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Design, synthesis and molecular docking of 1,4-benzodioxane thiazolidinedione piperazine derivatives as FabH inhibitors

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ABSTRACT

A series of novel 1,4-benzodioxane thiazolidinedione piperazine derivatives targeting FabH were designed and synthesized. The compounds exhibited better inhibitory activity against Gram-negative bacteria by computer-assisted screening, antibacterial activity test and *E. coli* FabH inhibitory activity test, wherein compound **6j** exhibited the most significant inhibitory activity (MIC = 1.80 μM for *P. aeruginosa*, MIC = 1.56 μM for *E. coli*). Besides, compound **6j** still showed the best *E. coli* FabH inhibitory activity (IC_{50} = 0.06 μM). Moreover, the antibacterial activities of all compounds were strongly correlated with the inhibitory ability of FabH, with a correlation coefficient of 0.954. Computational docking studies also showed that compound **6j** has interacting with FabH key residues in the active site.

1. Introduction

Currently, infections caused by bacteria are still an important cause of human illness or even death. Although the discovery of antibiotics has improved the current situation of bacterial infection, the antibacterial effect was gradually reduced due to the emergence of bacterial drug resistance [1–3]. Therefore, the development of new antibacterial agents is a very important task. FabH(*β*-ketoacyl-acyl carrier protein (ACP) synthase III) is a 35KDa protein that exists as a homodimer in pathogens and catalyzes the initial steps of the fatty acid synthesis pathway, controlling the extended cycle of the entire carbon chain and is critical for bacterial survival [4–6]. Most importantly, FabH is highly conserved in sequence and structure for Gram-positive and Gram-negative bacteria and does not have the same structure as human fatty acid synthesis [7]. Therefore, FabH has become the most attractive antibacterial target.

1,4-benzodioxane derivatives have a wide range of biological activities such as anti-tumor, antibacterial, anti-inflammatory, adrenaline antagonism [8,9]. In 2011, Mallesha et al. [10] first proved that 1,4-benzodioxane derivatives has good antibacterial activity. In 2014, Song et al. [11] synthesized a series of compounds containing 1,4-benzodioxane structure, and found that it can target FabH and play an antibacterial role. In addition, studies have shown that the introduction of thiazolidinedione structure on 1,4-benzodioxane can significantly enhance the antibacterial activity, and the development of a new class of 1,4-benzodioxane antibacterial drugs indicates the direction [12]. Piperazine is currently the most important building block for drug discovery, and a large number of positive hits are encountered in the biological screening of the heterocycle and its homologues. Literature investigations show that Piperazine derivatives are important pharmacophores in many different therapeutic fields [10]. For example, piperazine sulfonamide is the most widely used antibacterial agent in the world. It has low toxicity and excellent activity and can treat common bacterial diseases [13]. More importantly, Some piperazine analogues have the ability to bind to FabH [14]. In summary, as shown in Fig. 1, we extracted the structure of 1,4-benzodioxane and thiazolidione, and then introduce a synergistic group piperazine ring. A series of novel 1,4-benzodioxane thiazolidinedione piperazine derivatives were designed and synthesized, and the antibacterial activity and FabH inhibitory activity of these derivatives were tested.

Subsequently, in order to verify whether these designed compounds can target FabH, molecular docking was performed by fitting these designed compounds to the active binding sites of FabH (PDB code: 1HNJ) [15]. Then, the obtained results are plotted as a line scatter plot and shown in Fig. 2. It is clear from the corresponding -CDOCKER_INTERACTION_ENERGY values that all compounds have strong binding ability to the FabH active site, indicating that they are likely to exhibit more potent inhibitory activity against FabH. In addition, ADMET properties are important conditions and major components of pharmacokinetics, and ADMET predictions for the six

