Full Paper

Synthesis and Anti-Bacterial Activity of Some Heterocyclic Chalcone Derivatives Bearing Thiofuran, Furan, and Quinoline Moieties

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36 Novel heterocyclic chalcone derivatives were synthesized and tested for their anti-bacterial activity. Some compounds presented good anti-microbial activities against Gram-positive bacteria (including the multidrug-resistant clinical isolates). This class of compounds presented high potency against *Streptococcus mutans*, among which the derivatives **F2** with an MIC of 2 μg/mL was as active as the standard drug (norfloxacin) and less active than oxacillin. All the compounds did not inhibit the growth of Gram-negative bacteria (*Escherichia coli* CCARM 1924 or *Escherichia coli* CCARM 1356) at 64 μg/mL.

Keywords: Antibacterial activity / Heterocyclic chalcone

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Introduction

The treatment of bacterial infections remains a challenging therapeutic problem because of emerging infectious diseases and the increasing number of multidrug-resistant microbial pathogens. Despite the many antibiotics and chemotherapeutics available, the emergence of old and new antibiotic-resistant bacterial strains in the last decades constitutes a substantial need for new classes of anti-bacterial agents [1].

Chalcones, considered to be the precursor of flavonoids and isoflavonoids, are abundant in edible plants. They consist of open-chain flavonoids in which the two aromatic rings are joined by a three-carbon α,β-unsaturated carbonyl system. Studies revealed that compounds with a chalcone-based structure have anti-oncogenic [2], anti-inflammatory [3], anti-ulcerative [4], analgesic [5], anti-viral [6], anti-fungal [7], anti-malarial [8], and anti-bacterial activities [9]. Chalcones as well as some heterocyclic aromatic derivatives have already been recognized for their anti-bacterial activities. In the present study, the heterocyclic aromatic (furan, thiofuran, quinoline) ring nuclei and chalcone functionality have been incorporated in a single molecule with variation of substituents and their positions on the aromatic ring and evaluated for their anti-bacterial activities (Fig. 1).

Results and discussion

Synthesis

The route followed for the preparation of heterocyclic chalcones is illustrated in Scheme 1, based on Claisen-Schmidt condensation, by the reaction of substituted acetophenone with different heterocyclic aromatic aldehydes to form chalcones by a previously described method [10]. Intermediate 2-chloroquinolin-3-carbaldehyde were prepared by Vilsmeier-Hacck reaction using commercially available 4-dihydroquinolin-2(1*H*)-one (**3**) as a starting material. 36 Heterocycle-substituted chalcone derivatives were screened for their anti-microbial activity. The structures of the desired compounds were determined by IR, ^{1}H-NMR, mass spectral and elemental analyses.

Biological evaluation

In-vitro anti-microbial activity was evaluated using the minimum inhibitory concentration (MIC) with different strains (including multidrug-resistant clinical isolates).

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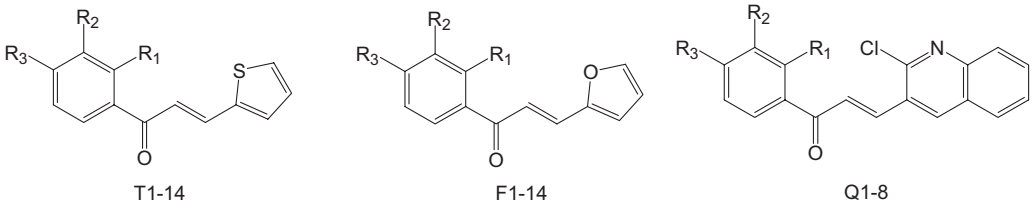


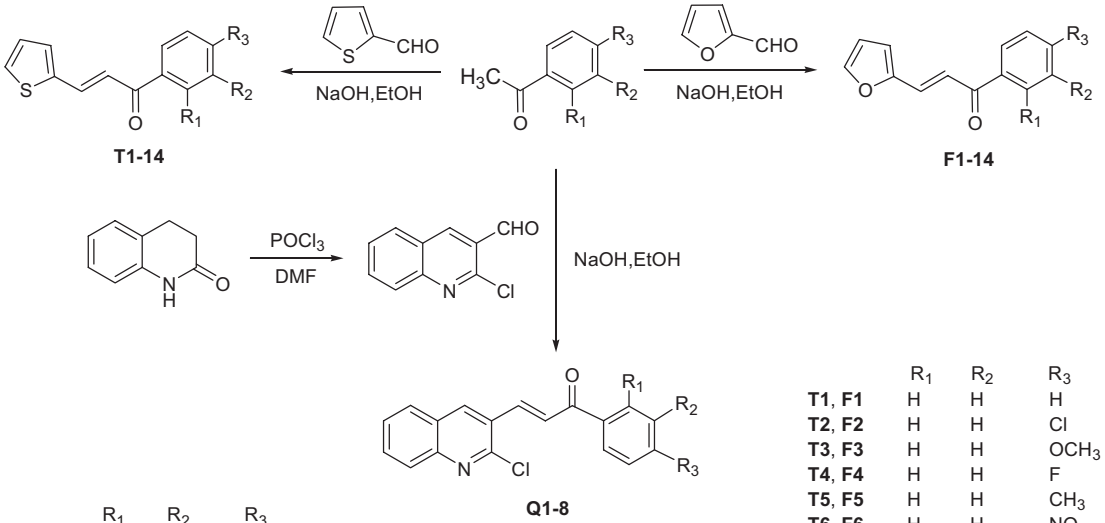
Figure 1. General formulas of the prepared compounds.

Oxacillin and norfloxacin were used as positive controls for bacteria.

The results of antimicrobial test were illustrated in Table 1, in which the compounds having the MIC value of >64 μg/mL (except for *Escherichia coli*) were not shown. As shown in Table 1, none of the compounds tested showed activity towards the Gram-negative bacterium E. coli, while some of the chalcones inhibited the growth of the Gram-positive bacteria (*Staphylococcus aureus*, methicillin-resistant *S. aureus* (MRSA), quinolone-resistant *S. aureus* (QRSA), and *Streptococcus mutans*). The series of **F1-14** incorporated with furan ring have better antimicrobial activity than the other two series of compounds. It seemed that the character of the type of the heterocyclic ring had a significant influence on the antimicrobial activity. This class of compounds presented high activity against *S. mutans*; 7 compounds out of the furan series showed potent inhibitory effects; the derivative **F2** with an MIC of 2 μg/mL was as active as the standard drug (norfloxacin) but less active than oxacillin.

