Research in Pharmaceutical Sciences, October 2008; 3(2): 87-93
Received: Mar 2008
Accepted: Jun 2008

School of Pharmacy & Pharmaceutical Sciences
Isfahan University of Medical Sciences

Original Article

Synthesis and the combination effects of dihydropyridine analogs with selected antibiotics against resistant *Staphylococcus aureus*

T. Akbarzadeh[1], S. Motagian[2], A. Fallah Tafti[3], A. Shafiee[1] and A.R. Shahverdi[2,*]

[1]*Pharmaceutical Sciences Research Center, Tehran University of Medical Sciences, Tehran, I.R.Iran.*
[2]*Department of Pharmaceutical Biotechnology and Biotechnology Research Center, Faculty of Pharmacy, Tehran University of Medical sciences, Tehran, I.R.Iran.*
[3]*Department of Medicinal Chemistry, Faculty of Pharmacy, Tehran University of Medical sciences, Tehran, I.R.Iran.*

Abstract

Bacterial resistance is a major drawback in chemotherapy of infectious diseases. In this investigation a new series of 3,5-diarylamide dihydropyridines containing 2-benzylsulfonylimidazol at 4 position have been synthesized and studied for their enhancing effect on the antibacterial activities of different penicillins against a resistant clinical isolate of *Staphylococcus aureus* using disc diffusion method. During preliminary screening, compound 6d showed the most enhancing effect on the antibacterial activity of amoxicillin against the test strain and the combination effect of this compound has been further studied with penicillin G and piperacillin against *S. aureus*. The result of this evaluation showed that the antibacterial activities of penicillin G and piperacillin can be also enhanced by compound 6d suggesting a possible utilization of this compound in combination therapy against penicillin resistant *S. aureus*.

Keywords: Synthesis**;** 3,5-Diarylamide dihydropyridines**;** Combination effect; Antibacterial activity; *Staphylococcus aureus*

INTRODUCTION

Bacterial resistance is a major drawback in chemotherapy of infectious disease (1). The emergence of bacterial resistance to antibiotics and its dissemination, however, are major health problems, leading to treatment drawbacks for a large number of drugs (2). Many attempts are currently doing for combating the bacterial resistance (2). Currently there has been increasing interest in the use of inhibitors of antibiotic resistance for combination therapy (2-5). In this approach, antimicrobial agents are co-administers with an inhibitor that deactivates the bacteria's resistance mechanism and increases the anti-microbial agents' effectiveness. It has the advantage of extending the usefulness of antibiotics with known pharmacological, toxicological and treatment properties (2-5). Recently different natural products or synthetic compounds have been reported to increase the antibacterial activity of current antibiotics against different clinical isolated resistant test strains (6-11). The natural product galbanic acid has been reported to enhance the activity of penicillins and cephalosporins against *Staphylococcus aureus*. In our further program's search we have been screening various new N, N′-diaryl-2,6-dimethyl-4-(2-benzylsulfonyl-1-methylimidazol-5-yl)-1,4-dihydropyridine-3,5-dicarboxamide analogs for their ability to decrease bacterial resistance to amoxicillin, which are extensively used to treat infections caused by bacteria. Compound 6d was selected for further investigation. The enhancing effects of this compound on the antimicrobial activity of other penicillins (penicillin G and piperacillin) were also evaluated by disc diffusion method against a penicillin resistant clinical strain of *S. aureus*.

