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Design, synthesis and antibacterial activities of 5-(pyrazin-2-yl) -4*H*-1,2,4-triazole-3-thiol derivatives containing Schiff base formation as FabH inhibitory

Fei Zhang, Qing Wen, She-Feng Wang, Baloch Shahla Karim, Yu-Shun Yang, Jia-Jia Liu, Wei-Ming Zhang *, Hai-Liang Zhu *

Nanjing Institute for the Comprehensive Utilization of Wild Plant, Nanjing 210042, People's Republic of China
State Key Laboratory of Pharmaceutical Biotechnology, Nanjing University, Nanjing 210093, People's Republic of China

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ABSTRACT

A series of novel schiff base derivatives ($\mathbf{H^1}$–$\mathbf{H^{20}}$) containing pyrazine and triazole moiety have been designed and synthesized, and their biological activities were also evaluated as potential inhibitors of β-ketoacyl-acyl carrier protein synthase III (FabH). These compounds were assayed for antibacterial activity against *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Bacillus subtilis* and *Bacillus amyloliquefaciens* and selected compounds among them were tested for their *Escherichia coli* FabH inhibitory activity. Based on the biological data, compound $\mathbf{H^{17}}$ showed the most potent antibacterial activity with MIC values of 0.39–1.56 μg/mL against the tested bacterial strains and exhibited the most potent *E. coli* FabH inhibitory activity with IC_{50} of 5.2 μM, being better than the positive control Kanamycin B with IC_{50} of 6.3 μM. Furthermore, docking simulation was performed to position compound $\mathbf{H^{17}}$ into the *E. coli* FabH active site to determine the probable binding conformation. This study indicated that compound $\mathbf{H^{17}}$ has demonstrated significant *E. coli* FabH inhibitory activity as a potential antibacterial agent and provides valuable information for the design of *E. coli* FabH inhibitors.

Certain bacterial diseases pose potential threat to human health and these bacterial diseases yet have not been overcome.[1] More than one-third of the world populations are infected by bacterial pathogens and nearly two million people per year die from bacterial infections.[2] The overuse of various antibiotics has caused resistance in certain bacteria and the human pathogen no longer response to these clinically used antibiotics.[3,4] Therefore, there is an urgent need for development of new antibacterial agents with novel target, and the newly designed antibiotics can overcome the shortcomings of previously developed antibacterial drugs.[5,6] To overcome the emerging drug resistance, the discovery of novel antibiotic chemical scaffolds with new mode of action is crucial for bacteria survival.

The fatty acid biosynthesis (FAS) is an essential metabolic process for prokaryotic organisms and it is required for cell viability and growth, and recently it has attracted the attention to be used as a target for new antibacterial drugs.[7,8] The human fatty acid synthesis occurs via a homodimeric multifunctional enzyme,[9,10] while in bacteria the pathway is consists of various discrete enzymes[11] and each one can be considered a supposed target. These features make the type II FAS pathway a potential target for new antimicrobial agents.[12]

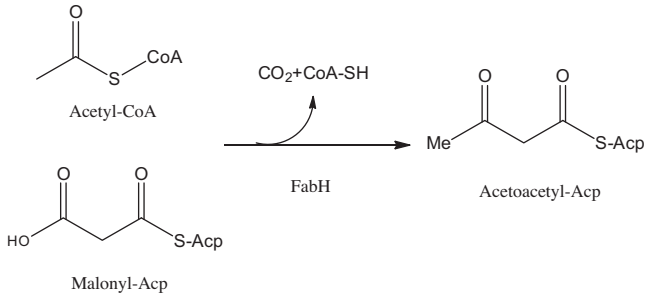

Figure 1. FabH accomplishes the initial condensation step in FAS II.

The β-ketoacyl-acyl carrier protein synthase III (FabH) is a key enzyme in bacterial FAS pathway, which initiates the FAB cycle by catalyzing the first condensation step between acetyl-CoA and malonyl-ACP, playing a key regulatory role in the bacterial FAB cycle (Fig. 1).[13] Furthermore, FabH has been confirmed as an essential for the survival of organism and it exists in a wide number of important human pathogens.[14,15] FabH has also no close homo-

* Corresponding author. Tel./fax: +86 25 83592672.
E-mail addresses: botanyzh@163.com (W.-M. Zhang), zhuhl@nju.edu.cn (H.-L. Zhu).

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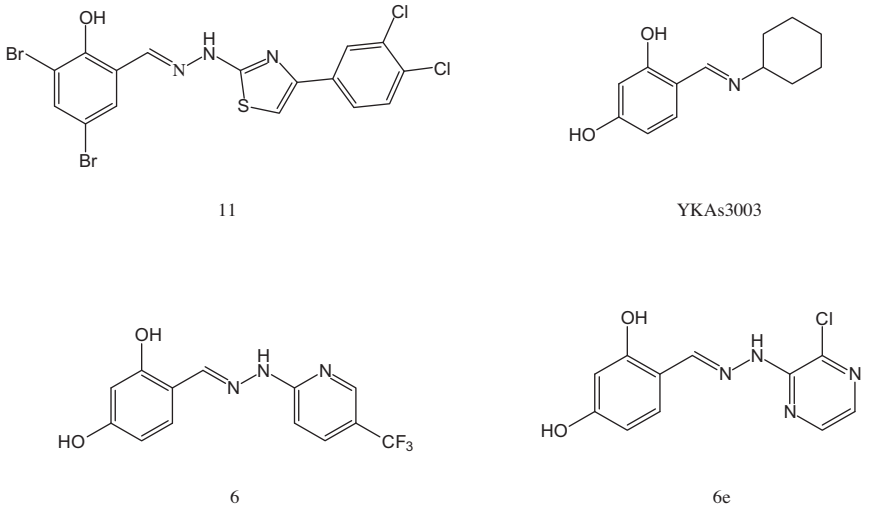