Compounds **F7**, **F8**, and **F9** showed potent inhibition against both Gram-positive methicillin-resistant *Staphylococcus aureus* (MRSA) and quinolone-resistant *Staphylococcus aureus* (QRSA) with an MIC value of 16 μg/mL. As for the relationship between antimicrobial activity and the different substitutions on the phenyl ring, we did not observe a significant difference between electron-donating and electron-withdrawing groups for the contribution to antimicrobial activity. This suggested that the electronic effect of the substituent on the phenyl ring was not a key factor affecting such activity.

In the series of **T1-14**, most of the compounds showed no activity against test bacterial, in which the compounds **T9** and **T13** possessing 3-OH and 2,4-OH groups on phenyl ring



	R_1	R_2	R_3
Q1	H	H	H
Q2	H	H	OCH_3
Q3	H	H	Cl
Q4	CH_3	H	CH_3
Q5	OH	H	OH
Q6	OH	H	H
Q7	H	H	CH_3
Q8	OH	H	OCH_2OCH_3

	R_1	R_2	R_3
T1, **F1**	H	H	H
T2, **F2**	H	H	Cl
T3, **F3**	H	H	OCH_3
T4, **F4**	H	H	F
T5, **F5**	H	H	CH_3
T6, **F6**	H	H	NO_2
T7, **F7**	H	H	Br
T8, **F8**	H	Cl	H
T9, **F9**	H	OH	H
T10, **F10**	H	OCH_3	H
T11, **F11**	CH_3	H	CH_3
T12, **F12**	Cl	H	Cl
T13, **F13**	OH	H	OH
T14, **F14**	OH	H	H

Scheme 1. Synthetic scheme for the synthesis of compounds **T1–14**, **F1–14**, and **Q1–8**.

Table 1. Inhibitory activity of compounds expressed as MIC (μg/mL).

Compound	*S. aureus*			MRSA		QRSA		*S.mutans*		*E. coli*	
	4220	503	209	3167	3506	3505	3519	3065	3289	1924	1356
T9	16	16	16	16	16	16	16	32	32	>64	>64
T13	16	16	16	16	16	16	16	16	16	>64	>64
F2	8	8	8	8	16	8	8	2	2	>64	>64
F5	32	32	32	32	32	32	32	8	8	>64	>64
F6	32	32	32	64	32	32	32	16	16	>64	>64
F7	16	32	16	16	16	16	16	8	8	>64	>64
F8	16	16	16	16	16	16	16	8	8	>64	>64
F9	16	16	16	16	16	16	16	4	4	>64	>64
F12	32	32	32	32	32	32	32	8	8	>64	>64
Q1	64	64	64	64	64	64	64	64	64	>64	>64
Oxacillin	1	1	1	>64	>64	1	1	1	1	>64	>64
Norfloxacin	2	2	4	8	4	>64	>64	2	2	16	16

Staphylococcus aureus RN4220, *S. aureus* RN4220; *S. aureus* 503, *S. aureus* 503; *S. aureus* 209, *S. aureus* 209; MRSA 3167, methicillin-resistant *S. aureus* CCARM 3167; MRSA 3506, methicillin-resistant *S. aureus* CCARM 3506; QRSA 3505, quinolone-resistant *S. aureus* CCARM 3505; QRSA 3519, quinolone-resistant *S. aureus* CCARM 3519. *S. mutans* 3065, *Streptococcus mutans* 3065; *S. mutans* 3289, *S. mutans* 3289; *Escherichia coli* 1924, *E. coli* CCARM 1924; *E. coli* 1356, *E. coli* CCARM 1356.

exhibited moderate antimicrobial activity against Gram-positive bacteria, while compound **T14** possessing 2-OH did not. Almost all chalcone derivatives (**Q1-8**) bearing quinoline moiety showed inactive against tested bacterial species except **Q1** that showed modest inhibition (64 μg/mL) against Gram-positive bacteria. It seems as if introducing quinoline ring to the chalcone could not increase the antimicrobial activity, and different heterocyclic chalcones might exert their antimicrobial activity through multiple mechanisms or different pathways.

Experimental

Chemistry

Melting points were determined in open capillary tubes and are uncorrected. Reaction courses were monitored by TLC on silica gel-precoated F254 Merck plates. Developed plates were examined with UV lamps (254 nm). IR spectra were recorded (in KBr) on a FTIR1730. ^{1}H-NMR spectra were measured on a Bruker AV-300 spectrometer using TMS as the internal standard. Mass spectra were measured on an HP1100LC (Agilent Technologies, USA). Elemental analyses for C, H, N, and S were within ±0.4% of the theoretical values and were carried out on a 204Q CHN Rapid Analyzer (Perkin–Elmer, USA). The major chemicals were purchased from Sigma-Aldrich and Fluka.

*General procedure for the preparation of compounds **T1–14**, **F1–14** and **Q1–8***

To a solution of substituted acetophenone (0.01 mol) and different aromatic and heterocyclic aldehydes (0.01 mol) in EtOH (10 mL) was added 2 M NaOH (8 mL), and the reaction mixture was stirred for 40 min and then kept in refrigerator overnight. The resulting products were collected by filtration and were purified by recrystallization (95% EtOH). The yield, melting point and spectral data of each compound are given below.

*(E)-1-Phenyl-3-(thiophen-2-yl)prop-2-en-1-one **T1***

Yield: 95%; m.p.: 58–60°C; ^{1}H-NMR ($CDCl_3$, 300 MHz, δ, ppm) δ: 8.00 (2H, d, J = 7.5 Hz, H-2,6), 7.93 (1H, d, J = 15.6 Hz, H-b), 7.37–7.61 (4H, m, H-3,4,5,5'), 7.42 (1H, d, J = 4.8 Hz, H-3'), 7.31 (1H, d, J = 15.6 Hz, H-a), 7.10 (1H, t, J = 4.2 Hz, H-4'); IR (KBr, ν_{max} cm^{-1}) 1627; ESI-MS m/z: 215 (M + 1); Anal. calcd. for $C_{13}H_{10}OS$: C, 72.87; H, 4.70; S, 14.96. Found: C, 73.00; H, 4.63; S, 14.88.

