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Synthesis and biological evaluation of novel sulfonyl-naphthalene-1,4-diols as FabH inhibitors

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ABSTRACT

A series of analogs of 2-tosylnaphthalene-1,4-diol were prepared and were found to be potent 10–20 nM reversible inhibitors of the *Escherichia coli* FabH enzyme. The inhibitors were also effective but to a lesser degree (30 nM–5 μM), against the *Mycobacterium tuberculosis* and *Plasmodium falciparum* FabH enzymes. Preliminary SAR studies demonstrated that the sulfonyl group and naphthalene-1,4 diol were required for activity against all enzymes but the toluene portion could be significantly altered and leads to either modest increases or decreases in activity against the three enzymes. The in vitro activity of the analogs against *E. coli* FabH parallel the in vivo activity against *E. coli* TolC strain and many of the compounds were also shown to have antimalarial activity against *P. falciparum*.

β-Ketoacyl-ACP-synthase III (FabH) is a key condensing enzyme in bacterial fatty acid biosynthesis.[1] This enzyme is part of the dissociated fatty acid synthase (FAS). FabH is ubiquitous in both Gram-negative and -positive bacteria, while it bears little homology to the mammalian multifunctional type I FAS.[2,3] The enzyme is also present in *Plasmodium falciparum*[4] and *Mycobacterium tuberculosis*[5,6] and is considered a target for developing promising new antibacterial, antiparasitic, and antimycobacterial agents.[7,8]

2-Tosylnaphthalene-1,4-diol (**1**) (Fig. 1) was identified as potent inhibitor of *P. falciparum* FabH (PfFabH) through a virtual screen using a pharmacophore developed based on thiolactomycin.[9] Here, we report our effort to further study **1** and develop more potent sulfonyl-naphthalene-1,4-diols against various FabH enzymes. A series of 14 compounds were prepared (compounds **1**–**14**, Fig. 2). Compounds **1**–**11** were prepared following a general synthetic strategy as shown in Scheme 1. Nucleophilic addition of alkyl- or arylsulfinic acids to a variety of 1,4-quinones resulted in the formation of the corresponding alkyl- or arylsulfonylhydroquinones. The reaction was conducted using a two-phase dichloromethane-water system in the presence of trifluoroacetic acid.[10] The sulfinic acid salts **15**, **16**, and **17** were not commercially available and were prepared as shown in Scheme 2. Sodium 4-propylbenzenesulfinate **15** and sodium naphthalene-2-sulfinate **16** were prepared by reacting the corresponding sulfonyl chloride with sodium sulfite and sodium bicarbonate in water,[11] while sodium 2-carboxyethanesulfinate **17** was prepared by oxidation of 3-mercaptopropanoic acid using *meta*-chloroperoxybenzoic acid (mCPBA).[12]

The diaryl sulfone **12** was prepared by palladium-catalyzed coupling of 2-bromonaphthalene with toluene sulfinic acid as shown in Scheme 3.[13] Oxidation of compound **1** using manganese dioxide gave the 1,4-quinone **13** (Scheme 3). Nucleophilic addition of 4-methylbenzenethiol to 1,4-naphthoquinone gave compound **14**. Reduction of **14** using zinc dust/acetic acid gave the corresponding 1,4-hydroquinone **18** that converted back to **14** by air oxidation (Scheme 4). All analogs were purified and characterized by ^{1}H NMR, melting point, and high-resolution mass spectroscopy (HRMS).

As shown in Table 1, **1** is an effective inhibitor of all three enzymes and is most potent against the *Escherichia coli* FabH (ecFabH) (IC_{50} of 13 nM). It was least effective against the *M. tuberculosis* FabH (mtFabH). The analogs **2**–**14** were then synthesized and evaluated against all three enzymes to establish a preliminary SAR. These efforts focused primarily on modifying either the toluene

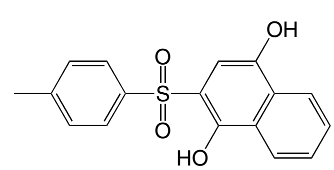

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Figure 1. FabH inhibitor **1**.

