



Synthesis and structure–activity relationship study of novel quinazolinone-based inhibitors of MurA



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ABSTRACT

MurA is an intracellular bacterial enzyme that is essential for peptidoglycan biosynthesis, and is therefore an important target for antibacterial drug discovery. We report the synthesis, *in silico* studies and extensive structure–activity relationships of a series of quinazolinone-based inhibitors of MurA from *Escherichia coli*. 3-Benzoyloxyphenylquinazolinones showed promising inhibitory potencies against MurA, in the low micromolar range, with an IC₅₀ of 8 μM for the most potent derivative (**58**). Furthermore, furan-substituted quinazolinones (**38**, **46**) showed promising antibacterial activities, with MICs from 1 μg/mL to 8 μg/mL, concomitant with their MurA inhibitory potencies. These data represent an important step towards the development of novel antimicrobial agents to combat increasing bacterial resistance.

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Antimicrobial agents have saved countless lives, with significantly improved quality of life achieved since the discovery of sulphonamides and β-lactams in the first half of the 20th century.¹ However, extensive use, and frequent misuse and abuse, of antibiotics have caused widespread emergence of antimicrobial-resistant pathogenic bacteria, which now present a serious threat to public health. Therefore, there is an urgent need for the discovery and development of new antibacterial agents, preferably with novel mechanisms of action.^{2,3}

The bacterial cell wall provides the necessary structural integrity for bacteria to withstand the osmotic pressure between the cytoplasm and the cell exterior. The enzymes involved in peptidoglycan biosynthesis are among the most important targets for antibacterial drug discovery, as inhibition of these enzymes can trigger cell lysis.^{4,5} The MurA enzyme (UDP-GlcNAc enolpyruvyl transferase) catalyses the first committed step of the intracellular stage of peptidoglycan biosynthesis: the transfer of enolpyruvate from phosphoenolpyruvate to UDP-N-acetylglucosamine. The product, UDP-GlcNAc-enolpyruvate, is then reduced by the MurB enzyme to UDP-acetylmuramic acid (UDP-MurNAc). In the next steps, four different ligases, MurC–F, sequentially add amino acids

to finally form UDP-MurNAc-pentapeptide, which is one of the main building blocks of the peptidoglycan cell wall.⁶ The Mur enzymes are essential and highly conserved in both Gram-negative and Gram-positive bacteria. Furthermore, eukaryotic cells do not have MurA-F,⁷ thereby providing inhibitors of these enzymes with the desired selectivity for bacteria.

Fosfomycin (Fig. 1, **1**) is a well-known naturally occurring inhibitor of MurA.⁸ It mimics phosphoenolpyruvate and forms a covalent adduct with the cysteine residue within the active site of MurA from different bacteria. Resistance to fosfomycin frequently occurs due to reduced uptake of antibiotics, (metabolic) modification of antibiotics, overexpression of MurA, or modification of the MurA active site.⁹ Therefore, to overcome this resistance, the development of structurally diverse MurA inhibitors with novel mechanism(s) of action is needed. However, although numerous inhibitors have been discovered in recent years, mainly through various high-throughput screening campaigns or classical medicinal chemistry approaches,¹⁰ none of these has reached clinical trials or been developed for therapeutic use.

In a recent virtual-screening campaign, some quinazolinone-based compounds (e.g., Fig. 1, **2**) were identified as potential MurA inhibitors.¹¹ Quinazolinone is a well-known scaffold in medicinal chemistry that is part of a diverse set of compounds that show numerous therapeutic and pharmacological properties¹⁴, including antimicrobial activity (e.g., Fig. 1, representative compounds **3**,¹² **4**¹³). Therefore, the aim of the present study was to explore the

Abbreviations: SAR, structure–activity relationship; UDP-GlcNAc, UDP-N-acetylglucosamine.

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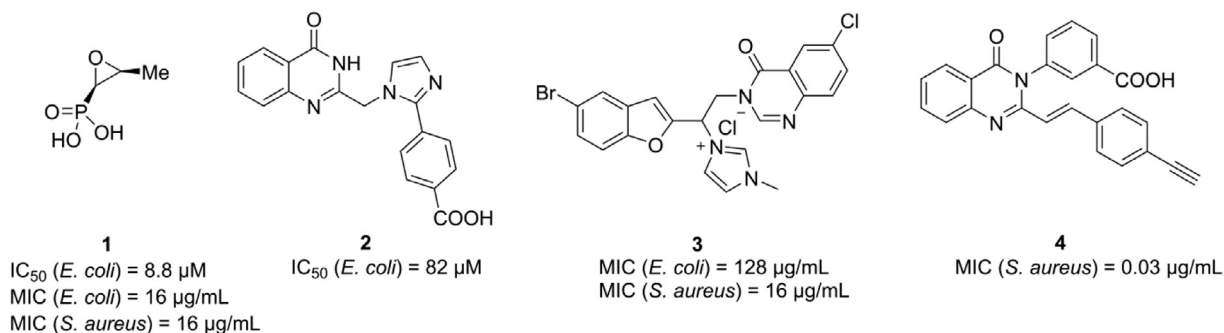