*(E)-1-(4-Chlorophenyl)-3-(thiophen-2-yl)prop-2-en-1-one **T2***

Yield: 96%; m.p.: 118–120°C; ^{1}H-NMR ($CDCl_3$, 300 MHz, δ, ppm) δ: 7.97–7.98 (1H, m, H-5'), 7.94 (2H, d, J = 8.4 Hz, H-2,6), 7.46 (1H, d, J = 8.4 Hz, H-3,5), 7.43 (1H, d, J = 15.6 Hz, H-b), 7.37 (1H, t, J = 3.0 Hz, H-3'), 7.31 (1H, d, J = 15.6 Hz, H-a) 7.10 (1H, t, J = 3.75 Hz, H-4'); IR (KBr, ν_{max} cm^{-1}) 1643; ESI-MS m/z: 249 (M + 1); Anal. calcd. for $C_{13}H_9ClOS$: C, 62.78; H, 3.65; S, 12.89. Found: C, 62.72; H, 3.63; S, 12.76.

*(E)-1-(4-Methoxyphenyl)-3-(thiophen-2-yl)prop-2-en-1-one **T3***

Yield: 95%; m.p.: 104–106°C; ^{1}H-NMR ($CDCl_3$, 300 MHz, δ, ppm) δ: 8.01 (2H, d, J = 8.4 Hz, H-2,6), 7.91 (1H, d, J = 15.6 Hz, H-b), 7.33–7.70 (2H, m, H-3',5'), 7.32 (1H, d, J = 15.6 Hz, H-a), 7.10 (1H, t, J = 4.2 Hz, H-4'), 6.96 (2H, d, J = 8.7 Hz H-3,5); IR (KBr, ν_{max} cm^{-1}) 1634; ESI-MS m/z: 245 (M + 1); Anal. calcd. for $C_{14}H_{12}O_2S$: C, 68.83; H, 4.95; S, 13.12. Found: C, 68.76; H, 4.84; S, 13.07.

*(E)-1-(4-Fluorophenyl)-3-(thiophen-2-yl)prop-2-en-1-one **T4***

Yield: 98%; m.p.: 118–120°C; ^{1}H-NMR ($CDCl_3$, 300 MHz, δ, ppm) δ: 8.03–8.08 (2H, dd, J = 8.4 Hz, H-2,6), 7.94 (1H, d, J = 15.6 Hz,

H-b), 7.43 (1H, d, $J = 4.8$ Hz, H-5'), 7.37 (1H, d, $J = 3.0$ Hz, H-3'), 7.29 (1H, d, $J = 15.6$ Hz, H-a), 7.15–7.21 (2H, dd, $J = 8.4$ Hz, H-3,5), 7.11 (1H, t, $J = 4.2$ Hz, H-4'); IR (KBr, ν_{max} cm^{-1}) 1635; ESI-MS *m/z*: 233 (M + 1); Anal. calcd. for $C_{13}H_9FOS$: C, 67.22; H, 3.91; S, 13.80. Found: C, 67.30; H, 3.83; S, 13.65.

(E)-3-(Thiophen-2-yl)-1-p-tolylprop-2-en-1-one **T5**

Yield: 98%; m.p.: 78–80°C; ^{1}H-NMR ($CDCl_3$, 300 MHz, δ, ppm) δ: 7.96 (1H, d, $J = 15.6$ Hz, H-b), 7.91 (2H, d, $J = 8.4$ Hz, H-3,5), 7.41 (1H, d, $J = 4.8$ Hz, H-5'), 7.29–7.36 (4H, m, H-a,2,6,3'), 7.09 (1H, t, $J = 4.2$ Hz, H-4'), 2.44 (3H, s, CH_3); IR (KBr, ν_{max} cm^{-1}) 1623; ESI-MS *m/z*: 229 (M + 1); Anal. calcd. for $C_{14}H_{12}OS$: C, 73.65; H, 5.30; S, 14.04. Found: C, 73.58; H, 5.23; S, 13.92.

(E)-1-(4-Nitrophenyl)-3-(thiophen-2-yl)prop-2-en-1-one **T6**

Yield: 95%; m.p.: 171–173°C; ^{1}H-NMR ($CDCl_3$, 300 MHz, δ, ppm) δ: 8.33 (2H, d, $J = 8.4$ Hz, H-3,5), 8.11 (2H, d, $J = 8.4$ Hz, H-2,6), 7.96 (1H, d, $J = 15.6$ Hz, H-b), 7.48 (1H, d, $J = 4.8$ Hz, H-5'), 7.41 (1H, d, $J = 3.0$ Hz, H-3'), 7.25 (1H, d, $J = 15.6$ Hz, H-a), 7.12 (1H, t, $J = 4.2$ Hz, H-4'); IR (KBr, ν_{max} cm^{-1}) 1647; ESI-MS *m/z*: 233 (M + 1); Anal. calcd. for $C_{13}H_9NO_3S$: C, 60.22; H, 3.50; N, 5.40; S, 12.37. Found: C, 60.28; H, 3.64; N, 5.39; S, 12.31.

(E)-1-(4-Bromophenyl)-3-(thiophen-2-yl)prop-2-en-1-one **T7**

Yield: 93%; m.p.: 133–135°C; ^{1}H-NMR ($CDCl_3$, 300 MHz, δ, ppm) δ: 7.93 (1H, d, $J = 15.6$ Hz, H-b), 7.86 (2H, d, $J = 8.4$ Hz, H-2,6), 7.63 (2H, d, $J = 8.4$ Hz, H-3,5), 7.44 (1H, d, $J = 4.8$ Hz, H-5'), 7.37 (1H, d, $J = 3.0$ Hz, H-3'), 7.25 (1H, d, $J = 15.6$ Hz, H-a), 7.11 (1H, t, $J = 4.2$ Hz, H-4'); IR (KBr, ν_{max} cm^{-1}) 1638; ESI-MS *m/z*: 294 (M + 1); Anal. calcd. for $C_{13}H_9BrOS$: C, 53.26; H, 3.09; S, 10.94. Found: C, 53.18; H, 3.05; S, 10.76.