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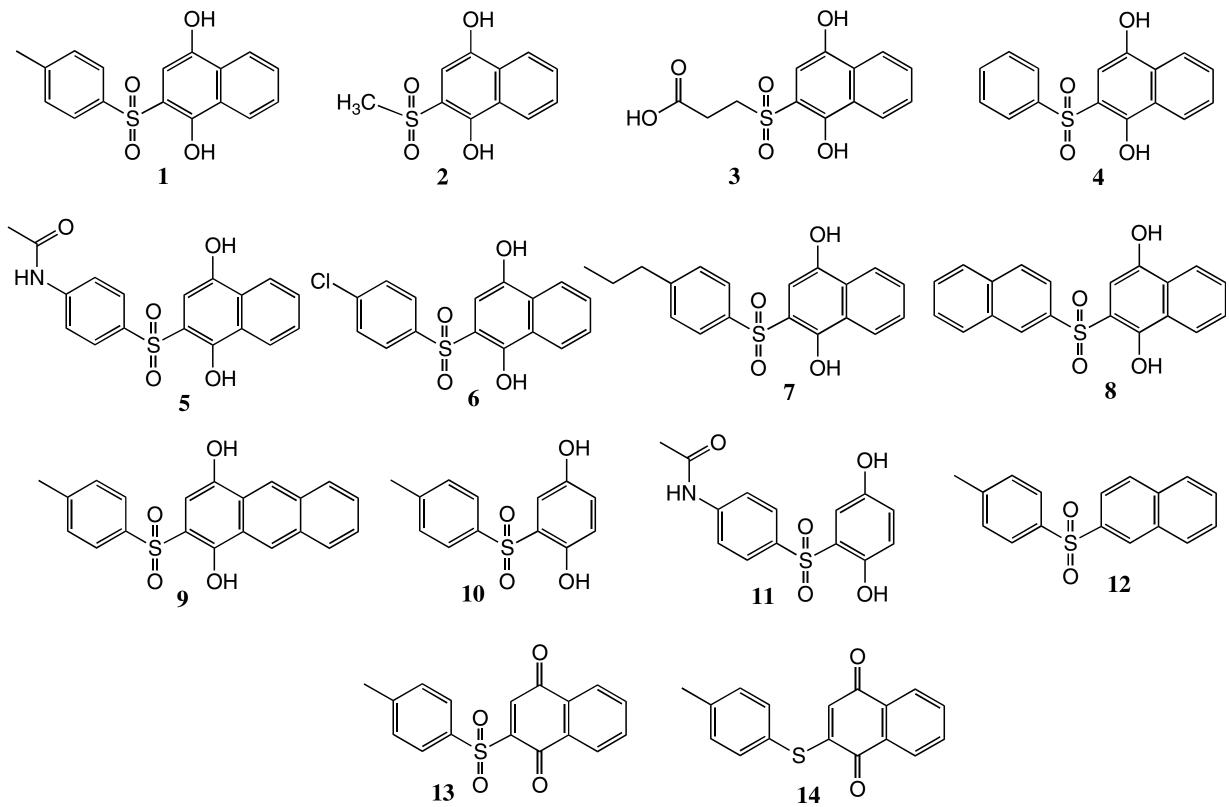
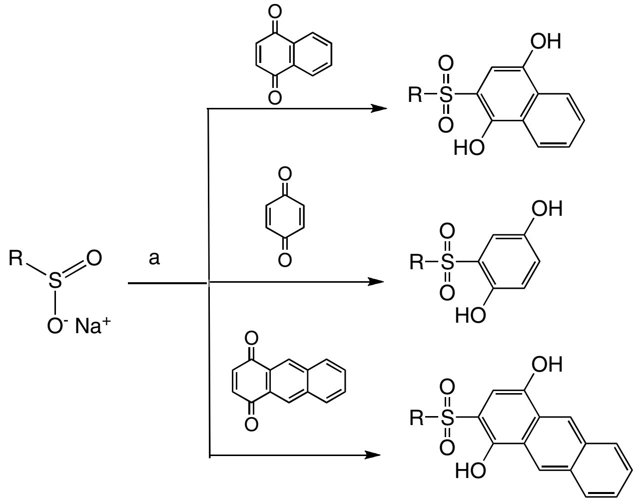


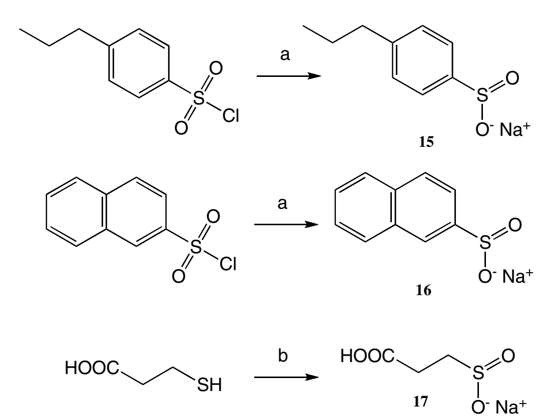
Figure 2. FabH inhibitors **1–14**.

or naphthalene portions of the molecule, or changing the oxidation state of the sulfur and 1,4-diol. The activity of each of these analogs with each enzyme is shown in Table 1. The toluene portion of **1** was very tolerant to modifications. Replacing the toluene ring with a methyl (**2**) or carboxy propyl (**3**) groups resulted in ~7-fold decrease in activity against ecFabH and ~5-fold decrease in activity against mtFabH. Interestingly, both compounds **2** and **3** were slightly more active against pfFabH than the parent compounds **1** (**2** was ~3 times more active against pfFabH than **1**). Replacing the toluene ring with a phenyl group (**4**) resulted in a decrease in activity against the three enzymes. Introducing a hydrophilic acetamide group (**5**) in place of the methyl group of **1** gave comparable activity against ecFabH and ~2.5 improvement in activity against pfFabH. A slight improvement in activity against ecFabH was observed when the methyl group of **1** was replaced by more hydrophobic groups such as chlolro and propyl (compounds **6** and **7**, respectively). However, these changes did not improve the activity against pfFabH or mtFabH. Increasing the size of the toluene portion of **1** by an extra phenyl group (**8**) resulted in no significant change in activity against ecFabH and a ~5 fold decrease in activity against pfFabH.

The naphthalene-1,4-diol portion of **1** was important for activity against all three FabH enzymes. Extending the size of the naphthalene-1,4-diol with an extra phenyl group (**9**) resulted in much lower activity against the three FabH enzymes. Decreasing the size of the naphthalene-1,4-diol by replacing it with a hydroquinone moiety (**10** and **11**) resulted in a major loss of activity against both



Scheme 1. Reagents: (a) TFA, CH_2Cl_2, H_2O.



Scheme 2. Reagents and condition: (a) Na_2SO_3, $NaHCO_3$, H_2O; (b) *m*CPBA, CH_2Cl_2, −30 °C.