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Phosphorylated hydroxyethylamines as novel inhibitors of the bacterial cell wall biosynthesis enzymes MurC to MurF

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ABSTRACT

Enzymes involved in the biosynthesis of bacterial peptidoglycan represent important targets for development of new antibacterial drugs. Among them, Mur ligases (MurC to MurF) catalyze the formation of the final cytoplasmic precursor UDP-*N*-acetylmuramyl-pentapeptide from UDP-*N*-acetylmuramic acid. We present the design, synthesis and biological evaluation of a series of phosphorylated hydroxyethylamines as new type of small-molecule inhibitors of Mur ligases. We show that the phosphate group attached to the hydroxyl moiety of the hydroxyethylamine core is essential for good inhibitory activity. The IC_{50} values of these inhibitors were in the micromolar range, which makes them a promising starting point for the development of multiple inhibitors of Mur ligases as potential antibacterial agents. In addition, 1-(4-methoxyphenylsulfonamido)-3-morpholinopropan-2-yl dihydrogen phosphate **7a** was discovered as one of the best inhibitors of MurE described so far.

1. Introduction

Treatment of infectious diseases is being compromised worldwide by the emergence of bacteria that are resistant to numerous antibiotics [1–3]. Increased morbidity and mortality are the most dramatic consequences of this resistance [4]. Therefore, there is an urgent need for the development of novel antibacterial agents. Some of the best known and most validated targets for antibacterial therapy are the enzymes involved in the biosynthesis of peptidoglycan [5,6]. β-Lactam and glycopeptide antibiotics are well known inhibitors of the late, extracellular stages of bacterial peptidoglycan biosynthesis. However, in the past few years, more attention has been focused on the early intracellular biosynthetic steps as potential drug targets [6–8].

Peptidoglycan is a major component of the cell wall of almost all eubacteria. Its main function is to provide the rigidity, flexibility and strength that are necessary for bacterial cells to grow and divide, while withstanding the high internal osmotic pressure [9]. Peptidoglycan is a complex heteropolymer that is composed of long glycan chains made up of alternating units of *N*-acetylglucosamine (GlcNAc) and *N*-acetylmuramic acid (MurNAc). The D-lactoyl group of each MurNAc residue is substituted by a peptide unit with a composition that is generally L-alanyl-γ-D-glutamyl-*meso*-diaminopimeloyl(or L-lysyl)-D-alanine [9]. The biosynthesis of peptidoglycan involves a number of ATP-dependant ligases (MurC to MurF), which contribute to the formation of UDP-MurNAc-pentapeptide by successive additions to UDP-MurNAc of L-Ala (MurC), D-Glu (MurD), *meso*-diaminopimelic acid or L-Lys (MurE) and D-Ala-D-Ala (MurF) [6]. The MurC to MurF ligases have the same reaction mechanism (Fig. 1), which consists of the activation of the carboxyl group of the nucleotide precursor by ATP, generating an acyl phosphate intermediate and ADP. The acyl phosphate is then attacked by the amino group of the incoming amino acid (or dipeptide in the case of MurF), leading to the formation of a high-energy tetrahedral intermediate; this eventually breaks down into the product and P_i [6].

Over the last few years, a number of Mur ligase inhibitors have been developed [6,8,10]. Among these, transition-state analogues, like phosphonates, phosphinates and sulfonamides, have been described as inhibitors of MurC [11,12], MurD [13–20], MurE [20–22] and MurF [23]. Our aim was to design novel types of transition-state analogues as potential inhibitors of these Mur ligases. We focused our attention on hydroxyethylamines (HEAs, Fig. 1), which have been described as analogues of high-energy tetrahedral reaction intermediates of different proteases [24–29] and which represent the fundamental moiety used in inhibitors of HIV protease [28–30], cathepsin D [28,31], angiotensin-converting enzyme [32], malarial proteases [28,29,33,34] and β-amyloid cleaving enzyme (β-secretase) [35–39]. However, so far they have not been used in the design of Mur ligase inhibitors. In a previous report [40], we presented phosphorylated HEA derivatives (compounds **6a–b** and **7a–b** in Fig. 2) as inhibitors of the bacterial peptidoglycan biosynthesis enzymes D-alanine:D-alanine ligase (DdlB) and