(E)-1-(4-Bromophenyl)-3-(thiophen-2-yl)prop-2-en-1-one **T8**

Yield: 97%; m.p.: 96–98°C; ^{1}H-NMR ($CDCl_3$, 300 MHz, δ, ppm) δ: 7.98 (1H, d, $J = 15.6$ Hz, H-b), 7.97 (1H, s, H-2), 7.86 (1H, d, $J = 8.4$ Hz, H-3,5), 7.44 (1H, d, $J = 4.8$ Hz, H-5'), 7.37 (1H, d, $J = 3.0$ Hz, H-3'), 7.25 (1H, d, $J = 15.6$ Hz, H-a), 7.11 (1H, t, $J = 4.2$ Hz, H-4'); IR (KBr, ν_{max} cm^{-1}) 1638; ESI-MS *m/z*: 294 (M + 1); Anal. calcd. for $C_{13}H_9BrOS$: C, 53.26; H, 3.09; S, 10.94. Found: C, 53.18; H, 3.05; S, 10.76.

(E)-1-(3-Hydroxyphenyl)-3-(thiophen-2-yl)prop-2-en-1-one **T9**

Yield: 97%; m.p.: 124–126°C; ^{1}H-NMR ($CDCl_3$, 300 MHz, δ, ppm) δ: 8.03 (1H, d, $J = 15.6$ Hz, H-b), 7.66–7.71 (2H, m, H-5',6), 7.53 (1H, t, $J = 4.8$ Hz, H-4'), 7.47–7.49 (1H, m, H-3'), 7.39 (1H, d, $J = 15.6$ Hz, H-a), 7.36 (1H, s, H-2), 7.19–7.22 (2H, m, H-4,5), 6.08 (1H, s, OH); IR (KBr, ν_{max} cm^{-1}) 1629; ESI-MS *m/z*: 231 (M + 1); Anal. calcd. for $C_{13}H_{10}O_2S$: C, 67.80; H, 4.38; S, 13.92. Found: C, 67.92; H, 4.58; S, 13.79.

(E)-1-(3-Methoxyphenyl)-3-(thiophen-2-yl)prop-2-en-1-one **T10**

Yield: 93%; m.p.: 102–104°C; ^{1}H-NMR ($CDCl_3$, 300 MHz, δ, ppm) δ: 7.92 (1H, d, $J = 15.6$ Hz, H-b), 7.53–7.59 (2H, m, H-3',5'), 7.39 (1H, d, $J = 15.6$ Hz, H-a), 7.38 (1H, t, $J = 4.8$ Hz, H-4'), 7.33–7.36 (2H, m, H-5,6), 7.26 (1H, s, H-2), 7.07–7.14 (2H, m, H-4,4'), 3.85 (3H, s, OCH_3); IR (KBr, ν_{max} cm^{-1}) 1627; ESI-MS *m/z*: 245 (M + 1); Anal. calcd. for $C_{14}H_{12}O_2S$: C, 68.83; H, 4.95; S, 13.12. Found: C, 68.93; H, 4.98; S, 13.01.

(E)-1-(2, 4-Dimethylphenyl)-3-(thiophen-2-yl)prop-2-en-1-one **T11**

Yield: 96%; m.p.: 61–63°C; ^{1}H-NMR ($CDCl_3$, 300 MHz, δ, ppm) δ: 7.61–7.66 (1H, d, $J = 15.6$ Hz, H-b), 7.28–7.46 (3H, m, H-6,3',5'), 7.05–7.10 (3H, m, H-3,5,4'), 6.95 (1H, d, $J = 15.6$ Hz, H-a), 2.45 (3H, s, CH_3), 2.38 (3H, s, CH_3); IR (KBr, ν_{max} cm^{-1}) 1618; ESI-MS *m/z*: 243 (M + 1); Anal. calcd. for $C_{15}H_{14}OS$: C, 74.34; H, 5.82; S, 13.23. Found: C, 74.41; H, 5.88; S, 13.11.

(E)-1-(2, 4-Dichlorophenyl)-3-(thiophen-2-yl)prop-2-en-1-one **T12**

Yield: 93%; m.p.: 61–63°C; ^{1}H-NMR ($CDCl_3$, 300 MHz, δ, ppm) δ: 7.58 (1H, d, $J = 15.6$ Hz, H-b), 7.42–7.48 (3H, m, H-3,5',6), 7.33–7.36 (2H, m, H-3',5), 7.38 (1H, t, $J = 4.8$ Hz, H-4'), 7.39 (1H, d, $J = 15.6$ Hz, H-a); IR (KBr, ν_{max} cm^{-1}) 1637; ESI-MS *m/z*: 284 (M + 1); Anal. calcd. for $C_{13}H_8Cl_2OS$: C, 55.14; H, 2.85; S, 11.32. Found: C, 55.18; H, 2.89; S, 11.27.

(E)-1-(2, 4-Dihydroxyphenyl)-3-(thiophen-2-yl)prop-2-en-1-one **T13**

Yield: 89%; m.p.: 154–156°C; ^{1}H-NMR ($CDCl_3$, 300 MHz, δ, ppm) δ: 13.42 (1H, s, 2-OH), 8.00 (1H, d, $J = 15.6$ Hz, H-b), 7.79 (1H, d, $J = 8.4$ Hz, H-6), 7.38–7.33 (1H, m, H-3'), 7.33 (1H, d, $J = 15.6$ Hz, H-a), 7.13 (1H, t, $J = 4.8$ Hz, H-4'), 6.47–6.43 (1H, m, H-5), 6.44 (1H, s, H-2), 5.91 (1H, s, 4-OH); IR (KBr, ν_{max} cm^{-1}) 1632; ESI-MS *m/z*: 247 (M + 1); Anal. calcd. for $C_{13}H_{10}O_3S$: C, 63.40; H, 4.09; S, 13.02. Found: C, 63.47; H, 4.13; S, 12.88.

(E)-1-(2-Hydroxyphenyl)-3-(thiophen-2-yl)prop-2-en-1-one **T14**

Yield: 91%; m.p.: 124–126°C; ^{1}H-NMR ($CDCl_3$, 300 MHz, δ, ppm) δ: 12.88 (1H, s, 2-OH), 8.04 (1H, d, $J = 15.3$ Hz, H-b), 7.88 (1H, d, $J = 8.4$ Hz, H-6), 7.42 (1H, d, $J = 15.3$ Hz, H-b), 7.41–7.53 (3H, m, H-4,3',5'), 7.13 (1H, t, $J = 4.5$ Hz, H-4'), 6.93–7.04 (2H, m, H-3,5); IR (KBr, ν_{max} cm^{-1}) 1623; ESI-MS *m/z*: 231 (M + 1); Anal. calcd. for $C_{13}H_{10}O_2S$: C, 67.77; H, 4.45; S, 13.92. Found: C, 67.83; H, 4.39; S, 13.87.