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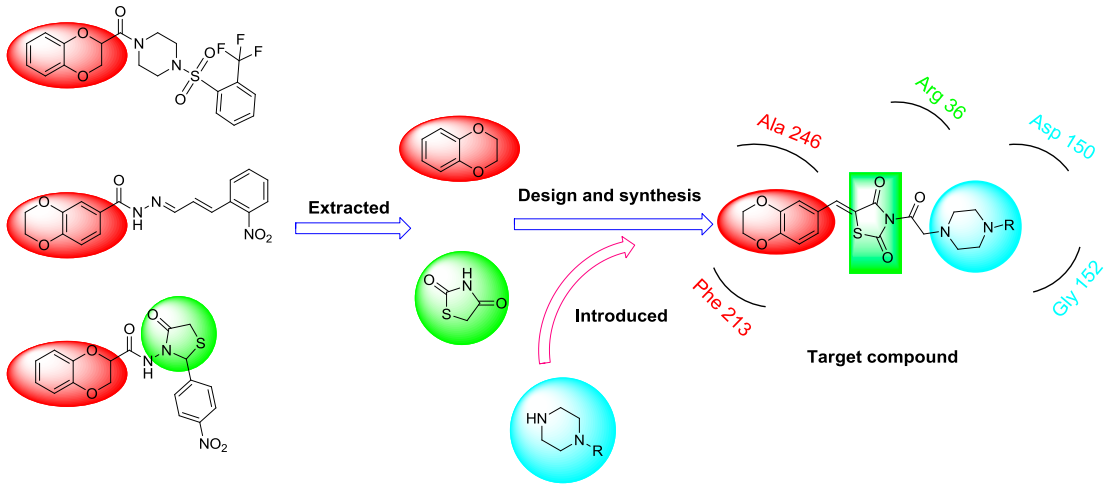
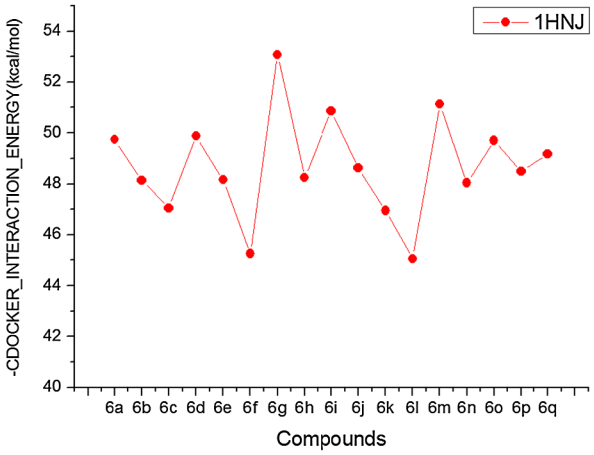


Fig. 1. Design strategy of the target compounds.



6a: R= 3-ClPh 6d: R= 2,3-CH_3Ph 6g: R= -CH_2-2Ph 6j: R= 2-Py 6m: R= 3-triFPh 6p: R= 3,4-ClPh
6b: R= 4-OMePh 6e: R= 4-NO_2Ph 6h: R= 2-OMePh 6k: R= 4-FPh 6n: R= 2,3-ClPh 6q: R= CH_2-Ph
6c: R= Ph 6f : R= 4-ClPh 6i: R= 2-ClPh 6l: R= 2-FPh 6o: R= 3-OMePh

Fig. 2. The CDOCKER_INTERACTION_ENERGY (kcal/mol) obtained from the docking study of all synthesized compounds by the CDOCKER protocol (Discovery Studio 3.1, Accelrys, Co. Ltd).

compounds show satisfactory results (Fig. 3). Therefore, these preliminary analyses were used as stimulators for the synthesis of these 1,4-benzodioxane thiazolidinedione piperazine derivatives.