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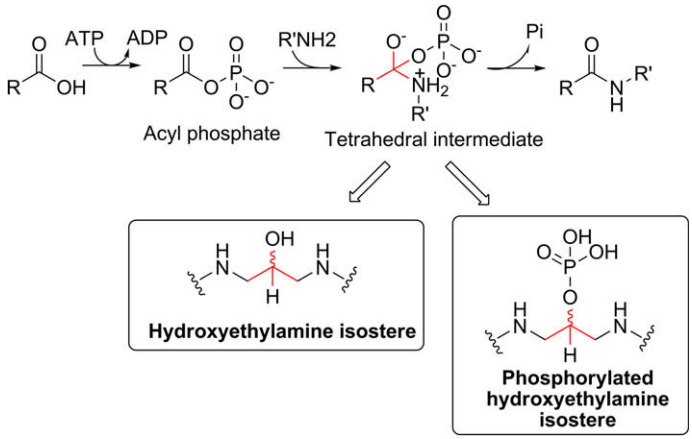


Fig. 1. Reaction mechanism of Mur ligases and design of hydroxyethylamine isosteres as transition-state analogues.

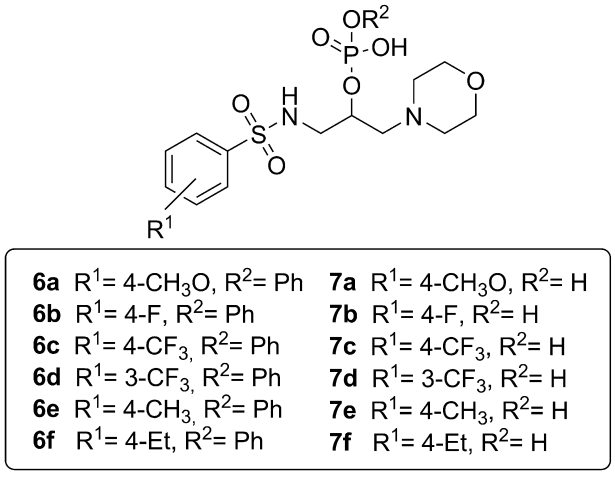


Fig. 2. General formulae of phosphorylated hydroxyethylamines as potential inhibitors of Mur ligases.

D-alanine:D-lactate ligase (VanA). These two enzymes are the ATP-dependent ligases. Although their three-dimensional structure is different, their reaction mechanism is similar to that of the Mur ligases [6]. In this paper we present the synthesis and initial structure–activity relationship of a series of phosphorylated HEAs as promising inhibitors of Mur ligases.

2. Methods and materials

2.1. Chemistry

All of the chemicals used were obtained from commercial sources (Acros, Aldrich, Fluka and Merck) and used without further purification. Biomol Green® reagent was purchased from Biomol® International, a brand of Enzo Life Sciences, Inc. Solvents were used without purification or drying, unless otherwise stated. Reactions were monitored using analytical TLC plates (Merck, silica gel 60 F_{254}, 0.25 mm), and compounds were visualized with ultraviolet light and ninhydrin or bromocresol green. Preparative thin-layer chromatography was carried out on PSC-Platten 20 × 20 cm Kieselgel 60 F_{254}, 2 mm (Merck). The microwave reactions were performed using a CEM Discover® microwave synthesis system. Circular chromatography was carried out on a Chromatotron® centrifugal thin-layer chromatograph (Harrison Research), using silica gel 60 GP_{254}-containing gypsum. Silica gel grade 60 (70–230 mesh, Merck) was used for column chromatography. NMR spectra were obtained on a Bruker Advance DPX 300 instrument. ^{1}H NMR were recorded at 300.13 MHz with tetramethylsilane as an internal standard. Mass spectra were obtained with a VG-Analytical Autospec Q mass spectrometer (Centre for Mass Spectrometry, Institute Jožef Stefan, Ljubljana). IR spectra were recorded on a Perkin–Elmer FTIR 1600 spectrometer. Microanalyses were carried out by the Department of Organic Chemistry, Faculty of Chemistry and Chemical Technology, University of Ljubljana, Ljubljana, on a 240 C Perkin Elmer elemental analyzer. Melting points were determined using a Reichert hot-stage microscope and are uncorrected. HPLC analyses were performed on a HP 1100 Agilent Technologies instrument with G1365B UV–vis detector (254 and 220 nm), using a Luna C18 column (4.6 mm × 250 mm) at a flow rate of 1 mL/min. The eluant was a mixture of 0.1% TFA in water (A) and acetonitrile (B). The gradient was from 5% B to 75% B in 15 min for compounds **6a–f** and **7a–f**, while for **6e** and **7e** the gradient was from 5% B to 95% B in 15 min.

