Med Chem Res (2014) 23:2985–2994
DOI 10.1007/s00044-013-0886-8

MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Vanillin derivatives as the selective small molecule inhibitors of FtsZ

Juan Sun · Ming-Hui Li · Xin-Yi Wang · Yang Zhang · Rong-Ju Yuan · Han-Yu Liu · Hai-Liang Zhu

Received: 22 September 2013 / Accepted: 23 November 2013 / Published online: 1 December 2013

Abstract A series of vanillin derivatives have been designed and synthesized and their biological activities were also evaluated as potential inhibitors of FtsZ. These compounds were assayed for antibacterial activity against *Escherichia coli*, *Pseudomonas aeruginosa*, *Bacillus subtilis,* and *Staphylococcus aureus*. Compounds with potent antibacterial activities were tested for their FtsZ inhibitory activity. Compound **4u** showed the most potent antibacterial activity with MIC of 0.28 μg/mL against *E. coli* strains and exhibited the most potent FtsZ inhibitory activity with polymerization IC_{50} of 2.1 μM. Docking simulation was performed to position compound **4u** into the FtsZ active site to determine the probable binding conformation.

Keywords Vanillin derivatives · Schiff base · Antibacterial activity · FtsZ inhibitors

Introduction

Although several classes of antibacterial agents are presently available, resistance in most of the pathogenic bacteria to these drugs constantly emerges. In order to prevent this serious medical problem, the elaboration of new types of antibacterial agents is a very important task (Martin, 2004). Vanillin (4-hydroxy-3-methoxybenzaldehyde), is the major component of natural vanilla, which is one of the most widely used and important flavoring materials worldwide. In common with many other low-molecular weight phenolic compounds, vanillin displays antioxidant, antimicrobial, anticarcinogenic, and antimutagenic properties and hence has the potential for use as a food preservative (Akihiro *et al*., 2011; Bythrow, 2005; Daniel *et al*., 2003; Fitzgerald *et al*., 2004). Synthetic vanillin is also used as an intermediate in the chemical and pharmaceutical industries for the synthesis of herbicides and drugs (Walton *et al*., 2003). In old medicinal literature, vanilla was described as a remedy for fevers (Sardari *et al*., 2000).

Schiff bases, named after Hugo Schiff (Faridbod and Ganjali, 2007), are some of the most widely used organic compounds. They are used as pigments and dyes, catalysts, intermediates in organic synthesis, and as polymer ultraviolet stabilizers (Ti-Feng and Ming-Hua, 2005). Schiff bases have also been shown to exhibit a broad range of biological activities, including antifungal, antibacterial, anti-malarial, antiproliferative, anti-inflammatory, antiviral, and antipyretic properties (Piotr *et al.,* 2009; Lei *et al.,* 2007; Mari *et al.,* 2006; Chohan *et al.,* 2007; Venugopala and Jayashree, 2008; Seshaiah and Atmakuru, 2001; Hacer *et al.,* 2009). Imine or azomethine groups are present in various natural, naturally derived, and non-natural compounds (Cleiton *et al*., 2011). The imine group present in such compounds has been shown to be critical to their biological activities (Bringmann *et al*., 2004; Ana *et al*., 2007; Zhan-Yong *et al*., 2007).

The bacterial cell division machinery consists of a set of proteins that are recruited to the site of division where they assemble to form the divisome. Recruitment of these proteins to the site of division occurs in a specific order, with FtsZ at the top of this hierarchy (Jeffery and Richard,

Juan Sun and Ming-Hui Li have contributed equally to this paper.

J. Sun · M.-H. Li · H.-L. Zhu (✉)
State Key Laboratory of Pharmaceutical Biotechnology, Nanjing University, Nanjing 210093, People's Republic of China
e-mail: zhuhl@nju.edu.cn

X.-Y. Wang · Y. Zhang · R.-J. Yuan · H.-Y. Liu · H.-L. Zhu
School of Life Sciences, Shandong University of Technology, Shandong 255049, People's Republic of China

2003). As such FtsZ is considered to be the most critical component of the division machinery. It is an essential protein for bacterial viability (Frederico and Richard, 2002; Laura and Petra, 2003; Mariana and Jeff, 2003) and it is a highly conserved and potentially broad-spectrum antibacterial target, it does have structural and functional homology, suggesting that FtsZ may also be amenable to inhibitor development. Finally, because cell division proteins are not targeted by any antibiotics in current clinical use, it is expected that there will not be any cross resistance from existing drug-resistant bacterial populations (Lloyd *et al*., 2012).

Molecular hybridization approach is one of the most valuable structural modification tools useful for the discovery of ligands and prototypes presenting either optimized affinity for one bioreceptor or the ability to modulate more than one bioreceptor associated with the target disease (Fraga, 2009; Claudio *et al*., 2007; Frye, 2010). The growing efforts to discover hybrid drugs resulting from the combination of pharmacophoric moieties of different known lead. Hence, the impressive results of Vanillin derivatives and various phenylamine fueled our interest in combining two scaffolds and exploring their possibilities as potential anti-FtsZ agents.

Results and discussion

Chemistry

Twenty-one Vanillin analogs (**4a**–**4u**) were synthesized by following the general pathway outlined in Scheme 1. To a stirred suspension of vanillin in ethyl ether under argon was added acetic anhydride and then DMAP, to form compound **2**. The next step involves a functional group transformation of the fuming nitric acid to acetylizad vanillin and afforded compound **3**. The final step involves reaction between the various aromatic amine and 4-hydroxy-3-methoxy-2-nitrobenzaldehyde, the mixture was dissolved in methanol or acetonitrile and then concentrated under reduced pressure, recrystallized from ethanol form a number of substituted (*E*)-2-methoxy-3-nitro-4-((phenylimino) methyl) phenol (Table 1). All of the synthetic compounds gave satisfactory analytical and spectroscopic data, which were in full accordance with their depicted structures.

Crystal structure determination of compound **4u** was carried out on a D-8 venture diffractometer equipped with graphite-monochromated MoKa ($\lambda = 0.71073$) radiation (Fig. 1). The structure was solved by direct methods and refined on F^2 by full-matrix least-squares methods using SHELX-97. The crystal data, data collection, and refinement parameter for the compound **4u** are listed in Table 2.