2. Results and discussion

2.1. Chemistry

The synthetic route to target compounds (**6b**, **6c**, **6e**, **6j**, **6k**, **6p**) were shown in Scheme 1. It was synthesized for the first time and prepared in three steps. First, 1,4-benzodioxan-6 formaldehyde is reacted with a thiazolidinedione by Mannich reaction to obtain an intermediate product **3**. Next, product **3** is reacted with bromoacetyl bromide in DMF using potassium carbonate as a catalyst to obtain product **4**. Finally, product **4** was reacted with piperazine containing different substituents in DMF at 120 °C to obtain the target compounds.

2.2. Antibacterial activities

The MIC (Minimum inhibitory concentration, μM) of screened compounds (**6b**, **6c**, **6e**, **6j**, **6k**, **6p**) against these bacterial strains are tested by MTT method and the activity data was presented in Table 1.

Based on the data obtained, we found that the six compounds showed some inhibitory activity. In particular, the inhibitory effect on Gram-negative bacteria was significantly stronger than that of Gram-positive bacteria, and the inhibitory activity was significantly higher than that of the positive control **penicillin**. Among them, compound **6j** has the highest inhibitory activity against two Gram-negative bacteria (MIC = 1.80 μM for *P. aeruginosa*, MIC = 1.56 μM for *E. coli*).

2.3. E. coli FabH inhibitory activity

E. coli FabH inhibition potency of selected compounds **6b**, **6c**, **6e**, **6j**, **6k**, **6p** was examined and the results are summarized in Table 2. As shown in Table 2, all of the compounds tested exhibited a certain inhibitory activity against *E. coli* FabH (IC_{50} = 0.06–3.18 μM) wherein the compound having the highest inhibitory activity remained Compound **6j** (IC_{50} = 0.06 μM). As shown in Fig. 4, the inhibitory activity of the test compound against *E. coli* was correlated with the inhibitory activity against *E. coli* FabH. A correlation coefficient of 0.954 was found by data analysis. This result indicates that the 1,4-benzodioxane thiazolidinedione piperazine derivatives can inhibit the function of FabH and the antibacterial effect was produced partly by interaction of FabH protein and the compounds.

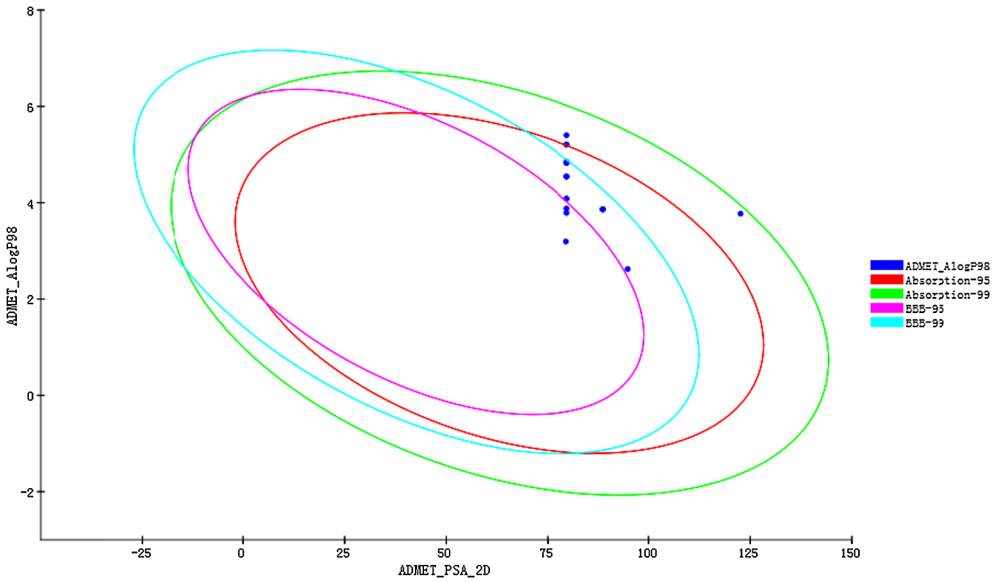


Fig. 3. ADMET properties predicted for seventeen novel compounds. Compounds located inside the innermost oval have the best results. The six compounds were as follows: **6k**, **6c**, **6p**, **6b**, **6j**, **6e** (from top to bottom, from left to right).