2.1.1. General procedure for the synthesis of compounds *2a–f*

To a solution of **1a–f** (10.0 mmol) in anhydrous dichloromethane (50 mL), allylamine (21.0 mmol, 1.57 mL) was added slowly at 0 °C, with the resulting mixture stirred for 1 h at room temperature. The reaction mixture was filtered and washed with 10% citric acid (2 × 25 mL), water (25 mL) and brine (25 mL). The organic phase was dried with anhydrous Na_2SO_4, filtered and evaporated *in vacuo* to obtain **2a–f**.

2.1.2. General procedure for the synthesis of compounds *3a–f*

To a solution of **2a–f** (5.0 mmol) in dichloromethane (30 mL), *meta*-chloroperoxybenzoic acid (1.48 g, 70% wt., 6.0 mmol) was added at 0 °C and the resulting mixture was stirred for 48 h at room temperature. The reaction mixture was filtered and dichloromethane removed under reduced pressure. The residue was dissolved in diethylether (or ethyl acetate in case of low solubility in diethylether) (50 mL) and washed with 10% Na_2SO_3 (3 × 25 mL), 10% $NaHCO_3$ (4 × 25 mL), water (25 mL) and brine (25 mL). The organic phase was dried with anhydrous Na_2SO_4, filtered and evaporated *in vacuo* to obtain **3a–f**.

2.1.3. General procedure for the synthesis of compounds *4a–f*

To a solution of **3a–f** (3.0 mmol) in anhydrous dioxane (6 mL), morpholine (3.3 mmol, 0.29 mL) and calcium trifluoromethanesulfonate (1.0 mmol, 0.348 g) were added and the resulting mixture was stirred in a microwave reactor for 5 min at 120 °C. The reaction mixture was cooled to room temperature and filtered. Dioxane was

evaporated under reduced pressure and the residue was purified by circular chromatography using ethyl acetate or ethyl acetate/methanol (4/1) as an eluent to obtain **4a–f**.

*2.1.4. General procedure for the synthesis of compounds **5a–f***

To a solution of **5a–f** (3.0 mmol) in anhydrous dichloromethane (15 mL), DMAP (3.9 mmol, 0.476 g) was added and the resulting solution was cooled to −10 °C. Then diphenyl chlorophosphate (3.6 mmol, 0.75 mL) was added dropwise. The reaction mixture was stirred for 30 min at 0 °C and 1 h at room temperature. This was followed by the addition of 10 mL water mixed with ice. After 5 min of stirring, the organic phase was separated from water and washed with 10% citric acid (2 × 10 mL), water (10 mL) and brine (10 mL). The organic phase was dried with anhydrous Na_2SO_4, filtered and evaporated *in vacuo*. The residue was purified by circular chromatography using ethyl acetate as an eluent to obtain **5a–f**.

*2.1.5. General procedure for the synthesis of compounds **6a-f** and **7a–f***

To a solution of **5a–f** (2.5 mmol) in anhydrous glacial acid (15 mL), PtO_2 (50% wt.) was added and the resulting solution was stirred for 4–5 days in a hydrogen atmosphere. The reaction mixture was filtered and the acid was evaporated under reduced pressure. The residue was purified by preparative thin-layer chromatography using acetonitrile/methanol/water (3/1/1) as mobile phase to obtain pure **6a–f** and **7a–f**.

Analyses of all compounds are presented in Supplementary Material.

2.2. Enzymatic assays

Compounds were tested for their inhibition of the addition of L-Ala, D-Glu, L-Lys or D-Ala-D-Ala to nucleotide precursors catalyzed by MurC from *Escherichia coli* [41], MurD from *E. coli* [42], MurE from *Staphylococcus aureus* [43], and MurF from *E. coli* [44], respectively. The detection of the orthophosphate generated during the reaction was based on the colorimetric Malachite green method [45] with slight modifications, using reaction mixtures (final volume, 50 μL) containing:

MurC: 50 mM Hepes, pH 8.0, 5 mM $MgCl_2$, 120 μM UDP-Mur-*N*Ac, 120 μM L-Ala, 450 μM ATP, 0.005% Triton X-114, purified MurC from *E. coli* [41] (diluted in 50 mM Hepes, pH 8.0, 1 mM dithiothreitol) and tested compound dissolved in DMSO.