(E)-3-(Furan-2-yl)-1-phenylprop-2-en-1-one **F1**

Yield: 90%; liquid; ^{1}H-NMR ($CDCl_3$, 300 MHz, δ, ppm) δ: 8.02 (2H, d, $J = 7.5$ Hz, H-2,6), 7.93 (1H, d, $J = 15.3$ Hz, H-b), 7.48 (1H, d, $J = 15.3$ Hz, H-a), 7.44–7.60 (4H, m, H-3,4,5,3'), 6.72 (1H, d, $J = 3.0$ Hz, H-5'), 6.52 (1H, t, $J = 1.5$ Hz, H-4'); IR (KBr, ν_{max} cm^{-1}) 1633; ESI-MS *m/z*: 199 (M + 1); Anal. calcd. for $C_{13}H_{10}O_2$: C, 78.77; H, 5.09. Found: C, 78.83; H, 5.12.

(E)-1-(4-Chlorophenyl)-3-(furan-2-yl)prop-2-en-1-one **F2**

Yield: 95%; m.p.: 72–74°C; ^{1}H-NMR ($CDCl_3$, 300 MHz, δ, ppm) δ: 7.96 (2H, d, $J = 8.4$ Hz, H-2,6), 7.58 (1H, d, $J = 15.3$ Hz, H-b), 7.57–7.54 (1H, m, H-3'), 7.38 (1H, d, $J = 15.3$ Hz, H-a), 7.98 (1H, d, $J = 8.4$ Hz, H-3,5), 6.73 (1H, d, $J = 3.0$ Hz, H-5'), 7.10 (1H, t, $J = 1.5$ Hz, H-4'); IR (KBr, ν_{max} cm^{-1}) 1629; ESI-MS *m/z*: 233 (M + 1); Anal. calcd. for $C_{13}H_9O_2$: C, 67.11; H, 3.90. Found: C, 67.17; H, 3.98.

(E)-3-(Furan-2-yl)-1-(4-methoxyphenyl)prop-2-en-1-one ***F3***

Yield: 97%; m.p.: 76–78°C; ^{1}H-NMR ($CDCl_3$, 300 MHz, δ, ppm) δ: 8.05 (2H, d, J = 8.4 Hz, H-2,6), 7.57 (1H, d, J = 15.6 Hz, H-b), 7.53–7.62 (1H, m, H-3'), 7.44 (1H, d, J = 8.4 Hz, H-3,5), 7.38 (1H, d, J = 15.6 Hz, H-a), 6.72 (1H, d, J = 3.0 Hz, H-5'), 6.53 (1H, t, J = 1.5 Hz, H-4'), 3.90 (3H, s, CH_3); IR (KBr, ν_{max} cm^{-1}) 1629; ESI-MS *m/z*: 233 (M + 1); Anal. calcd. for $C_{13}H_9O_2$: C, 73.67; H, 5.30. Found: C, 73.76; H, 5.36.

(E)-1-(4-Fluorophenyl)-3-(furan-2-yl)prop-2-en-1-one ***F4***

Yield: 95%; m.p.: 63–65°C; ^{1}H-NMR ($CDCl_3$, 300 MHz, δ, ppm) δ: 8.06 (2H, dd, J = 8.4 Hz, H-2,6), 7.59 (1H, d, J = 15.3 Hz, H-b), 7.47–7.55 (1H, m, H-3'), 7.38 (1H, d, J = 15.3 Hz, H-a), 7.18 (1H, dd, J = 8.4 Hz, H-3,5), 6.74 (1H, d, J = 3.0 Hz, H-5'), 6.54 (1H, t, J = 1.5 Hz, H-4'); IR (KBr, ν_{max} cm^{-1}) 1641; ESI-MS *m/z*: 217 (M + 1); Anal. calcd. for $C_{13}H_9FO_2$: C, 72.22; H, 4.20. Found: C, 72.18; H, 4.33.

(E)-3-(Furan-2-yl)-1-p-tolylprop-2-en-1-one ***F5***

Yield: 98%; m.p.: 62–64°C; ^{1}H-NMR ($CDCl_3$, 300 MHz, δ, ppm) δ: 7.94 (2H, d, J = 8.4 Hz, H-2,6), 7.62 (1H, d, J = 15.3 Hz, H-b), 7.53–7.57 (1H, m, H-3'), 7.44 (1H, d, J = 15.3 Hz, H-a), 7.28 (1H, d, J = 8.4 Hz, H-3,5), 6.70 (1H, d, J = 3.0 Hz, H-5'), 6.52 (1H, t, J = 1.5 Hz, H-4'), 2.43 (1H, s, CH_3); IR (KBr, ν_{max} cm^{-1}) 1635; ESI-MS *m/z*: 213 (M + 1); Anal. calcd. for $C_{14}H_{12}O_2$: C, 79.22; H, 5.70. Found: C, 79.27; H, 5.73.

(E)-3-(Furan-2-yl)-1-(4-nitrophenyl)prop-2-en-1-one ***F6***

Yield: 98%; m.p.: 148–150°C; ^{1}H-NMR ($CDCl_3$, 300 MHz, δ, ppm) δ: 7.94 (2H, d, J = 8.4 Hz, H-3,5), 7.28 (1H, d, J = 8.4 Hz, H-2,6), 7.67 (1H, d, J = 15.3 Hz, H-b), 7.62–7.66 (1H, m, H-3'), 7.38 (1H, d, J = 15.3 Hz, H-a), 6.81 (1H, d, J = 3.0 Hz, H-5'), 6.56 (1H, t, J = 1.5 Hz, H-4'); IR (KBr, ν_{max} cm^{-1}) 1625; ESI-MS *m/z*: 244 (M + 1); Anal. calcd. for $C_{13}H_9NO_2$: C, 64.20; H, 3.73; N, 5.76. Found: C, 64.27; H, 3.79; N, 5.66.