2.4. Docking simulations

Docking study was performed to fit compound **6j** into the active center of the *E. coli* FabH (PDB code: 1HNJ). Docking algorithm utilized: CDOCKER algorithm; definition of binding site: 28.449, 9.903, 33.443; radius: 13.832; scoring function: CDOCKER interaction energy; rigid receptor: PDB code 1HNJ; flexible ligand docking: YES; cluster analysis of docking poses: ten optimal poses were retained. The obtained results were presented in Fig. 5. Fig. 5A, B showed the binding mode of compound **6j** interacting with *E. coli* FabH protein and the docking results revealed that three amino acids ARG36, ASP150 and GLY152 located in the binding pocket of protein played a vital roles in the conformation with compound **6j**, which were stabilized by four hydrogen bonds and π–sigma interaction. One hydrogen bond with 3.6 Å was formed between ARG36 and O of the Thiazolidinedione. One hydrogen bond with 5.1 Å was formed between ARG36 and O of the Carbonyl group. One hydrogen bond with 5 Å was formed between ASP150 and N of the Pyridyl group, while other hydrogen bond with 4.3 Å was involved in ASP150 and H of the Pyridyl group. The amino acid residue GLY152 interacts with the pyridyl group to form a *Pi*-Sigma.

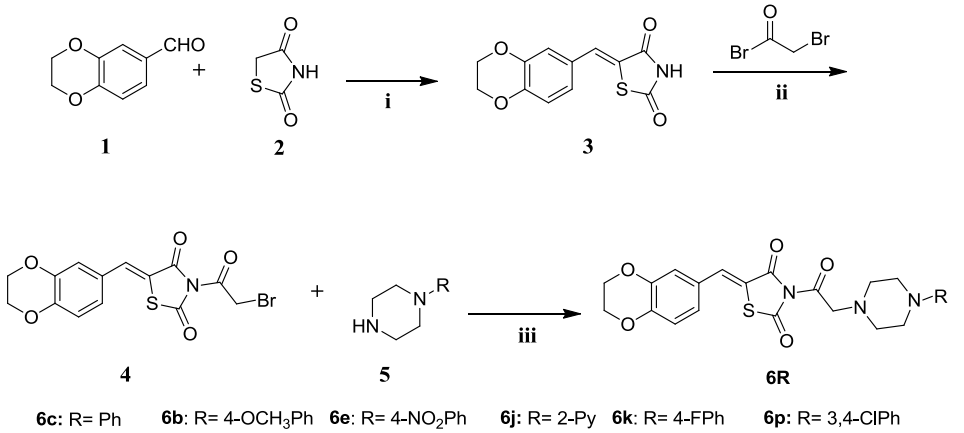
Table 1
Antibacterial activity (MIC) of the synthetic compounds.

Compounds	MIC[a] (μM)			
	B. subtilis	*S. aureus*	*P. aeruginosa*	*E. coli*
6b	8.94	8.02	2.28	6.86
6c	11.06	9.14	4.61	6.19
6e	9.24	7.27	3.27	1.98
6j	6.88	5.13	1.80	1.56
6k	5.37	11.86	2.76	3.36
6p	12.64	7.37	4.17	8.93
Penicillin	1.56	1.56	6.25	6.25

[a] The three-time average experiment, the experimental results take the average, the error is between 5% and 10%.

3. Conclusion

In summary, FabH was used as a drug target, and a series of 1,4-benzodioxane thiazolidinedione piperazine derivatives were designed and synthesized by computer simulation drug design technology, and



Reagents and conditions: (**i**) pyridine, Acetone, reflux, 4h. (**ii**)Potassium carbonate, N,N-dimethylformamide, reflux, 120℃,3 min. (**iii**)potassium carbonate, tetrabutylammonium bromide, N,N-dimethylformamide, 120℃,3 h.