MurD: 50 mM Hepes, pH 8.0, 5 mM $MgCl_2$, 80 μM UDP-Mur-*N*Ac-L-Ala, 100 μM D-Glu, 400 μM ATP, 0.005% Triton X-114, purified MurD from *E. coli* [42] (diluted in 50 mM Hepes, 1 mM dithiothreitol) and tested compound dissolved in DMSO.

MurE: 50 mM Hepes, pH 8.0, 15 mM $MgCl_2$, 100 μM UDP-Mur-NAc-L-Ala-D-Glu, 1.5 mM L-Lys, 700 μM ATP, 0.005% Triton X-114, purified MurE from *S. aureus* [43] (diluted in 50 mM Hepes, 1 mM dithiothreitol) and tested compound dissolved in DMSO.

MurF: 50 mM Hepes, pH 8.0, 50 mM $MgCl_2$, 100 μM UDP-Mur-*N*Ac-L-Ala-γ-D-Glu-*meso*-A_2pm, 600 μM D-Ala-D-Ala, 500 μM ATP, 0.005% Triton X-114, purified MurF from *E. coli* [44] (diluted in 50 mM Hepes, 1 mM dithiothreitol) and tested compound dissolved in DMSO.

In all cases, the DMSO concentration was 5%. The mixtures were incubated at 37 °C for 15 min (20 min for MurF assay), and then quenched with 100 μL Biomol® reagent. The absorbances were measured at 650 nm after 5 min. All of the experiments were run in duplicate. The residual activities were calculated with respect to a similar assay without the test compounds and with 5% DMSO. The IC_{50} values were determined by measuring the residual activities at seven different test compound concentrations, and they represent the concentrations of test compounds for which the residual activity was 50%.

2.3. Docking studies

Docking experiments were done on a computer workstation with four dual-core Opteron processors, 16 GB of RAM and 1.2 TB of hard-drive space running the Fedora 7 operating system. FlexX 3.1.2 from BioSolveIT GmbH [46] was used for active site preparation, docking of compound **7a**, and scoring. PyMol from DeLano Scientific was used for preparation of graphical representation of docking results. The crystal structure of MurE from *E. coli* (PDB entry: 1E8C) was used for our docking experiments. The active site was defined as the area within 6.5 Å of the co-crystallized ligand (UDP-Mur-*N*Ac-L-Ala-γ-D-Glu-*meso*-A_2pm). Docking and scoring were done with the default parameters of the programme.

3. Results

3.1. Synthesis

The first part of our study involved the development of the appropriate synthetic procedures to obtain initial hydroxyethylamines **4a–f** in high yields (Fig. 3). The starting sulfonyl chlorides **1a–f** were coupled with allylamine to give sulfonamides **2a–f**. This was followed by oxidation of the terminal double bond with *meta*-chloroperoxybenzoic acid, to obtain the epoxides **3a–f**. The HEA derivatives **4a–f** were then prepared by ring opening of the appropriate epoxides with morpholine, in the presence of microwaves and calcium trifluoromethanesulfonate ($Ca(OTf)_2$) as a catalyst [47].

The synthesis of compounds **6a–f** and **7a–f** (Fig. 3) proceeded from HEA derivatives **4a–f**, diphenyl chlorophosphate and 4-dimethylaminopyridine. The diphenyl phosphate esters **5a–f** obtained were deprotected by hydrogenation in the presence of Adam's catalyst (platinum oxide), which resulted in the formation of a mixture of free and monophenyl phosphates **6a–f** and **7a–f**, respectively. Isolation by preparative thin-layer chromatography gave pure **6a–f** and **7a–f**.

3.2. Biological activities

The HEA derivatives synthesized were tested for inhibitory activities against MurC, MurD, MurE and MurF. The Malachite green assay, which detects the orthophosphate generated during the reaction [45], was used for this purpose. The inhibitory activity was determined at 500 μM of each tested compound (Table 1). To exclude possible non-specific (promiscuous) inhibition, all of the compounds were tested in the presence of detergent (0.005% Triton X-114) [48]. If a tested HEA derivative inhibited Mur ligases activities by more than 30%, IC_{50} values were also determined.