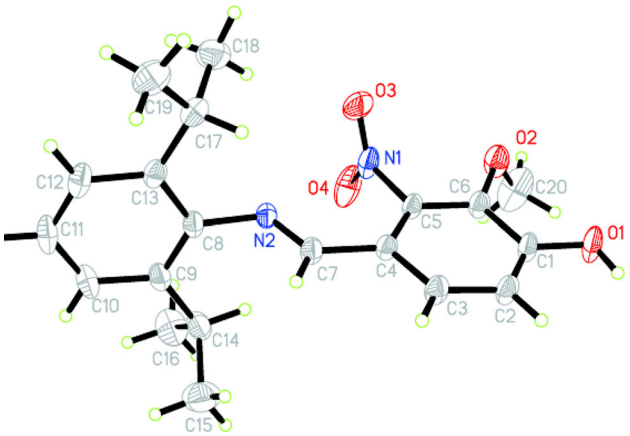
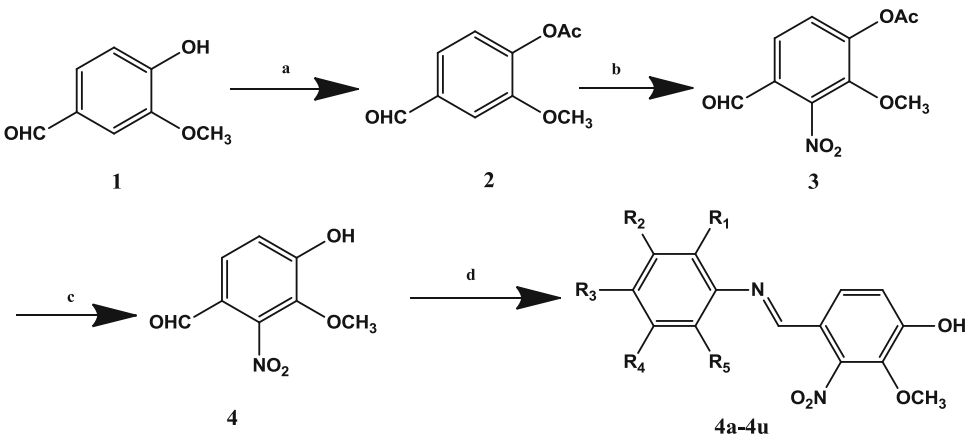


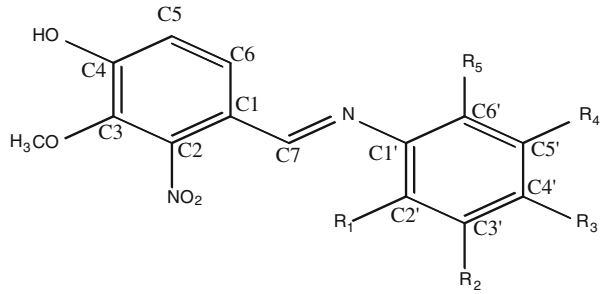
Fig. 1 Crystal structure diagrams of compound **4u**

Scheme 1 Synthetic route of vanillin derivatives (**4a**–**4u**)



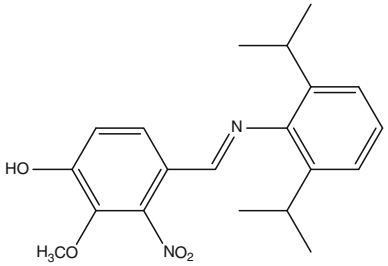
Reagents: (a) Ac_2O, DMAP, Et_2O; (b) HNO_3 fuming; (c) NaOH, H_2O; (d)methanol/acetonitrile, rt

Table 1 Structures of compounds **4a–4u**



Compounds	R1	R2	R3	R4	R5
4a	Cl	H	H	H	H
4b	CH_3	H	H	H	H
4c	CH_3O	H	H	H	H
4d	NO_2	H	H	H	H
4e	H	F	H	H	H
4f	H	CH_3	H	H	H
4g	H	CH_3O	H	H	H
4h	H	NO_2	H	H	H
4i	H	H	Br	H	H
4j	H	H	CH_3	H	H
4k	H	H	CH_3O	H	H
4l	H	H	NO_2	H	H
4m	H	Cl	Cl	H	H
4n	Cl	H	Cl	H	H
4o	Cl	H	H	Cl	H
4p	CH_3	H	H	CH_3	H
4q	H	CH_3	CH_3	H	H
4r	CH_3	H	H	H	CH_3
4s	H	Cl	CH_3	H	H
4t	NO_2	H	Cl	H	H
4u	$(CH_3)_2CH_2$	H	H	H	$(CH_3)_2CH_2$

Table 2 Crystallographical and experimental data for compound **4u**



Compound	**4u**
Empirical formula	$C_{20}H_{24}N_2O_4$
Formula weight	356.41
Crystal system	Monoclinic
Space group	C2/c
a (Å)	28.315(2)
b (Å)	7.8580(6)
c (Å)	18.0219(13)
α (°)	90
β (°)	104.138(90)
γ (°)	90
V (Å)	3888.4(5)
Z	8
D calc/g cm^{-3}	1.218
θ range (°)	2.70–30.83
F(000)	1,520
Reflections collected/unique	42,520/5,213[$R_{int} = 0.020$]
Data/restraints/parameters	4,146/0/241
Absorption coefficient (mm^{-1})	0.129
R_1: $_wR_2$ [$I > 2\sigma$ (*I*)]	0.0750/0.1951
R_1: $_wR_2$ (all date)	0.0932/0.2128
GOOF	1.05

Antibacterial activity

All the synthesized compounds (**4a**–**4u**) were screened for their antibacterial activities against two Gram-negative bacterial strains: *Escherichia coli* and *Pseudomanas aeruginosa* and two Gram-positive bacterial strains: *Bacillus subtilis* and *Staphylococcus aureus* by MTT method. The minimum inhibitory concentrations (MICs) of the compounds against these bacteria were presented in Table 3. Also included was the activity of reference compound Kanamycin under identical conditions for comparison. The results revealed that most of the synthesized compounds exhibited significant antibacterial activities. Among the twenty-one vanillin derivatives, the two substituted derivates **4m**–**4u**, whose MIC values ranging from 0.28 to 45.67 μg/mL, displayed higher antibacterial potencies than one substituted derivatives **4a**–**4l**, which showed the introduction of two substituents leads to the increase of the antibacterial activity.

Compound **4u** exhibited most potent activities with MIC values of 0.28 μg/mL against *E. coli*, which is superior to the positive control kanamycin with corresponding MIC of 0.40 μg/mL. Besides, the data showed compound **4r** displayed significant activities with MIC values ranging from 2.89 to 11.34 μg/mL against the four bacterial lines, respectively, indicating that it possessed broad-spectrum antibacterial activities. Moreover, compound **4p** showed the potent inhibitor against Gram-negative bacteria with MIC values of 3.45 and 5.12 μg/mL, respectively. Compound **4q** displayed significant activities with MIC values of 2.78 and 6.92 μg/mL against Gram-positive bacteria, respectively.

Table 3 Antibacterial activities of synthetic compounds

Compounds	Minimum inhibitory concentrations (MICs) (μg/mL)			
	Gram-negative bacteria		Gram-positive bacteria	
	E. coli ATCC35218	*P. aeruginosa* ATCC13525	*B. subtilis* ATCC6633	*S. aureus* ATCC6538
4a	>100	>100	>100	>100
4b	30.01	29.13	>50	33.00
4c	21.31	>50	20.96	>100
4d	>50	>50	>50	>50
4e	>100	>100	>100	>100
4f	>50	38.14	31.26	33.43
4g	>100	28.11	21.36	>50
4h	>50	>50	>50	>50
4i	>100	>100	>50	>100
4j	35.12	41.31	>50	41.30
4k	30.26	>50	>100	24.69
4l	>50	>50	>50	>50
4m	41.11	37.56	33.92	38.99
4n	32.18	38.92	41.00	45.67
4o	31.02	38.64	41.33	45.01
4p	3.45	5.12	21.58	17.19
4q	21.59	20.83	2.78	6.92
4r	6.12	5.02	2.89	11.34
4s	18.46	15.11	20.10	26.95
4t	31.20	28.47	33.89	37.82
4u	0.28	5.89	3.31	2.03
Kanamycin	0.40	0.61	1.10	0.89

Table 4 FtsZ inhibitory activity of compounds **4m–4u**

Compounds	Polymerization IC_{50} (μM)
4m	85.80
4n	77.64
4o	72.13
4p	15.47
4q	22.98
4r	9.40
4s	41.01
4t	50.11
4u	2.10
Colchicine	104.00

Based on the data obtained, we found that compounds **4p–4r** with substituted methyl group on benzoic acid component exhibited significant antibacterial activities with MICs of 2.78–21.59 μg/mL. A significant loss of activity was observed when introducing the chlorine group in the benzene-ring (**4m–4o**), with MIC values ranging from 31.02 to 45.67 μg/mL. We proposed that electron-donating groups on benzoic acid component were conducive to the antibacterial activity and compounds with electron-with-drawing halogen groups on benzoic acid component were not favorable for activity.