Scheme 1. The synthetic route to target compounds.

Table 2
Inhibition of the *E. coli* FabH.

Compounds	IC_{50}[a] (μM)
6b	1.58
6c	1.39
6e	0.32
6j	0.06
6k	0.97
6p	3.18

[a] The three-time average experiment, the experimental results take the average, the error is between 5% and 10%.

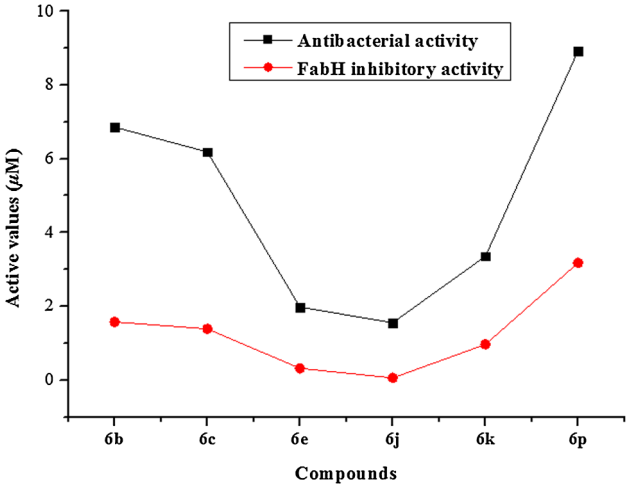


Fig. 4. Correlation between the antibacterial activity against *E. coli* and the *E. coli* FabH inhibitory activity, which indicated that there was a moderate correlation between FabH inhibition and antibacterial activity.

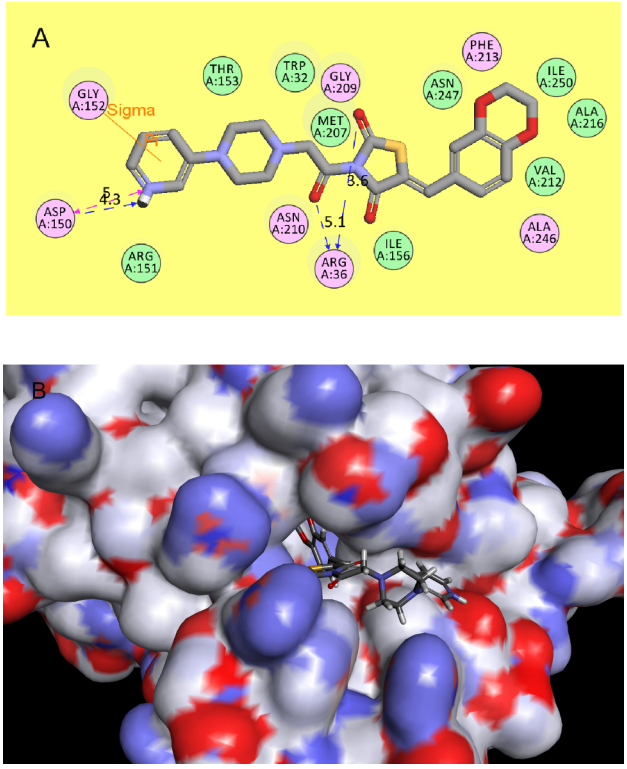


Fig. 5. (A) 2D molecular docking model of compound **6j** with 1HNJ. (B) 3D interaction map between compound **6j** and 1HNJ binding site.

the antibacterial activity and evaluation study of *E. coli* FabH inhibitory activity. The experimental results showed that some of the compounds showed strong anti-Gram-negative bacterial activity, and the compound **6j** had the best *E. coli* inhibitory activity (MIC = 1.80 μM for *P. aeruginosa*, MIC = 1.56 μM for *E. coli*), which was four times higher than the positive control drug penicillin (MIC = 6.25 μM). In the FabH inhibitory activity experiment, **6j** still showed the best enzyme inhibitory activity (IC_{50} = 0.06 μM), and the experimental results showed that the FabH inhibitory activity and the antibacterial activity showed a strong correlation with a correlation coefficient of 0.954. This indicates that the antibacterial activity of this series of compounds is produced by inhibiting FabH. The results of molecular docking also showed that compound **6j** binds perfectly to the FabH active site and forms hydrogen bonds and Pi-sigma interactions with the ARG36, ASP150 and GLY152 amino acid residues of the active site. A series of new 1,4-benzodioxane thiazolidinedione piperazine derivatives represented by **6j** are expected to be new antibacterial lead drugs targeting FabH.