Non-phosphorylated derivatives **4a–f** and phosphorylated compounds **6a–f** showed no or only weak (less than 25%) inhibition of Mur ligases at 500 μM. Only compounds **4b**, **6a** and **6d** were weak inhibitors of MurD (37%, 29% and 46% of inhibition, respectively). On the other hand, phosphorylated derivatives **7a–f** (Table 1) appeared as fairly good inhibitors of MurC, MurE and MurF, with IC_{50} values in micromolar range. The best inhibitor in this series was compound **7a**, which inhibited MurE with an IC_{50} value as low as 6 μM.

4. Discussion

In the present work, a series of HEA derivatives were synthesized and tested as potential inhibitors of the Mur ligases. It was found that those derivatives that were not substituted with a phosphate group (**4a–f**) (Fig. 3) did not significantly inhibit Mur ligases. Only compound **4b**, which had the fluoro substituent on the *para*

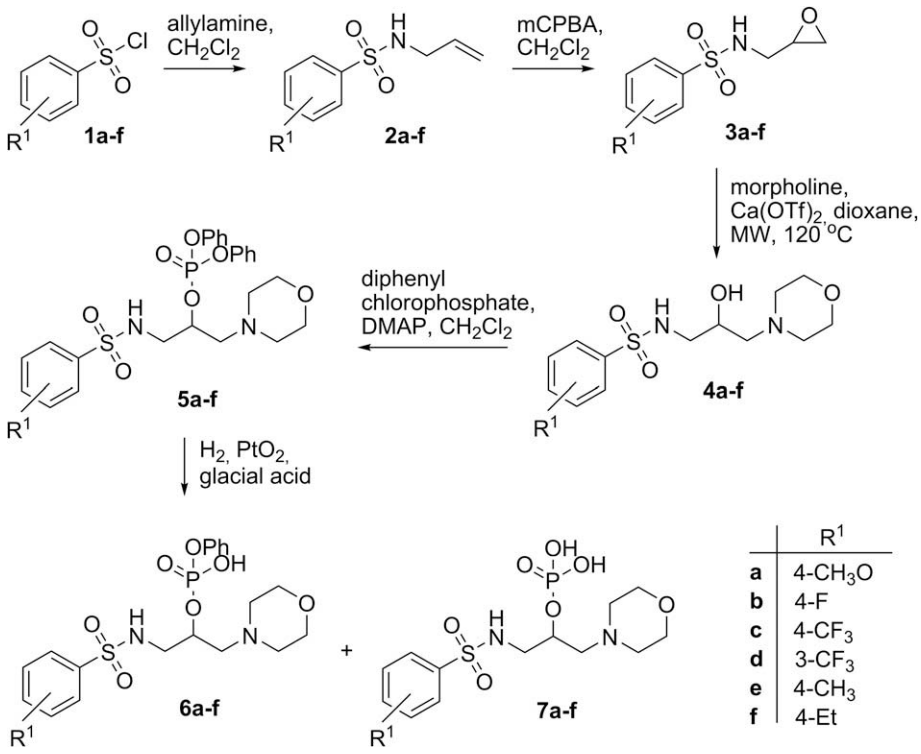
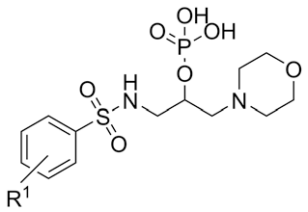


Fig. 3. Synthesis of non-phosphorylated (**4a–f**) and phosphorylated HEA derivatives (**6a–f** and **7a–f**).

Table 1
Mur ligase inhibitory activities of phosphorylated HEA derivatives **7a–f**.



Compound	R_1	% Inhibition at 500 μM	IC_{50} (μM)		
		MurD	MurC	MurE	MurF
7a	4-CH_3O	11	490	6	530
7b	4-F	18	790	120	270
7c	4-CF_3	18	200	57	240
7d	3-CF_3	26	530	160	150
7e	4-CH_3	8	540	120	560
7f	4-Et	28	760	61	360