Furthermore, compounds **4s** and **4t** exhibited moderate antibacterial activities. With MICs of 15.11–26.95 μg/mL and 28.47–37.82 μg/mL, respectively.

Table 5 The docking calculation of the synthesized compounds (**4a–4u**)

Compound	CDocker_interaction_energy [ΔGb (kcal/mol)]
4a	−30.0389
4b	−32.9862
4c	−33.8625
4d	−32.3104
4e	−30.0201
4f	−32.6593
4g	−33.6980
4h	−31.5544
4i	−30.7235
4j	−32.6216
4k	−33.2359
4l	−31.1086
4m	−37.5321
4n	−37.8962
4o	−38.0389
4p	−40.1212
4q	−40.0013
4r	−40.5544
4s	−39.7235
4t	−39.1086
4u	−43.5656

Inhibition of FtsZ polymerization

The GTPase FtsZ inhibitory potency of the selected compounds was examined and the results were summarized in Table 4. As shown in Table 4, among the tested compounds, compounds **4u** showed potent inhibitory activities with polymerization ID_{50} of 2.1 μM. Other tested compounds displayed moderate inhibitory activities with ID_{50} ranging from 9.4 to 85.8 μM. The results were corresponding to the structure relationships (SAR) of their antibacterial activities.

Binding model of compounds into FtsZ structure

Molecular docking of the synthesized compounds and FtsZ was performed on the binding model based on the FtsZ protein complex structure (2VAM. pdb). All docking runs

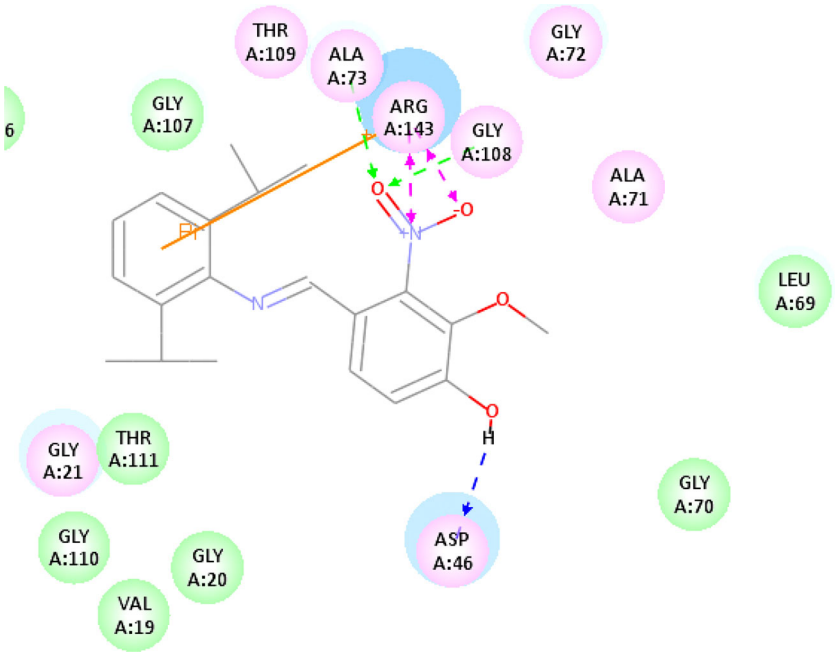


Fig. 2 2D molecular docking modeling of compound **4u** with 2VAM

were applied LigandFit Dock protocol of Discovery Studio 3.1. The docking calculation of the synthesized compounds was showed in Table 5. The interaction energy of the compounds and their antibacterial activity showed the corresponding results. Among the docking calculation of the synthesized compounds, compounds **4u** showed the lowest interaction energy. The binding model of compound **4u** and FtsZ was depicted in Fig. 2. In the binding model, compound **4u** was nicely bound to the FtsZ with five interaction bonds. The hydrogen of Ala 73, Gly 108, and Arg 143 were, respectively, formed three hydrogen bonds interaction with oxygen atom of nitro group of compound **4u**. Besides, between the oxygen atom of the hydroxyl group and nitrogen atom of Asp 46, as well as between the nitrogen atom of nitro group and amino hydrogen of Arg 143, there are two optimal H-bonds interaction. Moreover, the π-cation interactions were existed between benzene ring and amino acids Arg 143.

Conclusions

In summary, a series of novel vanillin derivatives **4a–4u** were synthesized and tested for their inhibitory activities against *E. coli*, *P. aeruginosa*, *B. subtilis,* and *S. aureus*. Many of them exhibited potent antibacterial and FtsZ inhibitory activities. Particularly, Compound **4u** were proved to be the most potent compounds against *E. coli*. Preliminary SARs and molecular modeling study provided further insight into interactions between the enzyme and its ligand. The result provided valuable information for the design of FtsZ inhibitors as antibacterial agents.

Experimental

Chemistry

All chemicals and reagents used in the current study were of analytical grade. The reactions were monitored by thin layer chromatography (TLC) on Merck pre-coated silica GF254 plates. Melting points (uncorrected) were determined on a XT4MP apparatus (Taike Corp., Beijing, China). ESI mass spectra were obtained on a Mariner System 5304 mass spectrometer, and all the NMR spectra were recorded on a Bruker DPX 400 model spectrometer at room temperature with TMS and solvent signals allotted as internal standards. Chemical shifts are reported in ppm (δ). Elemental analyses were performed on a CHN-O-Rapid instrument, and were within ± 0.4 % of the theoretical values.

Synthesis of 4-formyl-2-methoxyphenyl acetate (**2**)

To a stirred suspension of vanillin (4.0 g, 26.3 mmol) in dry ethyl ether (100 mL) under argon was added slowly acetic anhydride (3.91 mL, 40.8 mmol) and then DMAP (1 mg). The mixture was stirred at room temperature for 20 min and then the crystallized white solid were formed at the bottom of the vessel. The crystallized white solid was filtered off and washed with water to give the 4-formyl-2-methoxyphenyl acetate.

Synthesis of 4-formyl-2-methoxy-3-nitrophenyl acetate (**3**)

To a stirred and cooled fuming nitric acid (12 mL) was added slowly compound **2** (2.4 g) over 2 h. The dark

brown reaction mixture was stirred for 5 h and then poured into crushed ice. The yellow precipitate was filtered off and washed with cold water (300 mL), to form compound **3**.