4. Materials and methods

4.1. General

All of the synthesized compounds were chemically characterized by thin layer chromatography (TLC), proton nuclear magnetic resonance (^{1}H NMR) and elemental microanalyses (CHN). ^{1}H NMR spectra were measured on a Bruker AV-400 spectrometer at 25 °C and referenced to Me_4Si. Chemical shifts were reported in ppm (δ) using the residual solvent line as internal standard. Splitting patterns are designed as s, singlet; d, doublet; t, triplet; m, multiplet. ESI-MS spectra were recorded on a Mariner System 5304 Mass spectrometer. Elemental analyses were performed on a CHN-O-Rapid instrument and were within ± 0.4% of the theoretical values. Melting points were determined on a WRS-1B apparatus (Jingke Corp., Shanghai, China) and are as read. Analytic thin-layer chromatography (TLC) was performed on the glass-backed silica gel sheets (silica gel 60 Å GF254). All compounds were detected using UV light (254 nm or 365 nm).

4.2. General method for the preparation of target compounds

4.2.1. Synthesis of compound 3

The 1,4-benzodioxan-6-formaldehyde (10 mmol) and the thiazolidinedione (10 mmol) were dissolved in 50 mL of acetone, and 1 mL of pyridine was slowly added dropwise, followed by refluxing for 4 h, and TLC tracking was carried out. After the reaction was completed, it was extracted three times with ethyl acetate and distilled water, then the organic phase was collected, dried and evaporated to give compound **3**.

4.2.2. Synthesis of compound 4

The Compound 3 (8 mmol) and the Potassium carbonate (10 mmol) were dissolved in 30 mL of N,N-dimethylformamide (30 mL), and the bromoacetyl bromide (10 mmol) was slowly added dropwise, followed reaction at 120 °C for 30 min. The reaction was stopped and the reaction solution was poured into an ice water mixture. After solid precipitation, filtration and washing with ice diethyl ether three times to obtain compound **4**.

4.2.3. Synthesis of target compounds (6R)

The compound **4** (3 mmol) and the different substituents of the piperazine (3 mmol) were dissolved in N,N-dimethylformamide (30 mL), and after adding potassium carbonate (4.5 mmol) and tetrabutylammonium bromide (1 mmol) as a catalyst at 120 °C for 3 h, the solid was removed by filtration, and the liquid evaporated to dryness under reduced pressure. It was extracted three times with ethyl acetate and distilled water, dried, concentrated under reduced pressure, and then recrystallized from anhydrous ethanol to give the desired product.

4.2.3.1. 5-((2,3-dihydrobenzo[b][1,4]dioxin-6-yl)methylene)-3-(2-(4-(4-methoxyphenyl)piperazin-1-yl)acetyl)thiazolidine-2,4-dione ***(6b)***. White powder. Mp: 180.5–180.9 °C ^{1}H NMR (400 MHz, d_6-DMSO): 7.28 (s, 1H); 7.02–7.04 (m, 2H); 6.92–6.94 (m, 3H); 6.84–6.87 (m, 2H); 4.26–4.28 (m, 4H); 3.70(s, 3H); 3.35 (s, 2H);3.15 (s, 8H). MS (ESI): 496 ($C_{25}H_{26}N_3O_6S$, $[M + H]^+$) Anal. Calcd. (%) for $C_{25}H_{25}N_3O_6S$: C, 60.59; H, 5.08; N, 8.48%; Found (%): C, 60.71; H, 5.15; N, 8.32%.

