Efficient Synthesis of 1-Thiomansonones with Anti-MRSA Activity

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Abstract In this study, we developed an efficient and general synthetic strategy for thiaphenalene, a sulfur-containing polyaromatic heterocycle, and applied for the synthesis of 1-thio derivatives of mansonone I and F, natural 1-oxaphenalene orthoquinones. The pivotal steps for the construction of thiophenalene skeleton include formation of arylsulfide by Newman–Kwart rearrangement of thiocarbamate or palladium-catalyzed cross-coupling, and pericyclic ring closure. Three bioisostERICally modified orthoquinones were synthesized and were evaluated for anti-MRSA activity.

Key words Newman–Kwart, mansonones, palladium, orthoquinones, thiaphenalene, MRSA

Methicillin-resistant Staphylococcus aureus (MRSA) is one of the most important pathogenic bacteria. Rapid acquisition of multidrug resistance to various antibiotics and severe nosocomial infections caused by MRSA have become major problems in the clinic. Despite recent introduction of several new classes of antibiotics, including linezolid, quinupristin/dalfopristin, and new glycopeptide antibiotics, drug resistance, potency, and toxicity remain unsolved problems. Therefore, discovery of novel anti-MRSA agents persists as a focus of medicinal chemistry efforts.

One of the continuing research interests in our laboratory is the synthesis and evaluation of structurally novel small molecules with potent anti-MRSA activity, which could overcome multidrug resistance. We previously reported the isolation and synthesis of mansonone F, found in root bark of Ulmus davidiana, a Korean medicinal plant (Figure 1).5,6 Mansonone F is a phytoalexin and structurally belongs to naturally occurring sesquiterpenoid orthoquinones, with many congeners reported from different plants.6,7–9 Mansonones have a unique oxaphenalene skeleton and, due to orthoquinone moiety and high degree of conjugation, exhibit distinct colors in solution, e.g., deep purple color of CHCl₃ solution of mansonone F. Most importantly, mansonones show potent anti-MRSA activity comparable with vancomycin, a drug of choice for treating MRSA infections.10,11

Systematic structure–activity relationship study of mansonone F indicated that any change of the tricyclic oxaphenalene skeleton and the orthoquinone moiety markedly reduced anti-MRSA activity, implying that these features are essential pharmacophores for antibacterial activity. Maintaining the tricyclic orthoquinone core structure, subsequent SAR study showed that 1) loss of C1–C2 double bond slightly reduced the activity, and 2) any polar groups or electron-withdrawing ones at C3 also reduced or eliminated the potency, while saturated alkyl chains have little effect on activities. Most of the C6, C9 analogues were less potent than mansonone F regardless of substituents, while the steric effect was proven to be more important than the electronic effect. Unexpectedly, the 6-butylmansonone presented exceptionally powerful anti-MRSA and antibacterial effect for the Gram-positive pathogens.12,13

To discover new and more potent anti-MRSA compounds we extended the SAR analysis to 1-thiomansonone derivatives. We hypothesized that as orthoquinone moiety and oxaphenalene core are crucial for antimicrobial activity and as the structure is fully conjugated, substitution of...
oxygen in oxaphenalene with other atoms such as sulfur would alter electronic characteristics, and therefore biological activity of the compounds. Sulfur is one of the classic oxygen bioisosteres, and bioisosteric displacement is frequently used in medicinal chemistry. Synthetic strategy and retrosynthetic plan for the synthesis of 1-thio mansonones are briefly outlined in Figure 3 and Scheme 1.

1-Thiomansonone can be synthesized from tricyclic ketone 4, whereas the tricyclic thiophenalene skeleton can be constructed by Friedel–Crafts peri ring closure of acid 5. The key reaction of this synthesis is the creation of the aryl–sulfide bond. Formation of the carbon–sulfur bond could be achieved by Newman–Kwart rearrangement of an aryl thiocarbamate or by palladium-catalyzed cross-coupling of aryl O-triflate, starting from naphthol 6 and an appropriate thiol. 6- and 9-Methyl groups could be introduced by palladium-catalyzed methylation and sequential ortho-hydroxymethylation–benzylic dihydroxylation from 1,5-dihydroxynaphthalene (7), respectively. 2,5-Dimethyl-naphth-1-ol (6) was prepared by modifying our previously established procedure (Scheme 2).
Tricyclic ketone 4 was synthesized using an intramolecular pericyclic Friedel–Crafts reaction. Generation of acid chloride from acid 14 using oxalyl chloride, followed by aluminum chloride treatment resulted in the desired ketone 4 in 90% yield in two steps. Methyl substituent at C3 was introduced by Grignard reaction (MeMgl, Et2O). Sequential nitration at C7 by copper nitrate and reduction to aniline followed by oxidation with Fremy’s salt, delivered 1-thiomansonone I (1).25 Thiomansonone I (1) was dehydrated to 1-thiomansonone F (2) according to a previously described procedure for the synthesis of mansonone F from mansonone I, as shown in Scheme 5. Sulfone derivative 3 of mansonone I was synthesized by sulfide oxidation of 1 with mCPBA.

As depicted in Table 1, antimicrobial activities of the synthesized analogues were determined in vitro against MRSA strains. Vancomycin, mansonone I, and mansonone F were used as control compounds.