Synthesis of 4-hydroxy-3-methoxy-2-nitrobenzaldehyde (**4**)

Compound **3** was dissolved in a solution of NaOH (7.5 g) in water (200 mL) and the dark red solution stirred for 1 h. The solution was acidified (pH 1) with diluted hydrochloric acid, the precipitate filtered off, washed with water, and dried in vacuo to give compound **4** as yellow solid.

General method of synthesis of vanillin derivatives (**4a**–**4u**)

An equivocal compound **4** (1 mmol) and substituted aromatic amine (1 mmol) in methanol or acetonitrile was stirred for 4–6 h at room temperature, then reaction mixture was concentrated under reduced pressure, recrystallized from ethanol to give vanillin derivatives **4a–4z**.

*(E)-4(((2-Chlorophenyl)imino)methyl)-2-methoxy-3-nitrophenol (**4a**)*

M.p. 101–102 °C. ^{1}H NMR (300 MHz, $CDCl_3$): 3.81 (s, 3H), 6.47 (m, 1H), 6.96–6.97 (d, $J = 3.0$ Hz, 1H), 7.11–7.13 (m, 3H), 7.23–7.24 (d, $J = 3.0$ Hz, 1H), 8.34 (s, 1H), 9.74 (s, 1H). ^{13}C NMR (300 MHz, $CDCl_3$) δ: 125.18(C-1), 139.80(C-2), 144.72(C-3), 157.98(C-4), 118.70(C-5), 126.30(C-6), 168.12 (C-7), 152.69(C′-1), 127.45(C′-2), 130.41(C′-3), 128.00(C′-4), 131.59(C′-5), 115.35(C′-6), 61.94(–OCH_3). MS (ESI): 307 ($C_{14}H_{12}ClN_2O_4$, $[M+H]^+$). Anal. Calcd for $C_{14}H_{11}ClN_2O_4$: C, 54.83; H, 3.62; N, 9.13; Found: C, 54.62; H, 3.88; N, 9.35.

*(E)-2-Methoxy-3-nitro-4-((o-tolylimino)methyl)phenol (**4b**)*

M.p. 97–98 °C. ^{1}H NMR (300 MHz, $CDCl_3$): 2.96 (s, 3H), 3.71 (m, 3H), 6.88 (s, 1H), 7.10(m, 2H), 7.72 (m, 3H), 8.55 (s, 1H), 9.02 (s, 1H). ^{13}C NMR (300 MHz, $CDCl_3$) δ: 125.35(C-1), 139.94(C-2), 146.33(C-3), 154.18(C-4), 118.77(C-5), 127.20(C-6), 157.95(C-7), 166.45(C′-1), 127.20(C′-2), 130.30(C′-3), 127.55(C′-4), 129.01(C′-5), 115.98(C′-6), 61.70(–OCH_3), 19.08(–CH_3). MS (ESI): 287 ($C_{15}H_{15}N_2O_4$, $[M+H]^+$). Anal. Calcd for $C_{15}H_{14}N_2O_4$: C, 62.93; H, 4.93; N, 9.79; Found: C, 62.71; H, 5.11; N, 9.45.

*(E)-2-Methoxy-4-(((2-methoxyphenyl)imino)methyl)-3-nitrophenol (**4c**)*

M.p. 104–105 °C. ^{1}H NMR (300 MHz, $CDCl_3$): 3.72 (m, 3H), 3.88 (s, 3H), 7.01–7.03 (d, $J = 6.0$ Hz, 1H), 7.22 (m, 2H), 7.24 (m, 2H), 7.68–7.71 (m, 1H), 9.02 (s, 1H), 9.23 (s, 1H). ^{13}C NMR (300 MHz, $CDCl_3$) δ: 130.22(C-1), 141.82(C-2), 145.04(C-3), 156.05(C-4), 118.97(C-5), 127.31(C-6), 174.12(C-7), 136.31(C′-1), 151.64(C′-2), 115.75(C′-3), 124.44(C′-4), 125.48(C′-5), 118.06(C′-6), 56.52(–OCH_3), 62.81(R1–OCH_3). MS (ESI): 303 ($C_{15}H_{15}N_2O_5$, $[M+H]^+$). Anal. Calcd for $C_{15}H_{14}N_2O_5$: C, 59.60; H, 4.67; N, 9.27; Found: C, 59.85; H, 4.33; N, 9.11.

*(E)-2-Methoxy-3-nitro-4-(((2-nitrophenyl)imino)methyl)phenol (**4d**)*

M.p. 133–134 °C. ^{1}H NMR (300 MHz, $CDCl_3$): 3.35 (s, 3H), 6.81–6.83 (d, $J = 6.0$ Hz, 1H), 6.95 (m, 3H), 7.11 (s, 1H), 7.61 (m, 1H), 8.53 (s, 1H), 9.22 (s, 1H). ^{13}C NMR (300 MHz, $CDCl_3$) δ: 129.33(C-1), 139.32(C-2), 145.34(C-3), 153.75(C-4), 118.07(C-5), 125.00(C-6), 168.21(C-7), 148.15(C′-1), 135.19(C′-2), 125.81(C′-3), 129.33(C′-4), 134.78(C′-5), 122.71(C′-6), 61.90(–OCH_3). MS (ESI): 318 ($C_{14}H_{12}N_3O_6$, $[M+H]^+$). Anal. Calcd for $C_{14}H_{11}N_3O_6$: C, 53.00; H, 3.49; N, 13.24; Found: C, 53.24; H, 3.28; N, 13.55.

*(E)-4-(((3-Fluorophenyl)imino)methyl)-2-methoxy-3-nitrophenol (**4e**)*

M.p. 97–98 °C. ^{1}H NMR (300 MHz, $CDCl_3$): 3.80 (s, 3H), 6.82 (s, 1H), 7.01–7.02 (m, 3H), 7.03–7.04 (d, $J = 3.0$ Hz, 1H), 7.28 (m, 1H), 9.00 (s, 1H), 9.23 (s, 1H). ^{13}C NMR (300 MHz, $CDCl_3$) δ: 127.45(C-1), 142.93(C-2), 145.64(C-3), 154.15(C-4), 120.47(C-5), 127.45(C-6), 156.50(C-7), 163.31(C′-1), 104.02(C′-2), 168.13(C′-3), 114.33(C′-4), 127.57(C′-5), 121.63(C′-6), 62.50(–OCH_3). MS (ESI): 291 ($C_{14}H_{12}FN_2O_4$, $[M+H]^+$). Anal. Calcd for $C_{14}H_{11}FN_2O_4$: C, 57.93; H, 3.82; N, 9.65; Found: C, 58.12; H, 3.88; N, 9.61.