(E)-1-(4-Bromophenyl)-3-(furan-2-yl)prop-2-en-1-one ***F7***

Yield: 98%; m.p.: 80–82°C; ^{1}H-NMR ($CDCl_3$, 300 MHz, δ, ppm) δ: 7.89 (2H, d, J = 8.4 Hz, H-3,5), 7.62 (1H, d, J = 8.4 Hz, H-2,6), 7.58 (1H, d, J = 15.3 Hz, H-b), 7.54–7.57 (1H, m, H-3'), 7.37 (1H, d, J = 15.3 Hz, H-a), 6.74 (1H, d, J = 3.0 Hz, H-5'), 6.53 (1H, t, J = 1.5 Hz, H-4'); IR (KBr, ν_{max} cm^{-1}) 1628; ESI-MS *m/z*: 278 (M + 1); Anal. calcd. for $C_{13}H_9BrO_2$: C, 56.34; H, 3.27. Found: C, 56.42; H, 3.31.

(E)-3-(Furan-2-yl)-1-(3-hydroxyphenyl)prop-2-en-1-one ***F8***

Yield: 98%; m.p.: 44–46°C; ^{1}H-NMR ($CDCl_3$, 300 MHz, δ, ppm) δ: 8.00 (1H, s, H-2), 7.88 (1H, d, J = 8.4 Hz, H-6), 7.58 (1H, d, J = 15.3 Hz, H-b), 7.43–7.55 (3H, m, H-3',4,5), 7.36 (1H, d, J = 15.3 Hz, H-a), 6.74 (1H, d, J = 3.0 Hz, H-5'), 6.53 (1H, t, J = 1.5 Hz, H-4'); IR (KBr, ν_{max} cm^{-1}) 1639; ESI-MS *m/z*: 233 (M + 1); Anal. calcd. for $C_{13}H_9O_2$: C, 67.11; H, 3.90. Found: C, 67.17; H, 3.98.

(E)-3-(Furan-2-yl)-1-(3-chlorophenyl)prop-2-en-1-one ***F9***

Yield: 93%; m.p.: 71–73°C; ^{1}H-NMR ($CDCl_3$, 300 MHz, δ, ppm) δ: 8.85 (1H, s, OH), 7.49 (1H, d, J = 15.3 Hz, H-b), 7.40–7.47 (3H, m, H-3',2,6), 7.35 (1H, d, J = 15.3 Hz, H-a), 7.25–7.30 (1H, m, H-5), 7.03 (1H, d, J = 7.2 Hz, H-4), 6.67 (1H, d, J = 3.0 Hz, H-5'), 6.48 (1H, t, J = 1.5 Hz, H-4'); IR (KBr, ν_{max} cm^{-1}) 1639; ESI-MS *m/z*: 215 (M + 1); Anal. calcd. for $C_{13}H_{10}O_3$: C, 72.89; H, 4.71. Found: C, 72.94; H, 4.76.

(E)-3-(Furan-2-yl)-1-(3-methoxyphenyl)prop-2-en-1-one ***F10***

Yield: 93%; m.p.: 39–41°C; ^{1}H-NMR ($CDCl_3$, 300 MHz, δ, ppm) δ: 7.62 (1H, d, J = 15.3 Hz, H-b), 7.53–7.60 (3H, m, H-3',2,6), 7.40–7.46 (1H, m, H-5), 7.38 (1H, d, J = 15.3 Hz, H-a), 7.13 (1H, d, J = 7.2 Hz, H-4), 6.72 (1H, d, J = 3.0 Hz, H-5'), 6.52 (1H, t, J = 1.5 Hz, H-4'), 3.88 (3H, s, OCH_3); IR (KBr, ν_{max} cm^{-1}) 1637; ESI-MS *m/z*: 229 (M + 1); Anal. calcd. for $C_{14}H_{12}O_3$: C, 73.67; H, 5.30. Found: C, 73.74; H, 5.33.

(E)-3-(Furan-2-yl)-1-(2, 4-dimethylphenyl)prop-2-en-1-one ***F11***

Yield: 95%; m.p.: 58–60°C; ^{1}H-NMR ($CDCl_3$, 300 MHz, δ, ppm) δ: 7.51 (1H,d, J = 1.5 Hz, H-3'), 7.46 (1H, d, J = 8.1 Hz, H-6), 7.27 (1H, d, J = 15.3 Hz, H-b), 7.09–7.11 (2H, m, H-3,5), 7.06 (1H, d, J = 15.3 Hz, H-a), 6.65 (1H, d, J = 3.0 Hz, H-5'), 6.50 (1H, t, J = 1.5 Hz, H-4'), 2.45 (3H, s, CH_3), 2.37 (3H, s, CH_3); IR (KBr, ν_{max} cm^{-1}) 1632; ESI-MS *m/z*: 227 (M + 1); Anal. calcd. for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24. Found: C, 79.68; H, 6.31.

(E)-1-(2, 4-Dichlorophenyl)-3-(furan-2-yl)prop-2-en-1-one ***F12***

Yield: 95%; m.p.: 79–81°C; ^{1}H-NMR ($CDCl_3$, 300 MHz, δ, ppm) δ: 7.55 (1H,s, H-3), 7.47 (1H, d, J = 1.8 Hz, H-3'), 7.43 (1H, d, J = 8.4 Hz, H-6), 7.33 (1H, m, H-5), 7.24 (1H, d, J = 15.3 Hz, H-b), 6.99 (1H, d, J = 15.3 Hz, H-a), 6.72 (1H, d, J = 3.0 Hz, H-5'), 6.52 (1H, t, J = 1.5 Hz, H-4'); IR (KBr, ν_{max} cm^{-1}) 1621; ESI-MS *m/z*: 268 (M + 1); Anal. calcd. for $C_{13}H_8Cl_2O_2$: C, 58.46; H, 3.02. Found: C, 58.55; H, 3.07.

(E)-3-(Furan-2-yl)-1-(2, 4-dihydroxyphenyl)prop-2-en-1-one ***F13***

Yield: 75%; m.p.: 69–71°C; ^{1}H-NMR ($CDCl_3$, 300 MHz, δ, ppm) δ: 13.43 (1H, s, 2-OH), 7.83 (1H,d, J = 8.4 Hz, H-6), 7.63 (1H, d, J = 15.6 Hz, H-b), 7.45–7.50 (2H, m, H-3,5), 7.45 (1H, d, J = 15.3 Hz, H-a), 6.75 (1H, d, J = 3.0 Hz, H-5'), 6.55 (1H, d, J = 3.0 Hz, H-3'), 6.45 (1H, t, J = 1.5 Hz, H-4'), 6.43 (1H, s, 4-OH); IR (KBr, ν_{max} cm^{-1}) 1648; ESI-MS *m/z*: 231 (M + 1); Anal. calcd. for $C_{13}H_{10}O_4$: C, 67.82; H, 4.38. Found: C, 67.89; H, 4.37.