As previously reported, mansonone F (MIC50 = 2 μg/mL) shows anti-MRSA activity comparable to vancomycin (MIC50 = 1 μg/mL), whereas mansonone I is slightly less potent (MIC50 = 8 μg/mL). Thiomansonone I (1) displayed slightly lower activity (MIC50 = 16 μg/mL) compared to mansonone I, whereas 1-sulfonmansonone I (3) showed no notable anti-MRSA activity (MIC50 > 32 μg/mL) in the concentration range tested. Dehydrated analogue, 1-thiomansonone F (2) showed mild anti-MRSA activity, but did not enhance the antibacterial activity compared with mansonone F. In designing this experiment, we expected that,
Table 1 Anti-MRSA Activity

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound</th>
<th>MIC&lt;sub&gt;50&lt;/sub&gt; (μg/mL)</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt; (μg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>vancomycin</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>mansonone I</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>3</td>
<td>1-thiomansonone I (1)</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>4</td>
<td>1-sulfomansonone I (3)</td>
<td>&gt;32</td>
<td>&gt;32</td>
</tr>
<tr>
<td>5</td>
<td>mansonone F</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>1-thiomansonone F (2)</td>
<td>8</td>
<td>16</td>
</tr>
</tbody>
</table>

based on the differences in electronegativity and reactivity, substitution of 1-oxygen with sulfur or sulfone moiety would make a significant influence on compound anti-MRSA activity. However, 1-thio and 1-sulfomansonones displayed reduced anti-MRSA activity.

In conclusion, we designed new 1-thio- and 1-sulfomansonones I and F based on previous SAR studies and carried out total synthesis of three sulfur-substituted analogues of mansonone F. The two methyl substituents were introduced using Stille reaction and sequential hydroxy-methylation–hydrogenolysis, respectively. The carbon–sulfur bond was formed through Newman–Kwart rearrangement or palladium-catalyzed thioalkylation, where-as intramolecular Friedel–Crafts cyclization completed the tricyclic ring system. In summary, three sulfur-containing mansonone analogues were successfully synthesized and evaluated for anti-MRSA activity. The compounds did not show enhanced activity; however, our results provide valuable information for future mechanistic and SAR studies.

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Supporting Information
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References and Notes

(23) Procedure for Newman–Kwart Rearrangement: S-(2,5-Dimethylphenalalin-1-yl)-dimethylcarbamothioate (12)
A solution of O-(2,5-dimethylphenalalin-1-yl)dimethylcarbamothioate (11, 300 mg, 1.15 mmol) in N,N-diethylalanine (10 mL) was equipped with sure-sealed round-bottom flask. And the solution was stirred for 12 h at 240 °C. After cooling, the solution was quenched with 10% HCl and diluted with EtOAc. The organic layer was washed with H<sub>2</sub>O and brine and dried with MgSO<sub>4</sub>. The filtered solution was concentrated, and the residue was purified with SiO<sub>2</sub> column chromatography (EtOAc/hexane = 1:10) to obtain the desired product as a yellowish oil (214 mg, 71%). <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>): δ = 8.30 (d, J = 9.0 Hz, 1H), 8.01 (d, J = 9.0 Hz, 1H), 7.47 (d, J = 8.4 Hz, 1H), 7.40 (t, J = 7.2 Hz, 1H), 7.26 (d, J = 7.2 Hz, 1H), 3.27 (s, 3H), 3.01 (s, 3H), 2.68 (s, 3H), 2.64 (s, 3H) ppm. <sup>1</sup>C NMR (150 MHz, CDCl<sub>3</sub>): δ = 165.9, 142.6, 131.6, 134.6, 131.8, 128.4, 126.7, 126.3, 126.1, 124.9, 124.0, 22.5, 19.6 ppm. HRMS (ESI-TOF): m/z [M + H]<sup>+</sup> calc for C<sub>19</sub>H<sub>23</sub>NOS: 260.1104; found: 260.1103.
(24) Synthesis of Ethyl 2-[(2,5-dimethylnaphthalen-1-yl)thio]acetate (15)
To a solution of 2,5-dimethylnaphthalen-1-yl trifluoromethanesulfonate (14, 283 mg, 0.930 mmol) in degassed toluene was added Pd$_2$(dba)$_3$ (85 mg, 0.093 mmol), 1,1’-bis(diphenylphosphino)ferrocene (57 mg, 0.102 mmol), NaOt-Bu (156 mg, 1.39 mmol), and then ethyl thioglycolate (97 μL, 1.39 mmol) was added. And the reaction mixture was refluxed for 1 day. And then the reaction solvent was evaporated. The residue was purified with SiO$_2$ column chromatography with EtOAc/hexane (20:1) to obtain the desired product as a colorless oil (104 mg, 43%). $^1$H NMR (600 MHz, CDCl$_3$): δ = 8.53 (d, $J$ = 8.4 Hz, 1 H), 7.95 (d, $J$ = 8.4 Hz, 1 H), 7.46 (t, $J$ = 7.2 Hz, 1 H), 7.43 (d, $J$ = 9.0 Hz, 1 H), 7.30 (d, $J$ = 7.2 Hz, 1 H), 3.97 (q, $J$ = 7.2 Hz, 2 H) 3.44 (s, 2 H), 2.78 (s, 3 H), 2.69 (s, 3 H) ppm. $^{13}$C NMR (150 MHz, CDCl$_3$): δ = 169.9, 141.9, 135.4, 134.8, 132.0, 129.1, 128.4, 126.7, 126.2, 125.7, 124.4, 61.2, 37.5, 22.3, 19.6, 13.9 ppm. HRMS (ESI-TOF): m/z [M + H]$^+$ calcld for C$_{15}$H$_{17}$O$_2$S: 261.0944; found: 261.0942.