position of the benzene ring, was found as a weak inhibitor of MurD enzyme (37% of inhibition at 500 μM). In the series of monophenyl phosphates **6a–f** (Fig. 3), two moderate inhibitors of MurC were found (29% of inhibition for **6a** and 46% for **6d**). When the hydroxyl group of the HEA moiety was substituted with a free phosphate group (compounds **7a–f**, Table 1), the inhibitory activities for MurC, MurF, and mainly MurE, increased. Curiously, in this series of compounds, only weak inhibition of MurD was observed. The most potent inhibitor of MurC was compound **7c** (IC_{50}, 200 μM), which had an electron-withdrawing trifluoromethyl group on the *para* position of the benzene ring. If the position of the trifluoromethyl group was changed from *para* to *meta* (compound **7d**) or if another *para* substituent was used (compounds **7a–b**, **7e–f**), the inhibitory activity on MurC dropped (IC_{50} values close to or above 500 μM). Interestingly, HEA derivatives **7a–f** were potent inhibitors of MurE with IC_{50} values between 6 μM and 160 μM. The best inhibitor, 1-(4-methoxyphenylsulfonamido)-3-morpholinopropan-2-yl dihydrogen phosphate **7a**, had a *para* methoxy group on the benzene ring. If the methoxy group was replaced by an ethyl substituent (compound **7f**), a 10-fold increase in IC_{50} was seen. Promising MurE inhibitory activity was obtained also for compound **7c** (IC_{50} = 57 μM), which has an electron-withdrawing trifluoromethyl substituent on the *para* position of the benzene ring. If this group was moved to the *meta* position (compound **7d**), the IC_{50} increased to 160 μM. Interestingly, we observed the opposite situation in the case of MurF, where **7d** (IC_{50} = 150 μM) was

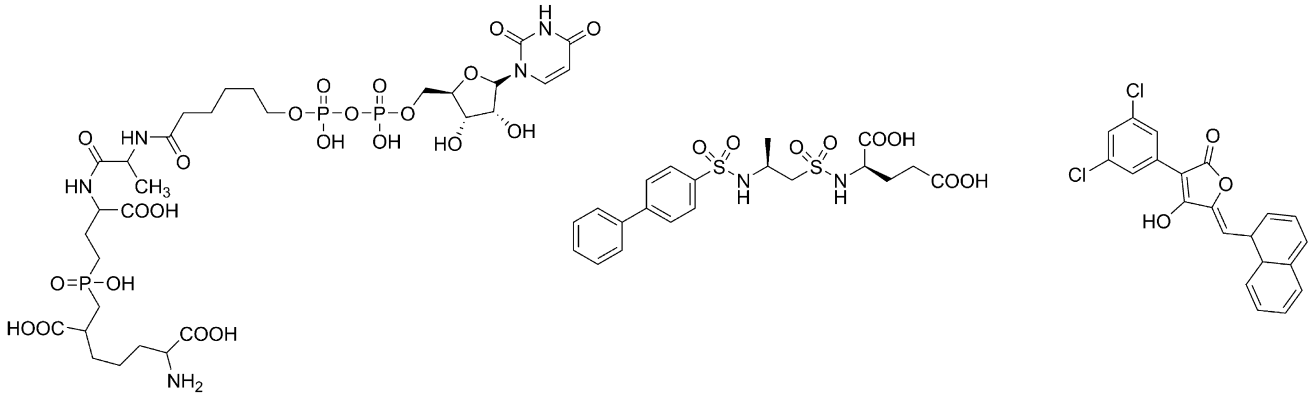


Fig. 4. Structures and IC_{50} values of known MurE inhibitors.

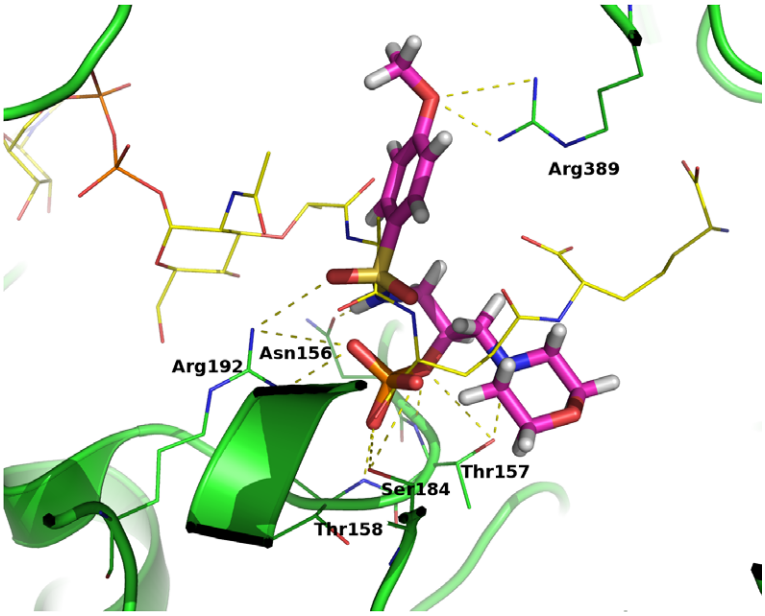


Fig. 5. Docking of compound **7a** (magenta) into the active site of MurE from *E. coli* (pdb entry 1E8C). The amino acids that form interactions with compound **7a** (green sticks) and UDP-MurNAc-L-Ala-γ-D-Glu-*meso*-A_2pm (yellow) are also shown. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