*(E)-2-Methoxy-3-nitro-4-((m-tolylimino)methyl)phenol (**4f**)*

M.p. 102–103 °C. ^{1}H NMR (300 MHz, $CDCl_3$): 3.51 (s, 3H), 3.79 (m, 3H), 6.86–6.87 (d, $J = 3.0$ Hz, 1H), 6.91 (m, 1H), 7.23–7.24 (m, 2H), 7.61–7.62 (m, 2H), 9.11 (s, 1H), 9.42 (s, 1H). ^{13}C NMR (300 MHz, $CDCl_3$) δ: 127.98(C-1), 139.98(C-2), 144.21(C-3), 154.18(C-4), 118.71(C-5), 127.45(C-6), 160.70(C-7), 144.21(C′-1), 121.07(C′-2), 139.86(C′-3), 123.22(C′-4), 130.35(C′-5), 115.36(C′-6), 61.91(–OCH3), 19.85(–CH_3). MS (ESI): 287 ($C_{15}H_{15}N_2O_4$, $[M+H]^+$). Anal. Calcd for $C_{15}H_{14}N_2O_4$: C, 62.93; H, 4.93; N, 9.79; Found: C, 63.01; H, 4.79; N, 9.91.

*(E)-2-Methoxy-4-(((3-methoxyphenyl)imino)methyl)-3-nitrophenol (**4g**)*

M.p. 104–106 °C. ^{1}H NMR (300 MHz, $CDCl_3$): 2.82 (m, 3H), 3.88 (m, 3H), 7.02–7.03 (d, $J = 3.0$ Hz, 1H), 7.19 (s, 1H), 7.25–7.27 (m, 3H), 7.96–7.97 (d, $J = 3.0$ Hz, 1H), 8.88

(s, 1H), 8.90 (s, 1H). ^{13}C NMR (300 MHz, $CDCl_3$) δ: 127.86(C-1), 140.93(C-2), 144.73(C-3), 154.17(C-4), 118.37 (C-5), 127.86(C-6), 157.05(C-7), 154.17(C′-1), 102.13(C′-2), 162.10(C′-3), 108.85(C′-4), 131.59(C′-5), 109.29(C′-6), 60.10(–OCH_3), 57.07(R2–OCH_3). MS (ESI): 303 ($C_{15}H_{15}N_2O_5$, $[M+H]^+$). Anal. Calcd for $C_{15}H_{14}N_2O_5$: C, 59.60; H, 4.67; N, 9.27; Found: C, 59.49; H, 4.78; N, 9.08.

*(E)-2-Methoxy-3-nitro-4-(((3-nitrophenyl)imino)methyl)phenol (**4h**)*

M.p. 151–152 °C. ^{1}H NMR (300 MHz, $CDCl_3$): 4.00 (s, 3H), 6.99 (s, 1H), 7.11–7.13 (m, 3H), 7.23–7.24 (m, 2H), 9.01 (s, 1H), 9.22 (s, 1H). ^{13}C NMR (300 MHz, $CDCl_3$) δ: 126.01(C-1), 142.13(C-2), 145.94(C-3), 156.05(C-4), 120.17(C-5), 126.01(C-6), 157.43(C-7), 154.58(C′-1), 112.12(C′-2), 149.55(C′-3), 121.89(C′-4), 131.71(C′-5), 122.35(C′-6), 59.90(–OCH_3). MS (ESI): 318 ($C_{14}H_{12}N_3O_6$, $[M+H]^+$). Anal. Calcd for $C_{14}H_{11}N_3O_6$: C, 53.00; H, 3.49; N, 13.24; Found: C, 52.89; H, 3.56; N, 13.09.

*(E)-4-(((4-Bromophenyl)imino)methyl)-2-methoxy-3-nitrophenol (**4i**)*

M.p. 153–155 °C. ^{1}H NMR (300 MHz, $CDCl_3$): 3.77 (m, 3H), 7.06 (s, 2H), 7.19–7.20 (m, 2H), 7.25–7.27 (m, 2H), 9.02 (s, 1H), 9.45 (s, 1H). ^{13}C NMR (300 MHz, $CDCl_3$) δ: 127.45(C-1), 139.80(C-2), 144.94(C-3), 154.15(C-4), 118.71 (C-5), 128.97(C-6), 160.70(C-7), 152.68(C′-1), 120.85(C′-2), 132.70(C′-3), 118.03(C′-4), 131.59(C′-5), 122.88(C′-6), 61.83(–OCH_3). MS (ESI): 350 ($C_{14}H_{12}BrN_2O_4$, $[M+H]^+$). Anal. Calcd for $C_{14}H_{11}BrN_2O_4$: C, 47.89; H, 3.16; N, 7.98; Found: C, 47.95; H, 3.30; N, 7.72.

*(E)-2-Methoxy-3-nitro-4-((p-tolylimino)methyl)phenol (**4j**)*

M.p. 101–102 °C. ^{1}H NMR (300 MHz, $CDCl_3$): 2.80 (s, 3H), 3.81 (m, 3H), 7.19 (s, 1H), 7.35–7.36 (m, 2H), 7.55–7.57 (m, 2H), 7.66–7.67 (d, $J = 3.0$ Hz, 1H), 8.34 (s, 1H), 8.60 (s, 1H). ^{13}C NMR (300 MHz, $CDCl_3$) δ: 127.82(C-1), 139.92(C-2), 145.04(C-3), 154.15(C-4), 118.75(C-5), 127.97(C-6), 154.15 (C-7), 152.67(C′-1), 118.34(C′-2), 130.41(C′-3), 134.11 (C′-4), 130.41(C′-5), 121.66(C′-6), 62.80(–OCH_3), 19.05 (–CH_3). MS (ESI): 287 ($C_{15}H_{15}N_2O_4$, $[M+H]^+$). Anal. Calcd for $C_{15}H_{14}N_2O_4$: C, 62.93; H, 4.93; N, 9.79; Found: C, 63.11; H, 4.82; N, 9.57.

*(E)-2-Methoxy-4-(((4-methoxyphenyl)imino)methyl)-3-nitrophenol (**4k**)*

M.p. 104–105 °C. ^{1}H NMR (300 MHz, $CDCl_3$): 3.41 (s, 3H), 3.52 (m, 3H), 6.82–8.83 (d, $J = 3.0$ Hz, 1H), 6.99 (s, 1H), 7.01–7.03 (m, 3H), 7.55–7.56 (m, 2H), 8.83 (s, 1H), 8.99 (s, 1H). ^{13}C NMR (300 MHz, $CDCl_3$) δ: 127.36(C-1), 140.93(C-2), 144.75(C-3), 157.85(C-4), 118.70(C-5), 127.97(C-6), 157.85(C-7), 145.60(C′-1), 121.07(C′-2), 115.35(C′-3), 160.43(C′-4), 114.77(C′-5), 119.94(C′-6), 61.90(–OCH_3), 56.53(R3–OCH_3). MS (ESI): 303 ($C_{15}H_{15}N_2O_5$, $[M+H]^+$). Anal. Calcd for $C_{15}H_{14}N_2O_5$: C, 59.60; H, 4.67; N, 9.27; Found: C, 59.39; H, 4.48; N, 9.13.