*4.2.3.2. 5-((2,3-dihydrobenzo[b][1,4]dioxin-6-yl)methylene)-3-(2-(4-phenylpiperazin-1-yl)acetyl)thiazolidine-2,4-dione(****6c****)*. White powder. Mp: 179.8–180.8 °C ^{1}H NMR (400 MHz, d_6-DMSO): 7.20–7.28 (m, 3H); 6.92–7.05 (m, 5H); 6.85 (s, 1H); 4.49(s, 2H); 4.27–4.33 (m, 4H); 3.25–3.27(m, 4H); 3.13–3.15 (m,4H). MS (ESI): 466 (C24H24N3O5S, [M + H] +) Anal. Calcd. (%) for C24H23N3O5S: C, 61.92; H, 4.98; N, 9.03%; Found (%): C, 62.79; H, 5.11; N, 9.12%.

*4.2.3.3. 5-((2,3-dihydrobenzo[b][1,4]dioxin-6-yl)methylene)-3-(2-(4-(4-nitrophenyl)piperazin-1-yl)acetyl)thiazolidine-2,4-dione(****6e****)*. Light yellow powder. Mp: 208.8–209.0 °C ^{1}H NMR (400 MHz, d_6-DMSO): 8.07–8.10 (m, 2H); 7.38 (s, 1H); 7.04–7.08 (m, 4H); 6.94–6.96(d, J = 8 Hz, 1H); 4.26–4.29 (m, 4H); 3.54–3.57(m, 4H); 3.38 (s, 2H), 3.06–3.09(m, 4H). MS (ESI): 511 (C24H23N4O7S, [M + H] +) Anal. Calcd. (%) for C24H22N4O7S: C, 56.46; H, 4.34; N, 10.97%; Found (%): C, 56.55; H, 4.47; N, 10.81%.

*4.2.3.4. 5-((2,3-dihydrobenzo[b][1,4]dioxin-6-yl)methylene)-3-(2-(4-(pyridin-3-yl)piperazin-1-yl)acetyl)thiazolidine-2,4-dione(****6j****)*. White powder. Mp: 98.3–100.5 °C ^{1}H NMR (400 MHz, d_6-DMSO): 7.91(S, 2H); 7.17–7.19 (m, 4H); 6.85 (s, 1H); 7.04–7.06(d, J = 8.0 Hz, 2H); 4.48 (s, 2H); 4.33–4.34 (m, 8H); 4.15–4.20(m, 4H). MS (ESI): 467 (C24H23N4O5S, [M + H] +) Anal. Calcd. (%) for C23H22N4O5S: C, 59.22; H, 4.75; N, 12.01%; Found (%): C, 59.35; H, 4.58; N, 12.13%.

*4.2.3.5. 5-((2,3-dihydrobenzo[b][1,4]dioxin-6-yl)methylene)-3-(2-(4-(4-fluorophenyl)piperazin-1-yl)acetyl)thiazolidine-2,4-dione(****6k****)*. White powder. Mp: 189.0–190.0 °C ^{1}H NMR (400 MHz, d_6-DMSO): 7.29 (S, 1H); 7.07–7.11 (m, 2H); 7.04 (s, 1H); 6.99–7.02 (m, 3H); 6.92–6.94 (d, J = 8 Hz, 1H); 4.26–4.28 (m, 4H); 3.34–3.40 (m, 2H); 3.19–3.22 (m, 4H); 3.13–3.16 (m, 4H). MS (ESI): 484 (C24H23FN3O5S, [M + H] +) Anal. Calcd. (%) for C24H22FN3O5S: C, 59.62; H, 4.59; N, 8.69%; Found (%): C, 56.81; H, 4.33; N, 8.82%.