the most potent inhibitor amongst the phosphorylated HEA derivatives **7a–f**. Introduction of an electron-donating group, such as methyl, ethyl or methoxy, decreased the inhibitory activity of MurF (**7a**, **7e–f**, IC_{50} values between 360 and 560 μM) in comparison with inhibitors with electron-withdrawing trifluoromethyl or fluoro substituents on the *para* position of the benzene ring (**7b–c**, IC_{50} values around 250 μM).

The most promising inhibitor in this series was compound **7a**, which is a potent inhibitor of MurE from *S. aureus*. Only few structurally diverse inhibitors of MurE have been published to date. *N*-Acyl-dipeptide derivatives were only weak inhibitors of MurE from *E. coli* (IC_{50} values 0.6–10 mM) [49,50], whereas phosphinate transition-state anlogue inhibitor **8** (Fig. 4) inhibited this enzyme with IC_{50} value of 1.1 μM [22]. Beside these, only peptidosulfonamide **9** [20], some phosphinates [21] and naphthyl tetronic acids (e.g. **10**) [51] were described as inhibitors of MurE with inhibitory activities in the micromolar range. If we compare the structure and MurE inhibitory activity of compound **7a** with the literature inhibitors, we can see that it is the best low-molecular weight inhibitor described so far. Additionally, inhibitory activities against MurC and MurF make it a very good starting point for development of more potent multiple Mur ligases inhibitors. Development of multiple Mur ligases enzyme inhibitors with antibacterial activity appears very attractive as these inhibitors would reduce the frequency of bacterial resistance due to mutations.

To obtain information about the possible binding mode of this inhibitor, we docked it into the active site of MurE from *E. coli*, which is the only MurE orthologue whose three-dimensional structure is available (pdb code 1E8C) [52]. FlexX [46] predicted the binding position of compound **7a** as presented in Fig. 5. In this simulation, the phosphate moiety of the inhibitor forms interactions with Thr157, Thr158, Ser184 and Arg192. The sulfonamide group makes hydrogen bonds with Asn156 and Arg192, the tertiary amine of the morpholine ring forms interactions with Thr157, and the oxygen of the methoxy group is H-bonded to the side chain of Arg389. The predicted binding mode of compound **7a** is well aligned with the co-crystallized product of the MurE reaction, UDP-MurNAc-L-Ala-γ-D-Glu-*meso*-A_2pm. It is noteworthy that the

phosphate moiety of docked inhibitor **7a** forms interactions with the same amino acids (Thr157, Thr158, Ser184 and Arg192) as the α-carboxyl group of D-Glu of the co-crystallized product. Although HEA derivatives were designed as potential tetrahedral transition-state analogue inhibitors, this docking study and the micromolar affinities of our compounds suggest that they are not analogues of the high-energy intermediate, which should have nanomolar affinities and should display different types of interactions, but most probably classical inhibitors interacting with the binding site of the UDP-MurNAc-dipeptide substrate.

5. Conclusions

In summary, we have synthesized a series of HEA derivatives as potential inhibitors of Mur ligases. We have shown that only phosphorylated HEA derivatives are inhibitors. The most interesting of them inhibit the activities of MurC, MurE and MurF at micromolar concentrations, therefore are multiple inhibitors of Mur ligases. The most potent inhibitor is 1-(4-methoxyphenylsulfonamido)-3-morpholinopropan-2-yl diphenyl phosphate (**7a**), which is one of the best inhibitor of MurE so far with an IC_{50} value of 6 μM. As these inhibitors contain a very polar phosphate groups attached to the HEA moiety, we do not expect them to have good antibacterial activity. However, they do represent important hit compounds and promising starting points for further structural optimization and development of multiple inhibitors of Mur ligases with antibacterial activity.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bioorg.2009.09.001.

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