*(E)-2-Methoxy-3-nitro-4-(((4-nitrophenyl)imino)methyl)phenol (**4l**)*

M.p. 143–145 °C. ^{1}H NMR (300 MHz, $CDCl_3$): 3.76 (s, 3H), 6.96–6.97 (d, $J = 3.0$ Hz, 1H), 7.23–7.24 (m, 3H), 7.68–7.71 (m, 2H), 9.12 (s, 1H), 9.62 (s, 1H). ^{13}C NMR (300 MHz, $CDCl_3$) δ: 127.82(C-1), 140.93(C-2), 145.94(C-3), 156.15(C-4), 119.97(C-5), 130.07(C-6), 157.96(C-7), 166.33(C′-1), 118.30(C′-2), 124.54(C′-3), 145.87(C′-4), 124.96(C′-5), 118.98(C′-6), 61.50(–OCH_3). MS (ESI): 318 ($C_{14}H_{12}N_3O_6$, $[M+H]^+$). Anal. Calcd for $C_{14}H_{11}N_3O_6$: C, 53.00; H, 3.49; N, 13.24; Found: C, 53.11; H, 3.57; N, 13.33.

*(E)-4-(((3,4-Dichlorophenyl)imino)methyl)-2-methoxy-3-nitrophenol (**4m**)*

M.p. 95–96 °C. ^{1}H NMR (300 MHz, $CDCl_3$) : 3.71 (s, 3H), 6.96–6.97 (d, $J = 3.0$ Hz, 1H), 7.12–7.14 (m, 2H), 7.33–7.34 (d, $J = 3.0$ Hz, 1H), 7.72 (s, 1H), 8.79 (s, 1H), 8.86 (s, 1H). ^{13}C NMR (300 MHz, $CDCl_3$) δ: 128.01(C-1), 140.93(C-2), 144.34(C-3), 155.05(C-4), 119.97(C-5), 127.82(C-6), 161.83 (C-7), 149.55(C′-1), 118.71(C′-2), 132.92(C′-3), 126.95 (C′-4), 132.15(C′-5), 121.52(C′-6), 61.50(–OCH_3). MS (ESI): 350 ($C_{14}H_{11}Cl_2N_2O_4$, $[M+H]^+$). Anal. Calcd for $C_{14}H_{10}Cl_2N_2O_4$: C, 49.29; H, 2.95; N, 8.21; Found: C, 49.33; H, 2.78; N, 8.36.

*(E)-4-(((2,4-d-Dichlorophenyl)imino)methyl)-2-methoxy-3-nitrophenol (**4n**)*

M.p. 107–108 °C. ^{1}H NMR (300 MHz, $CDCl_3$): 3.82 (s, 3H), 6.77–6.78 (m, 2H), 7.19 (s, 1H), 7.55 (s, 1H), 7.68–7.71 (m, 1H), 9.12 (s, 1H), 9.45 (s, 1H). ^{13}C NMR (300 MHz, $CDCl_3$) δ: 127.45(C-1), 139.73(C-2), 145.94(C-3), 156.75(C-4), 118.91(C-5), 127.80(C-6), 160.06(C-7), 148.60(C′-1), 122.88 (C′-2), 130.41(C′-3), 131.65(C′-4), 130.69(C′-5), 121.67 (C′-6), 61.91(–OCH_3). MS (ESI): 350 ($C_{14}H_{11}Cl_2N_2O_4$, $[M+H]^+$). Anal. Calcd for $C_{14}H_{10}Cl_2N_2O_4$: C, 49.29; H, 2.95; N, 8.21; Found: C, 49.41; H, 2.99; N, 8.09.

*(E)-4-(((2,5-Dichlorophenyl)imino)methyl)-2-methoxy-3-nitrophenol (**4o**)*

M.p. 115–116 °C. ^{1}H NMR (300 MHz, $CDCl_3$): 4.00 (s, 3H), 6.86–6.87 (d, $J = 3.0$ Hz, 1H), 7.25–7.27 (m, 3H),

7.55 (s, 1H), 8.65 (s, 1H), 8.84 (s, 1H). ^{13}C NMR (300 MHz, $CDCl_3$) δ: 127.45(C-1), 139.88(C-2), 152.82 (C-3), 154.07(C-4), 118.75(C-5), 127.77(C-6), 160.74(C-7), 145.64(C′-1), 124.60(C′-2), 134.10(C′-3), 127.99(C′-4), 131.96(C′-5), 115.49(C′-6), 62.41(–OCH_3). MS (ESI): 350 ($C_{14}H_{11}Cl_2N_2O_4$, $[M+H]^+$). Anal. Calcd for $C_{14}H_{10}Cl_2N_2O_4$: C, 49.29; H, 2.95; N, 8.21; Found: C, 49.20; H, 2.81; N, 8.33.

*(E)-4-(((2,5-Dimethylphenyl)imino)methyl)-2-methoxy-3-nitrophenol (**4p**)*

M.p. 175–176 °C. ^{1}H NMR (300 MHz, $CDCl_3$): 2.75 (s, 2H), 2.99–3.01 (m, 4H), 3.71 (s, 3H), 6.99 (s, 1H), 7.21–7.23 (d, $J = 6.0$ Hz, 1H), 7.47–7.49 (m, 2H), 7.68–7.70 (m, 1H), 8.34 (s, 1H), 8.46 (s, 1H). ^{13}C NMR (300 MHz, $CDCl_3$) δ: 127.10(C-1), 141.21(C-2), 145.66(C-3), 157.02 (C-4), 119.97(C-5), 127.25(C-6), 159.31(C-7), 152.90(C′-1), 122.95(C′-2), 132.61(C′-3), 129.82(C′-4), 134.11(C′-5), 118.23(C′-6), 61.50(–OCH_3), 19.05(R1–CH_3),22.31(R4–CH_3). MS (ESI): 301 ($C_{16}H_{17}N_2O_4$, $[M+H]^+$). Anal. Calcd for $C_{16}H_{16}N_2O_4$: C, 63.99; H, 5.37; N, 9.33; Found: C, 64.77; H, 5.41; N, 9.24.

*(E)-4-(((3,4-Dimethylphenyl)imino)methyl)-2-methoxy-3-nitrophenol (**4q**)*

M.p. 165–166 °C. ^{1}H NMR (300 MHz, $CDCl_3$) : 2.80 (m, 4H), 3.01 (s, 1H), 3.03 (s, 1H), 3.79 (s, 3H), 7.25–7.27 (m, 3H), 7.71 (s, 1H), 7.72–7.74 (d, $J = 6.0$ Hz, 1H), 8.23 (s, 1H), 8.62 (s, 1H). ^{13}C NMR (300 MHz, $CDCl_3$) δ: 127.34(C-1), 140.93(C-2), 149.94(C-3), 154.18(C-4), 118.92(C-5), 128.08(C-6), 160.22(C-7), 143.53(C′-1), 118.23(C′-2), 145.04(C′-3), 127.53(C′-4), 131.59(C′-5), 115.36(C′-6), 61.30(–OCH_3), 19.06(R2–CH_3), 18.60(R3–CH_3). MS (ESI): 301 ($C_{16}H_{17}N_2O_4$, $[M+H]^+$). Anal. Calcd for $C_{16}H_{16}N_2O_4$: C, 63.99; H, 5.37; N, 9.33; Found: C, 65.08; H, 5.48; N, 9.22.