4.2.3.6. 3-(2-(4-(3,4-dichlorophenyl)piperazin-1-yl)acetyl)-5-((2,3-dihydrobenzo[b][1,4]dioxin-6-yl)methylene)thiazolidine-2,4-dione ***(6p)***. White powder. Mp: 177.4–178.4 °C ^{1}H NMR (400 MHz, d_6-DMSO): 7.43–7.46 (d, J = 3.2 Hz 1H); 7.33 (s, 1H); 7.20–7.21 (d, J = 3.2 Hz, 1H); 7.03–7.05(m, 2H); 6.93–7.00 (m, 2H); 4.26–4.29 (m, 4H); 3.30–3.35(m, 6H); 3.09–3.12(m, 4H). MS (ESI): 535 (C24H22Cl2N3O5S, [M + H] +) Anal. Calcd. (%) for C24H21Cl2N3O5S: C, 53.94; H, 3.96; N, 7.86%; Found (%): C, 54.12; H, 3.78; N, 7.96%.

4.3. Antibacterial assay

The antibacterial activity of the synthesized compounds was tested against *Bacillus subtilis*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Staphylococcus aureus* using LB medium (Luria-Bertani medium: yeast extract 5.0 g, peptone 10.0 g, sodium chloride 5.0 g, distilled water 1000 mL). Minimum inhibitory concentration of the test compounds was determined by a colorimetric method using the dye MTT (3-(4, 5-dimethylth-iazol-2-yl)-2, 5-diphenyl tet-razoliumbromide). Also included was the activity of reference compound Penicillin under identical conditions for comparison. A stock solution of the synthesized compound (1000 μmol/mL) in DMSO was prepared and graded quantities of the test compounds were incorporated in specified quantity of sterilized liquid LB medium. Drug stocks were formulated in DMSO and then the compounds were diluted in media to final working concentrations of 25, 12.5, 6.25, 3.125, 1.5625 μg/mL. A specified amount of medium containing the compound is added to a 96-well plate. Then, a bacterial suspension having a concentration of about 10^5 cfu/mL was added to a 96-well plate and incubated at 37 °C for 24 h. Afterwards, 10 μL of PBS containing MTT 4 mg/mL was added to each well. Incubation was continued at 37 °C for 4 h. The content of each well was removed, and 150 μL of DMSO was added to extract the dye. The optical density (OD) was measured with an ELISA plate reader at 492 nm.

4.4. Kinase selectivity assay

The *E. coli* FabH Assay Kit were purchased from Bio-Swamp. The experiments were performed according to the manufacturer's instructions.

4.5. Molecular modeling

4.5.1. Docking methodology

Molecular docking of compounds into the three dimensional X-ray structure of *E. coli* FabH (PDB code: 1HNJ) was carried out using the Discovery Studio (version 3.1) as implemented through the graphical user interface DS-CDOCKER protocol [14]. The 3D structure of *E. coli* FabH (PDB code: 1HNJ) in docking study was downloaded from Protein Data Bank. The three-dimensional structures of the aforementioned compounds were constructed using Chem. 3D ultra 12.0 software [Chemical Structure Drawing Standard; Cambridge Soft corporation, USA (2010)], then they were energetically minimized by using MMFF94 with 5000 iterations and minimum RMS gradient of 0.10. All bound waters and ligands were eliminated from the protein and the polar hydrogen was added to the proteins. Each compounds would retain 10 poses, and were ranked by CDOCKER_INTERACTION_ENERGY.

4.5.2. ADMET prediction

Absorption, distribution, metabolism, excretion, and toxicity properties (ADMET) of the 17 novel compounds were calculated using the DS software. The aqueous solubility, blood brain barrier penetration, cytochrome P450 2D6 inhibition, hepatotoxicity, human intestinal absorption and plasma protein binding were predicted using this software.

4.6. Statistical analysis

Statistical analysis was performed with SPSS Version 11.0 statistic software package. Comparisons between groups were performed with analysis of non-parametric test. A value of $P < 0.05$ was considered statistically significant.

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