenzyloxy)-3,4-dihydroquinolin-2(1*H*)-ones (**3a**–**3h**), which were subsequently reacted under Vilsmeier–Haack conditions to give the corresponding 6-(substitutedbenzyloxy)-2-chloroquinoline-3-carbaldehydes (**4a**–**4h**). The rhodanine intermediates (**5a**–**c**) were prepared according to a method previously described in the literature.[17] The target compounds **6a**–**h**, **7a**–**g**, and **8a**–**e** were synthesized by the Knoevenagel condensation reactions of **4** with compounds **5a**–**5c** in ethanol in the presence of glacial acid and piperidine. The structures of the synthesized compounds were confirmed by Fourier transform infra-red (FTIR), ^{1}H and ^{13}C NMR, and mass spectroscopy.[20]

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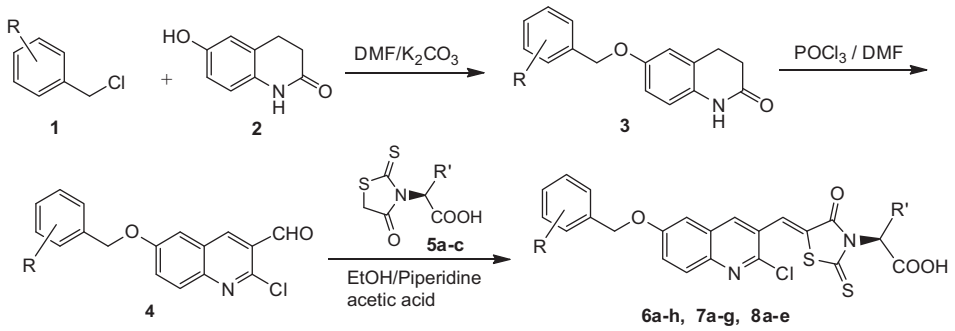
http://dx.doi.org/10.1016/j.bmcl.2013.05.082



R= 6a: 2-Cl, b: 3-Cl, c: 4-Cl, d: 2-F, e: 3-F, f: 4-F, g: 4-CH_3, h: 2-Br.
7a: 2-Cl, b: 3-Cl, c: 4-Cl, d: 2-F, e: 3-F, f: 4-F, g: 4-CH_3.
8a: 2-Cl, b: 3-Cl, c: 4-Cl, d: 4-F, e: 4-CH_3.

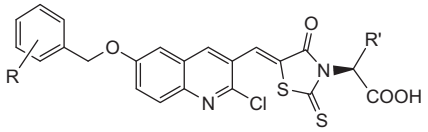
R'= 5a: -$CH_2C_6H_5$
R'= 5b: -$CH(CH_3)CH_2CH_3$
R'= 5c: -$CH_2CH(CH_3)_2$

Scheme 1. Synthetic route for the construction of target compounds **6a**–**6h**, **7a**–**7g**, and **8a**–**8e**.

The in vitro antimicrobial activities of the newly synthesized compounds were evaluated against eight different bacterial strains, including multidrug-resistant clinical isolates, using a 96-well microtiter plate format and a broth microdilution method to obtain their minimum inhibitory concentration (MIC) values. Norfloxacin, oxacillin, gatifloxacin, and moxifloxacin were used as positive controls against the different bacterial strains.

The newly synthesized compounds were also screened for their antibacterial activity against several different Gram-positive organisms, including *Staphylococcus aureus* RN4220, *S. aureus* KCTC 503, and *S. aureus* KCTC 209, as well as the Gram-negative organism, *Escherichia coli* 1356. As shown in Table 1,[21] the majority of the compounds showed potent in vitro antibacterial activities against the three different types of Gram-positive bacteria, with MIC values in the range of 1-64 μg/mL. Furthermore, compounds **7f**, **8a**, **8c**, and **8e** were particularly active against the Gram-positive strain *S. aureus* RN4220 with an MIC value of 1 μg/mL in both cases, slightly less active than gatifloxacin and moxifloxacin (MIC = 1 μg/mL). Most of the test compounds presented moderate inhibitory activities against *S. aureus* KCTC 503 (MIC = 4–8 μg/mL). Among the desired compounds, **6c**, **6e**, **6f**, **7b**–**d**, **7f**, **7g**, and **8c** showed potent inhibitory activities against *S. aureus* KCTC 503 (MIC = 4 μg/mL), which was comparable to gatifloxacin (MIC = 4 μg/mL) but less active than moxifloxacin (MIC = 2 μg/

Table 1
Inhibitory activities (MIC, μg/mL) of compounds **6a**–**6h**, **7a**–**7g**, and **8a**–**8e** against bacteria



Compound	R	R′	Gram-positive strains *S. aureus*			Gram-negative strains *E. coli*
			4220	209	503	1356
6a	2-Cl	$-CH_2C_6H_5$	4	64	8	>64
6b	3-Cl	$-CH_2C_6H_5$	2	64	8	>64
6c	4-Cl	$-CH_2C_6H_5$	4	8	4	>64
6d	2-F	$-CH_2C_6H_5$	4	64	8	>64
6e	3-F	$-CH_2C_6H_5$	4	64	4	>64
6f	4-F	$-CH_2C_6H_5$	4	32	4	>64
6g	4-CH_3	$-CH_2C_6H_5$	2	8	8	>64
6h	2-Br	$-CH_2C_6H_5$	4	8	8	>64
7a	2-Cl	$-CH(CH_3)CH_2CH_3$	4	64	8	>64
7b	3-Cl	$-CH(CH_3)CH_2CH_3$	2	>64	4	>64
7c	4-Cl	$-CH(CH_3)CH_2CH_3$	2	8	4	>64
7d	2-F	$-CH(CH_3)CH_2CH_3$	2	32	4	>64
7e	3-F	$-CH(CH_3)CH_2CH_3$	2	32	8	>64
7f	4-F	$-CH(CH_3)CH_2CH_3$	1	2	4	>64
7g	4-CH_3	$-CH(CH_3)CH_2CH_3$	2	4	4	>64
8a	2-Cl	$-CH_2CH(CH_3)_2$	1	4	8	>64
8b	3-Cl	$-CH_2CH(CH_3)_2$	2	4	64	>64
8c	4-Cl	$-CH_2CH(CH_3)_2$	1	4	4	>64
8d	4-F	$-CH_2CH(CH_3)_2$	2	8	8	>64
8e	4-CH_3	$-CH_2CH(CH_3)_2$	1	8	8	>64
Norfloxacin			2	2	2	16
Oxacillin			1	1	1	>64
Gatifloxacin			0.25	2	4	16
Moxifloxacin			0.25	2	2	>64

S. aureus RN 4220, *Staphylococcus aureus* RN 4220; *S. aureus* 503, *Staphylococcus aureus* 503; *S. aureus* 209, *Staphylococcus aureus* 209; *E. coli* 1356, *Escherichia coli* CCARM 1356.