*(E)-4-(((2,6-Dimethylphenyl)imino)methyl)-2-methoxy-3-nitrophenol (**4r**)*

M.p. 171–173 °C. ^{1}H NMR (300 MHz, $CDCl_3$): 2.99 (s, 2H), 3.03–3.05 (m, 3H), 3.33 (s, 1H), 3.81–3.83 (m, 3H), 6.89–6.90 (d, $J = 3.0$ Hz, 1H), 7.19 (s, 1H), 7.25–7.27 (m, 3H), 8.60 (s, 1H), 9.47 (s, 1H). ^{13}C NMR (300 MHz, $CDCl_3$) δ: 127.12(C-1), 139.94(C-2), 144.75(C-3), 160.37(C-4), 118.97(C-5), 127.83(C-6), 154.25(C-7), 148.33(C′-1), 124.54(C′-2), 129.28(C′-3), 126.07(C′-4), 130.55(C′-5), 123.74(C′-6), 62.81(–OCH3), 19.06(R1–CH3), 15.92(R5–CH3). MS (ESI): 301 ($C_{16}H_{17}N_2O_4$, $[M+H]^+$). Anal. Calcd for $C_{16}H_{16}N_2O_4$: C, 63.99; H, 5.37; N, 9.33; Found: C, 65.11; H, 5.21; N, 9.45.

*(E)-4-(((3-Chloro-4-methylphenyl)imino)methyl)-2-methoxy-3-nitrophenol (**4s**)*

M.p. 67–68 °C. ^{1}H NMR (300 MHz, $CDCl_3$): 2.80–2.82 (m, 3H), 3.03–3.06 (m, 3H), 7.19–7.20 (m, 2H), 7.27–7.28 (m, 1H), 7.55 (s, 1H), 7.60–7.61 (d, $J = 3.0$ Hz, 1H), 8.92 (s, 1H), 9.74 (s, 1H). ^{13}C NMR (300 MHz, $CDCl_3$) δ: 127.75(C-1), 140.93(C-2), 145.60(C-3), 154.95(C-4), 121.68(C-5), 127.57 (C-6), 160.93(C-7), 150.49(C′-1), 115.93(C′-2), 137.37(C′-3), 130.41(C′-4), 139.85(C′-5), 118.75(C′-6), 62.82(–OCH_3), 19.05(–CH_3). MS (ESI): 321 ($C_{15}H_{14}ClN_2O_4$, $[M+H]^+$). Anal. Calcd for $C_{15}H_{13}ClN_2O_4$: C, 56.17; H, 4.09; N, 8.73; Found: C, 56.26; H, 3.91; N, 8.90.

*(E)-4-(((4-Chloro-2-nitrophenyl)imino)methyl)-2-methoxy-3-nitrophenol (**4t**)*

M.p. 152–153 °C. ^{1}H NMR (300 MHz, $CDCl_3$): 3.80 (s, 3H), 6.96–6.97 (d, $J = 3.0$ Hz, 1H), 7.00 (s, 1H), 7.32–7.33 (m, 2H), 7.55 (s, 1H), 8.56 (s, 1H), 8.81 (s, 1H). ^{13}C NMR (300 MHz, $CDCl_3$) δ: 130.21(C-1), 139.37(C-2), 144.99(C-3), 154.75(C-4), 118.97(C-5), 124.26(C-6), 161.39(C-7), 143.90(C′-1), 136.61(C′-2), 127.84(C′-3), 131.38(C′-4), 136.31(C′-5), 121.60(C′-6), 61.98(–OCH_3). MS (ESI): 352 ($C_{14}H_{11}ClN_3O_6$, $[M+H]^+$). Anal. Calcd for $C_{14}H_{10}ClN_3O_6$: C, 47.81; H, 2.87; N, 11.95; Found: C, 47.67; H, 42.96; N, 12.08.

*(E)-4-(((2,6-Diisopropylphenyl)imino)methyl)-2-methoxy-3-nitrophenol (**4u**)*

M.p. 178–179 °C. ^{1}H NMR (300 MHz, $CDCl_3$): 3.15–3.18 (m, 3H), 3.22–3.24 (m, 4H), 3.25–3.26 (m, 3H), 3.28–3.29 (d, $J = 3.0$ Hz, 1H), 3.30–3.32 (m, 4H), 3.55 (s, 3H), 3.56–3.57 (d, $J = 3.0$ Hz, 1H), 7.11–7.13 (m, 3H), 7.23–7.24 (d, $J = 3.0$ Hz, 1H), 7.68–7.71 (m, 1H), 8.52 (s, 1H), 8.92 (s, 1H). ^{13}C NMR (300 MHz, $CDCl_3$) δ: 126.71(C-1), 141.33(C-2), 145.64(C-3), 153.85(C-4), 118.97(C-5), 127.71(C-6), 161.01(C-7), 143.56(C′-1), 130.16(C′-2), 127.98(C′-3), 124.55(C′-4), 128.33(C′-5), 131.55(C’-6), 61.96(–OCH_3), R1: 19.06(CH_3)–28.05(CH_2)–21.55(CH_3), R5: 21.98(CH_3)–28.87(CH_2)–23.40(CH_3). MS (ESI): 357 ($C_{20}H_{25}N_2O_4$, $[M+H]^+$). Anal. Calcd for $C_{20}H_{24}N_2O_4$: C, 67.40; H, 6.79; N, 7.86; Found: C, 67.55; H, 6.61; N, 7.93.

Antibacterial activity

The antibacterial activity of the synthesized compounds was tested against *B. subtilis, E. coli, P. aeruginosa*, and *S. aureus* using MH medium (Mueller–Hinton medium:

casein hydrolysate 17.5 g, soluble starch 1.5 g, beef extract 1,000 mL). The MICs of the test compounds were determined by a colorimetric method using the dye MTT (3-(4,5-dimethylth-iazol-2-yl)-2,5-diphenyl tetrazoliumbromide). A stock solution of the synthesized compound (100 μg/mL) in dimethyl sulfoxide (DMSO) was prepared and graded quantities of the test compounds were incorporated in specified quantity of sterilized liquid MH medium. A specified quantity of the medium containing the compound was poured into microtitration plates. Suspension of the microorganism was prepared to contain approximately 10^5 cfu/mL and applied to microtitration plates with serially diluted compounds in DMSO to be tested and incubated at 37 °C for 24 h. After the MICs were visually determined on each of the microtitration plates, 50 μL of PBS (phosphate buffered saline 0.01 mol/L, pH 7.4, $Na_2HPO_4{\cdot}12H_2O$ 2.9 g, KH_2PO_4 0.2 g, NaCl 8.0 g, KCl 0.2 g, and distilled water 1,000 mL) containing 2 mg of MTT/mL was added to each well. Incubation was continued at room temperature for 4–5 h. The content of each well was removed, and 100 μL of isopropanol containing 5 % 1 mol/L HCl was added to extract the dye. After 12 h of incubation at room temperature, the optical density was measured with a microplate reader at 550 nm. The observed MICs are presented in Table 3.

Inhibition of FtsZ polymerization

The FtsZ was expressed and purified with the following modification (White *et al*., 2000). A polymerization/depolymerization step was added before preparative gel filtration. This improved purification gave a protein preparation that was >99 % pure with a 1:1 molar ratio of GDP to FtsZ.