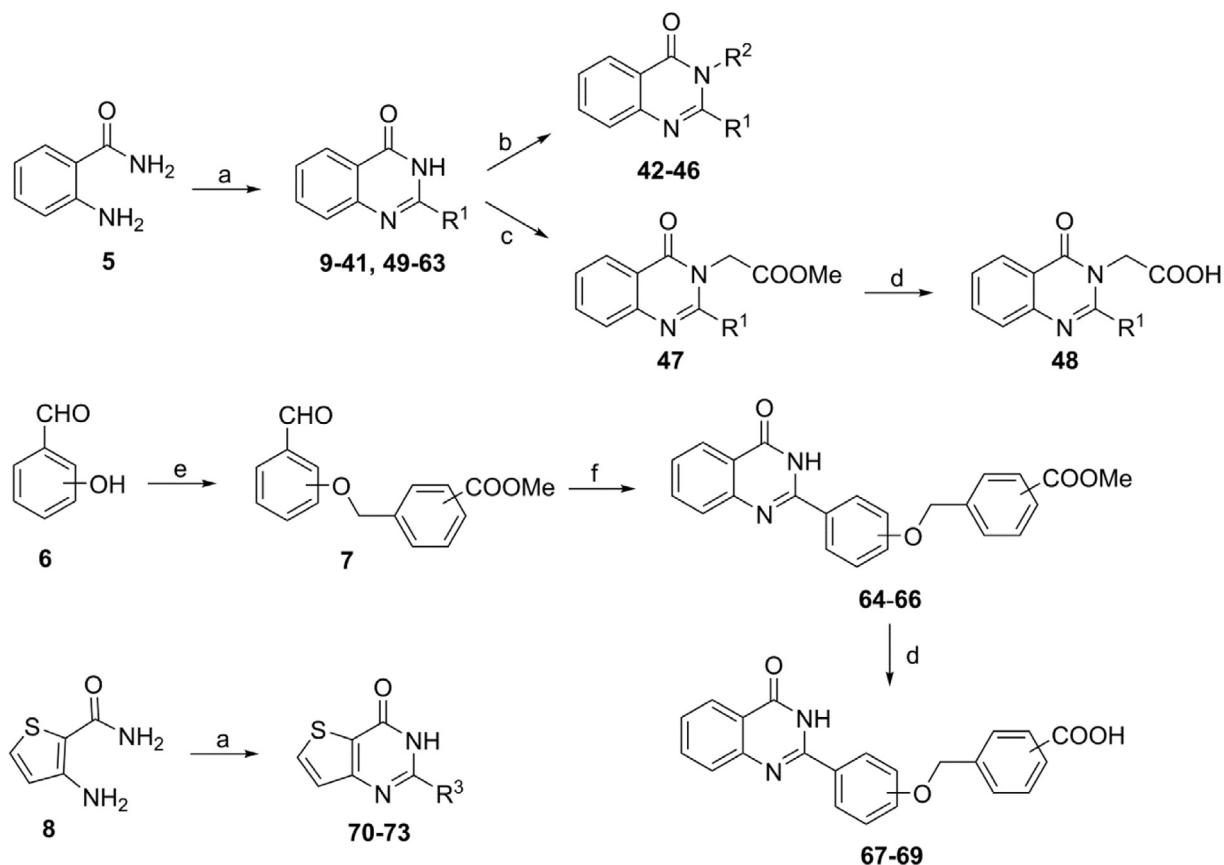
Fig. 1. Fosfomycin **1**⁸ and quinazolinone **2**¹¹, as inhibitors of MurA, and two representative quinazolinone derivatives **3**¹² and **4**¹³ that show antimicrobial activity.

structure–activity relationships (SARs) of this quinazolinone-based hit compound (**2**) from virtual screening, and to improve its antibacterial activity. A series of novel quinazolinone derivatives was synthesised and then evaluated for inhibitory activity against *Escherichia coli* MurA, and antibacterial activity against two representative bacterial strains: *E. coli* and *Staphylococcus aureus*.

There are many methods available for the synthesis of the quinazolinone scaffold.¹⁴ In the present study, quinazolinones **9–63** were prepared from anthranilamide (**5**) and different aldehydes, in dimethylsulphoxide (DMSO) via aerobic oxidative cyclisation (Scheme 1).¹⁵ After construction of the quinazolinone core (**9–41**, **49–63**), alkylation was carried out using various alkyl bromides in dimethylformamide (DMF) under basic conditions. Furthermore, when an ester group was attached to the quinazolinone core via

alkylation (**47**), further hydrolysis in alkaline medium was performed, to obtain carboxylic acid **48**. Quinazolinones with the benzyloxyphenyl moiety and a carboxylic group (**64–69**) were prepared from the corresponding 3- or 4-hydroxy aldehydes, via alkylation with methyl 3- or 4-bromomethyl benzoate and subsequent reaction with anthranilamide in DMSO (**64–66**). Deprotection in alkaline medium yielded the corresponding benzoic acid derivatives **67–69**. As possible isosteres of quinazolinones, thienopyrimidinones **70–73** were synthesised from 3-aminothiophene-2-carboxamide (**8**) and the corresponding aldehydes, according to the same general procedure used for compounds **9–63**.

The synthesised quinazolinones **9–69** (Table 1, Supporting Information Table S1) and thienopyrimidinones **70–73** (Table 2) were evaluated biochemically for their inhibition of *E. coli* MurA,



Scheme 1. Synthesis of quinazolinones **9–69** and thienopyrimidinones **70–73**. Reagents and conditions: (a) aldehyde (R^1 CHO or R^3 CHO), DMSO, 100 °C, 16–24 h; (b) K_2CO_3 , DMF, R^2 Br; (c) K_2CO_3 , DMF, $BrCH_2COOMe$; (d) NaOH, acetone/water; (e) K_2CO_3 , acetone, methyl 3- or 4-bromomethyl benzoate; (f) anthranilamide (**5**), DMSO, 100 °C, 16–24 h.

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