(E)-3-(Furan-2-yl)-1-(2-hydroxyphenyl)prop-2-en-1-one ***F14***

Yield: 96%; m.p.: 103–105°C; ^{1}H-NMR ($CDCl_3$, 300 MHz, δ, ppm) δ: 12.90 (1H, s, 2-OH), 7.93 (1H, d, J = 6), 7.68 (1H, d, J = 15.3 Hz, H-b), 7.55 (1H, d, J = 15.3 Hz, H-a), 7.47–7.60 (2H, m, H-4,3'), 7.03 (1H, d, J = 8.4 Hz, H-3), 6.96 (1H, t, J = 7.5 Hz, H-5), 6.80 (1H, d, J = 3.0 Hz, H-5'), 6.56 (1H, t, J = 1.5 Hz); IR (KBr, ν_{max} cm^{-1}) 1627; ESI-MS *m/z*: 215 (M + 1); Anal. calcd. for $C_{14}H_{12}O_3$: C, 72.89; H, 4.71. Found: C, 73.94; H, 4.63.

(E)-3-(2-Chloroquinolin-3-yl)-1-phenylprop-2-en-1-one ***Q1***

Yield: 83%; m.p.: 138–140°C; ^{1}H-NMR ($CDCl_3$, 300 MHz, δ, ppm) δ: 8.49 (1H, s, H-8'), 8.18 (1H, d, J = 15.6 Hz, H-b), 8.02–8.08

(3H, m, H-2,6,7'), 7.88 (1H, d, J = 8.1 Hz,H-4'), 7.79 (1H, t, J = 7.65 Hz, H-4), 7.59 (1H, d, J = 15.6 Hz, H-a), 7.52–7.63 (4H, m, H-3,5,5',6'); IR (KBr, ν_{max} cm^{-1}) 1624; ESI-MS *m/z*: 294 (M + 1); Anal. calcd. for $C_{18}H_{12}ClNO$: C, 73.60; H, 4.12; N, 4.77. Found: C, 73.42; H, 4.33; N, 4.65.

(E)-3-(2-Chloroquinolin-3-yl)-1-(4-methoxyphenyl)prop-2-en-1-one **Q2**

Yield: 85%; m.p.: 143–145°C; ^{1}H-NMR ($CDCl_3$, 300 MHz, δ, ppm) δ: 8.50 (1H, s, H-8'), 8.17 (1H, d, J = 15.6 Hz, H-b), 8.07 (2H, d, J = 8.7 Hz, H-2,6), 8.03–8.06 (1H, d, J = 9.3 Hz, H-4'), 7.88 (1H, d, J = 8.4 Hz, H-7'), 7.79 (1H, t, J = 7.65 Hz, H-5'), 7.61 (1H, d, J = 15.6 Hz, H-a), 7.64 (1H, t, J = 7.65 Hz, H-6'), 7.00 (2H, d, J = 8.7 Hz, H-3,5), 3.92 (3H, s, OCH_3); IR (KBr, ν_{max} cm^{-1}) 1628; ESI-MS *m/z*: 324 (M + 1); Anal. calcd. for $C_{19}H_{14}ClNO_2$: C, 70.48; H, 4.36; N, 4.33. Found: C, 70.43; H, 4.23; N, 4.55.

(E)-1-(4-Chlorophenyl)-3-(2-chloroquinolin-3-yl)prop-2-en-1-one **Q3**

Yield: 35%; m.p.: 173–175°C; ^{1}H-NMR ($CDCl_3$, 300 MHz, δ, ppm) δ: 8.50 (1H, s, H-8'), 8.20 (1H, d, J = 15.6 Hz, H-b), 8.06 (1H, m, H-4'), 8.00 (1H, d, J = 8.7 Hz, H-2,6), 7.89 (1H, d, J = 8.1 Hz, H-7'), 7.80 (1H, t, J = 7.35 Hz, H-5'), 7.62 (1H, m, H-6'), 7.56 (1H, d, J = 15.6 Hz, H-a), 7.41 (2H, d, J = 8.4 Hz, H-3,5); IR (KBr, ν_{max} cm^{-1}) 1627; ESI-MS *m/z*: 329 (M + 1); Anal. calcd. for $C_{18}H_{11}Cl_2NO$: C, 65.87; H, 3.38; N, 4.27. Found: C, 65.78; H, 3.33; N, 4.35.

(E)-3-(2-Chloroquinolin-3-yl)-1-(2, 4-dimethylphenyl)prop-2-en-1-one **Q4**

Yield: 86%; m.p.: 123–125°C; ^{1}H-NMR ($CDCl_3$, 300 MHz, δ, ppm) δ: 8.45 (1H, s, H-8'), 8.01 (1H, d, J = 8.4 Hz, H-4'), 7.92 (1H, d, J = 15.6 Hz H-b), 7.87 (1H, d, J = 8.1 Hz, H-7'), 7.80 (1H, t, J = 7.35 Hz, H-5'), 7.63 (1H, d, J = 15.6 Hz, H-a), 7.53–7.60 (1H, m, H-6'), 7.31 (1H, d, J = 8.4 Hz, H-6), 7.13 (1H, s, H-3), 7.11 (1H, m, H-5), 2.50 (3H, s, CH_3), 2.40 (3H, s, CH_3); IR (KBr, ν_{max} cm^{-1}) 1630; ESI-MS *m/z*: 322 (M + 1); Anal. calcd. for $C_{20}H_{16}ClNO$: C, 74.65; H, 5.01; N, 4.35. Found: C, 74.68; H, 5.27; N, 4.28.