The polymerization and depolymerization of purified FtsZ at 0.5 mg/mL. The effect of different compounds on FtsZ polymerization and depolymerization was monitored using the light-scattering assay described above (White *et al*., 2000). Compounds were added to the reaction mixture, and a baseline was established. They were initially evaluated at 100 μM. If inhibition was observed, the compounds were retested at several concentrations. GTP was added to initiate polymerization, and light-scattering data were collected for an additional 50–60 min. The maximum light scattering was calculated by subtracting the baseline value from the peak value. The percentage of control activity was calculated by comparison with an assay without the compound. When DMSO was used as the solvent, the control contained the same amount of DMSO (2 to 4 %). A semilog plot of percentage of control activity versus compound concentration was used to calculate the 50 % inhibition concentration (IC_{50}).

Experimental protocol of docking study

Automated docking studies were carried out using Discovery Studio (version 3.1) as implemented through the graphical user interface DS-CDocker protocol.

The three-dimensional structures of the aforementioned compounds were constructed using Chem. 3D ultra 11.0 software [Chemical Structure Drawing Standard; Cambridge Soft corporation, USA (2009)], then they were energetically minimized by using MOPAC with 100 iterations and minimum RMS gradient of 0.10. The Gasteiger-Hückel charges of ligands were assigned. The crystal structures of FtsZ protein (PDB code: 2VAM) complex were retrieved from the RCSB Protein Data Bank (http://www.rcsb.org/pdb/home/home.do). All bound waters and ligands were eliminated from the protein and the polar hydrogens and the Kollman-united charges were added to the proteins.

Acknowledgments This work was supported by Major Projects on Control and Rectification of Water Body Pollution (No. 2011ZX07204-001-004), and was supported by the project (No. BY2012136) from the Science & Technology Agency of Jiangsu Province and by the projects (Nos. CXY1213 & CXY1222) from the Science & Technology Bureau of Lianyuangang City of Jiangsu Province.

References:

Akihiro T, Takeshi S, Futoshi Y, Hideyuki I et al (2011) Evaluation of antioxidant activity of vanillin by using multiple antioxidant assays. Biochim Biophys Acta 1810:170–177

Ana OS, Fabio CSG, Célio LS, Beatriz B et al (2007) Antimycobacterial and cytotoxicity activity of synthetic and natural compounds. Quim Nova 30:1563–1566

Bringmann G, Dreyer M, Faber JH, Dalsgaard PW et al (2004) Ancistrotanzanine C and related 5,1′-and 7,3′-couple naphthylisoquinoline alkaloids from Ancistrocladus tanzaniensis. J Nat Prod 67:743–748

Bythrow JD (2005) Vanilla as a medicinal plant. Semin Integr Med 3:129–131

Chohan ZH, Arif M, Sarfraz M (2007) Metal-based antibacterial and antifungal amino acid derived Schiff bases: their synthesis, characterization and in vitro biological activity. Appl Organomet Chem 21:294–302

Claudio VJ, Amanda D, da Vanderlan SB, Eliezer JB, Carlos AMF (2007) Molecular hybridization: a useful tool in the design of new drug prototypes. Curr Med Chem 14:1829–1852

Cleiton MS, Daniel LS, Luzia VM et al (2011) Schiff bases: a short review of their antimicrobial activities. J Adv Res 2:1–8

Daniel JF, Malcolm S, Arjan N (2003) Analysis of the inhibition of food spoilage yeasts by vanillin. Int J Food Microbiol 86:113–122

Faridbod F, Ganjali MR (2007) Ion recognition: application of symmetric and asymmetric schiff bases and their complexes for the fabrication of cationic and anionic membrane sensors to determine ions in real samples. Comb Chem High Throughput Screen 10:527–546

Fitzgerald DJ, Stratford M, Gasson MJ, Narbad A (2004) The potential application of vanillin in preventing yeast spoilage of soft drinks and fruit juices. J Food Protect 67:391–395

Fraga CAM (2009) Drug hybridization strategies: before or after lead identification? Expert Opin Drug Dis 4:605–609

Frederico JG, Richard L (2002) A widely conserved bacterial cell division protein that promotes assembly of the tubulin-like protein FtsZ. Genes Dev 16:2544–2566

Frye SV (2010) The art of the chemical probe. Nat Chem Biol 6:159–161

Hacer B, Ahmet D, Sengül AK, Neslihan D (2009) Synthesis of some new 1,2,4-riazoles, their Mannich and Schiff bases and evaluation of their antimicrobial activities. N Eur J Med Chem 44:1057–1066

Jeffery E, Richard AD (2003) Cytokinesis in bacteria. Microbiol Mol Biol Rev 67:52–65

Laura R, Petra AL (2003) Assembly dynamics of the bacterial cell division protein FtsZ: poised at the edge of stability. Annu Rev Microbiol 57:125–154

Lei S, Hui-Ming G, Shu-Hua T, Huan-Qiu L, Yong-Chun S, Hai-Liang Z, Ren-Xiang T (2007) Synthesis and antimicrobial activities of Schiff bases derived from 5-chloro-salicylaldehyde. Eur J Med Chem 42:558–564

Lloyd GC, Neil RS, Steve R, David JH (2012) Antibacterial inhibitors of the essential cell division protein FtsZ. Antibiotic Discov Dev 30:957–968

Mari SK, Dasappa JP, Boja P (2006) Synthesis and biological activity of Schiff and Mannich bases bearing 2,4-dichloro-5-fluorophenyl moiety. Bioorg Med Chem 14:7482–7489

Mariana GP, Jeff E (2003) Dispersed mode of *Staphylococcus aureus* cell wall synthesis in the absence of the division machinery. Mol Microbiol 50:871–881

Martin L (2004) Antibiotics: a shot in the arm. Nature 431:892–893

Piotr P, Adam H, Krystian P, Bogumil B, Franz B (2009) Biological properties of schiff bases and azo derivatives of phenols. Curr Org Chem 13:124–148

Sardari S, Nishibe S, Daneshtalab M (2000) Coumarins, the bioactive structures with antifungal property. Stud Nat Prod Chem 23:335–393

Seshaiah KS, Atmakuru R (2001) Synthesis and pharmacological activities of hydrazones, schiff and mannich bases of isatin derivatives. Biol Pharm Bull 24:1149–1152

Ti-Feng J, Ming-Hua L (2005) Supramolecular assemblies and molecular recognition of amphiphilic Schiff bases with barbituric acid in organized molecular films. J Phys Chem B 109:2532–2539

Venugopala KN, Jayashree BS (2008) Microwave-induced synthesis of Schiff bases of aminothiazolyl bromocoumarins as antibacterials. Indian J Pharm Sci 70:88–91

Walton NJ, Mayer MJ, Narbad A (2003) Vanillin. Phytochem 63:505–515

White EL, Ross LJ, Reynolds RC, Seitz LE, Moore GD, Borhani DW (2000) Slow polymerization of *Mycobacterium tuberculosis* FtsZ. J Bacteriol 182:4028–4034

Zhan-Yong G, Ronge X, Song L, Zhi-Mei Z, Xia J, Peng-Cheng L (2007) Antifungal properties of Schiff bases of chitosan, *N*-substituted chitosan and quaternized chitosan. Carbohydr Res 342:1329–1332