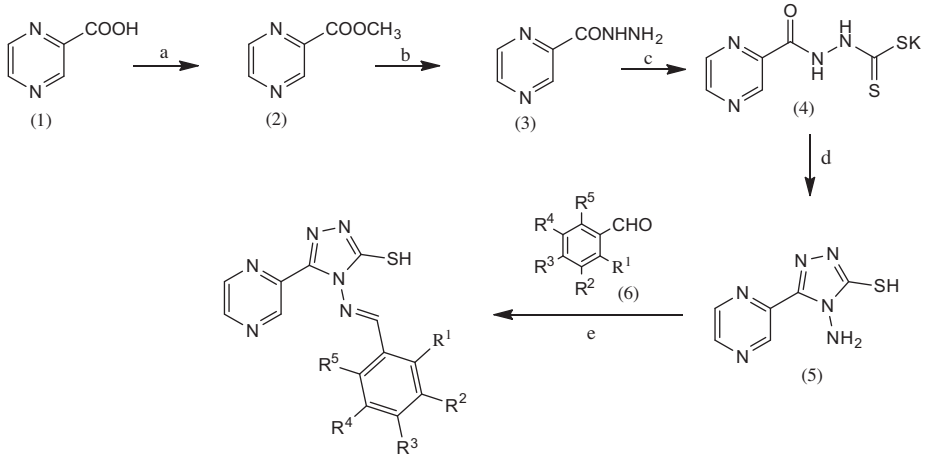
Figure 2. New potential FabH inhibitors: **11** discovered by Zhu et al.; **YKAs3003**, **6** and **6e** discovered by Kim et al.

logue in humans and its selectivity for acetyl-CoA over acyl-ACP differs from the other condensing enzymes involved in fatty acid synthesis in bacteria.[16,17] In addition, some chemical compounds from various organisms have been revealed to inhibiting the FabH,[18–22] consequently making FabH as an new target for the development of new antimicrobial agents.

Previously various kinds of compounds were screened by using structure guided drug design methods.[23–26] The compounds containing Schiff base moiety or hydrozone moiety show effective antimicrobial activity against various bacteria, including inhibitors of FabH, as reported previously by our laboratory[24,25,38] and Kim and co-workers[26,27] Compounds such as (**11**;[24] **YKAs3003**;[27] **6** and **6e**[26]) reported as inhibitors of *Escherichia coli* FabH showed the most effective antibacterial activity and FabH inhibitory activity several times in each article that are displayed in Figure 2. As shown in Figure 2, these compounds always have a Schiff base moiety (—C═N—) or a hydrazone moiety (—NH—N═CH—) in the core structures. Moreover, triazole moiety have attracted considerable attention because of their particular physical, chemical and biological activities based on their particular structures and wide spectrum of biological properties such as antimicrobial activity against several strains of bacteria.[28,29]

In addition, the introduction of different heterocyclic compounds to the backbone of carbon chain will affect its biological activities, which has drawn widespread attention.[30,31] Ligands containing a pyrazine ring are generally studied especially π-donor properties.[32] Pyrazine has been paid wide attention, due to the diazine rings form a significant class of compounds existed in several natural and synthetic compounds.[33] Pyrazine derivatives have been widely used in the field of pharmaceutical chemistry for the skeleton of biologically active sites.[34]

Some Schiff base derivatives have been reported as FabH inhibitors.[6,24,26] In continuation to widen our research on antibacterial compounds with FabH inhibitory activity, we sought to synthesis a set of Schiff base derivatives containing pyrazine and triazole moiety as antibacterial agents. The antimicrobial activity of these compounds against two Gram-negative bacterial strains (*Escherichia coli and Pseudomonas fluorescence*) and three Gram-positive bacterial strains (*Staphylococcus aureus*, *Bacillus subtilis and Bacillus amyloliquefaciens*) were also determined. Meanwhile, docking simulations were performed using the X-ray crystallographic structure of the FabH of *E. coli* complexed with the most potent inhibitors[6,35] to explore the binding modes of these compounds at the active site.



Scheme 1. The synthetic routes of compounds H^1–H^{20}. Reagents and conditions: (a), methanol, concentrated sulfuric acid, reflux, 12 h; (b) hydrazine hydrate (85%), ethanol, reflux, 4–5 h; (c) KOH (0.9 N), CS_2, ethanol, rt, 8 h; (d) hydrazine hydrate (85%), ethanol, reflux,12 h; (e) ethanol, acetic acid, reflux,4–5 h.

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