(E)-3-(2-Chloroquinolin-3-yl)-1-(2, 4-dihydroxyphenyl)-prop-2-en-1-one **Q5**

Yield: 82%; m.p.: 314–316°C; ^{1}H-NMR (DMSO, 300 MHz, δ, ppm) δ: 13.36 (1H, s, OH), 10.78 (1H, s, OH), 8.62 (1H, s, H-8'), 8.34 (1H, d, J = 15.6 Hz, H-b), 7.98 (1H, d, J = 9.0 Hz, H-4'), 7.85 (1H, d, J = 15.6 Hz, H-a), 7.70 (1H, d, J = 7.65 Hz, H-7'), 7.55 (1H, t, J = 7.35 Hz, H-6'), 7.33 (1H, d, J = 8.4 Hz, H-6), 7.24 (1H, t, J = 7.35 Hz, H-5'), 6.45 (1H, d, J = 8.7 Hz, H-5), 6.30 (1H, s, H-3); IR (KBr, ν_{max} cm^{-1}) 3498, 1632; ESI-MS *m/z*: 326 (M + 1); Anal. calcd. for $C_{18}H_{12}ClNO_3$: C, 66.37; H, 3.71; N, 4.30. Found: C, 66.42; H, 3.85; N, 4.38.

(E)-3-(2-Chloroquinolin-3-yl)-1-(2-hydroxyphenyl)prop-2-en-1-one **Q6**

Yield: 85%; m.p.: 172–174°C; ^{1}H-NMR (DMSO, 300 MHz, δ, ppm) δ: 12.65 (1H, s, OH), 8.53 (1H, s, H-8'), 8.32 (1H, d, J = 15.6 Hz, H-b), 8.04 (1H, d, J = 8.4 Hz, H-4'), 7.82–7.98 (3H, m, H-6,6',7'), 7.76 (1H, d, J = 15.6 Hz, H-a), 7.64 (1H, t, J = 7.35 Hz, H-5'), 7.55 (1H, t, J = 7.65 Hz, H-4), 7.06 (1H, d, J = 8.1 Hz, H-3), 6.99 (1H, t, J = 7.35 Hz, H-5); IR (KBr, ν_{max} cm^{-1}) 3496, 1622; ESI-MS *m/z*: 310 (M + 1); Anal. calcd. for $C_{18}H_{12}ClNO_2$: C, 66.80; H, 3.90; N, 4.52. Found: C, 66.84; H, 3.78; N, 4.55.

(E)-3-(2-Chloroquinolin-3-yl)-1-p-tolylprop-2-en-1-one **Q7**

Yield: 85%; m.p.: 128–130°C; ^{1}H-NMR ($CDCl_3$, 300 MHz, δ, ppm) δ: 8.51 (1H, s, H-8'), 8.18 (1H, d, J = 15.6 Hz, H-b), 8.03–8.06 (1H, d, J = 8.4 Hz,H-4'), 7.98 (2H, d, J = 8.4 Hz, H-2,6), 7.89 (1H, d, J = 8.1 Hz, H-7'), 7.79 (1H, t, J = 7.65 Hz, H-5'), 7.66 (1H, d, J = 15.6 Hz, H-a), 7.62 (1H, t, J = 7.65 Hz, H-6'), 7.33 (2H, d, J = 8.1 Hz, H-3,5), 3.92 (3H, s, CH_3); IR (KBr, ν_{max} cm^{-1}) 1638; ESI-MS *m/z*: 308 (M + 1); Anal. calcd. for $C_{19}H_{14}ClNO$: C, 74.15; H, 4.58; N, 4.55. Found: C, 74.11; H, 4.63; N, 4.68.

(E)-3-(2-Chloroquinolin-3-yl)-1-(2-hydroxy-4-(methoxymethoxy)phenyl)prop-2-en-1-one **Q8**

Yield: 84%; m.p.: 132–134°C; ^{1}H-NMR ($CDCl_3$, 300 MHz, δ, ppm) δ: 13.10 (1H, s, OH), 8.50 (1H, s, H-8'), 8.27 (1H, d, J = 15.6 Hz, H-b), 8.04 (1H, d, J = 8.4 Hz, H-4'), 7.86–7.92 (2H, m, H-6,7'), 7.80 (1H, t, J = 7.65 Hz, H-5'), 7.67 (1H, d, J = 15.6 Hz, H-a), 7.62 (1H, t, J = 7.65 Hz, H-6'), 6.68 (1H, s, H-3), 6.61(1H, d, J = 8.7 Hz, H-5), 5.25 (2H, s, CH_2), 3.50 (3H, s, CH_3); IR (KBr, ν_{max} cm^{-1}) 3488, 1627; ESI-MS *m/z*: 370 (M + 1); Anal. calcd. for $C_{20}H_{16}ClNO_4$: C, 64.96; H, 4.36; N, 3.79. Found: C, 66.89; H, 4.28; N, 3.75.

Pharmacology

The micro-organisms used in the present study were *S. aureus* (*S. aureus* RN4220, *S. aureus* KCTC 503, and *S. aureus* KCTC 209), *S. mutans* (*S. mutans* KCTC 3065 and *S. mutans* KCTC 3289), and *Escherichia coli* (*E. coli* 1924 and *E. coli* 1356). The strains of multidrug-resistant clinical isolates were multidrug-resistant *Staphylococcus aureus* (MRSA CCARM 3167 and MRSA CCARM 3506) and quinolone-resistant *Staphylococcus aureus* (QRSA CCARM 3505 and QRSA CCARM 3519). Clinical isolates were collected from various patients hospitalized in several clinics.

A twofold serial dilution technique [11] was followed to determine the minimum inhibitory concentration (MIC) of the compounds against the susceptible micro-organisms in the preliminary test (Gram-positive bacteria and Gram-negative bacteria) and against strains of clinical isolates of multidrug-resistant Gram-positive bacteria. Test compounds dissolved in DMSO were added to culture media (Brain Heart Infusion for *S. mutans* and Müller-Hinton agar for other bacteria) to obtain final concentrations of 64–0.5 μg/mL. The final amount applied was of 10^5 CFU/mL for bacteria. MIC values were read after incubation at 37°C for 20 h. The lowest concentration of the test substance that completely inhibited growth of the micro-organism was recorded as the MIC (expressed in μg/mL). Oxacillin and norfloxacin were used as the standard drugs. All experiments were carried out three times.

Conclusion

Three series of hetereocyclic chalcone derivatives bearing thiofuran, furan, and quinoline moieties were synthesized and tested for their anti-bacterial activity. Some compounds presented good anti-microbial activities against Gram-positive bacteria (including the multidrug-resistant clinical

isolates). Several furan derivatives presented high potency against *S. mutans*, among which the derivatives **F2** with an MIC of 2 μg/mL was as active as the standard drug norfloxacin and less active than oxacillin. More compounds need to be designed and synthesized for further investigation using **F2** as the lead compound.

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