*****Corresponding author: Dr. Ahmad Reza Shahverdi
Tel. 0098 21 66482706
Email: shahverd@sina.tums.ac.ir

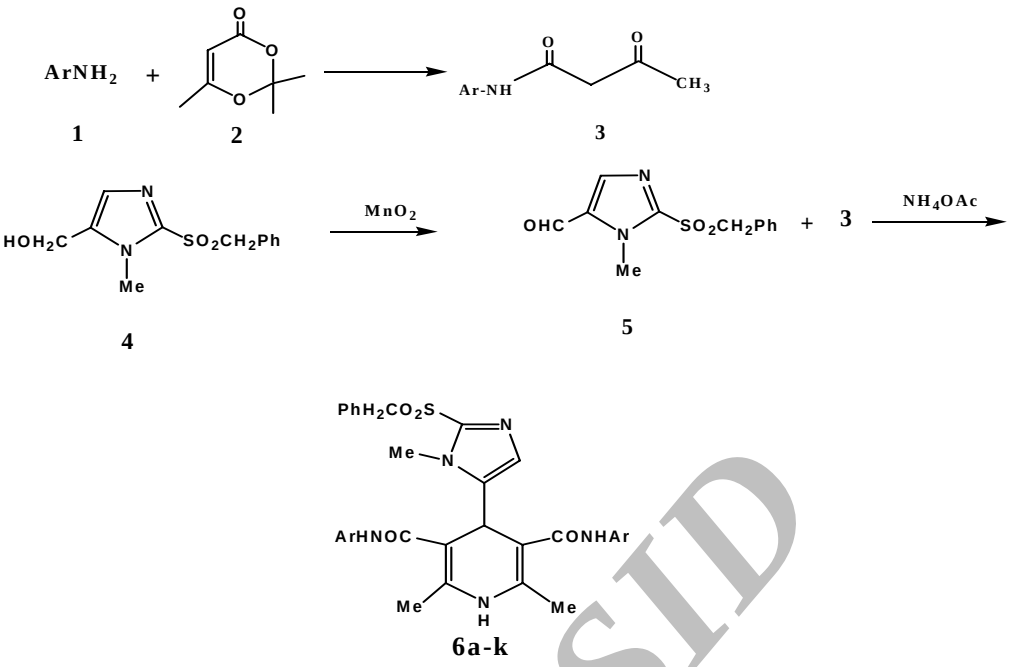


Fig. 1. Synthetic routes of 1,4-dihydropyridine analogs

MATERIALS AND METHODS

Chemistry

All solvents and reagents were obtained from commercial sources and used without further purification. Melting points were determined using a Kofler hot stage apparatus. ^{1}H-NMR spectra were run on Bruker FT-80 and FT-500 spectrometer system (Brukers, Rheinsteetteen, Germany). TMS was used as internal standard. Mass spectra were measured with a Finnigan TSQ-70 spectrometer (Finnigan Mat, Bremen, Germany). Infrared spectra were acquired on a Nicolet 550-FT spectrometer (Maidson, WI, USA). Elemental analyses were carried out with a Perkin-Elmer model 240-C apparatus (Perkin-elmer, Norwalk, CT, USA). The results of the elemental analysis (C, H, N) were within ±0.4% of the calculated amounts.

Synthesis of 2-benzylsulfonyl-1-methylimidazole-5-carboxaldehyde (compound 5)

To a stirred solution of 1-methyl-2-benzyl-sulfonyl-5-hydroxymethylimidazole, compound 4, (3.5 g, 26.3 mmol) in chloroform (100 ml), Manganese dioxide (15 g) was added. The reaction mixture was refluxed overnight and filtered. The filtrate was evaporated and the residue was crystallized from diethylether to give 4 g (90%) of compound 5; m.p. 142-144 C, IR (KBr): 1655 (NHC=O), ^{1}H-NMR ($CDCl_3$) δ: 9.81 (s, 1H, CHO), 7.83 (s, 1H, C_4-H imidazole), 7.50 (m, 5H, aromatic), 4.33 (s, 2H, CH_2), 3.98 (s, 3H, CH_3N); Mass: m/z (%) 264 (M^+, 100), 236 (28), 220 (39), 159 (98), 145 (52), 143 (64), 77 (100)

General procedure for the synthesis of N, N'-diaryl-2,6-dimethyl-4-(2-benzylsulfonyl-1-methylimidazol-5-yl)-1,4-dihydropyridine-3,5-dicarboxamides (compound 6a-k)

The reaction of appropriate amine (compound 1**)** with 2,2,6-trimethyl-4H-1,3-dioxine-4-one (compound 2**)** resulted the corresponding N-arylacetoactamide (compound 3). A solution of ammonium hydroxide (26%, 0.5 ml) was added to a stirring solution of compound 5 (240 mg, 1.26 mmol) and compound 3a-k (2.54 mmol) in methanol (5 ml). The mixture was protected from light and refluxed under argon overnight. After cooling the precipitate was filtered and crystallized from methanol to give the title compounds **6**. The yield was 51-88%.

Selected data for N,N'-diphenyl-2,6-dimethyl-4-(2-benzylsufonyl-1-methylimidazol-5-yl)-1,4-dihydropyridine-3,5-dicarboxamide (compound 6a)

Yield 52%, m.p. 201-203 °C, IR (KBr): 1652 (NHC=O), ^{1}HNMR (DMSO-d_6) δ: 9.50 (s, 2H, NH), 8.33 (s, 1H, N_1-H DHP), 7.59 (d, 4H, aromatic), 7.27 (t, 4H, H-aromatic), 7.07 (m, 3H, aromatic), 7.01 (m, 2H, aromatic), 6.96 (s, 1H, C_4-H imidazole), 6.89 (d, 2H, aromatic), 5.11 (s, 1H, C_4-H DHP), 4.63 (s, 2H, CH_2), 3.32 (s, 3H, N-CH_3), 2.10 (s, 6H, 2,6 CH_3). Mass: m/z (%) 581 (M^+, 2%), 461 (40), 446 (90), 367 (100), 328 (65), 261 (78), 125 (48). Anal. Calcd. For $C_{32}H_{31}N_5O_4S$: C, 66.09; H, 5.33; N, 12.05; Found: C, 66.28; H, 5.12; N, 12.38.

N,N'-bis(4-chlorophenyl)-2,6-dimethyl-4-(2-benzylsufonyl-1-methylimidazol-5-yl)-1,4-dihydropyridine-3,5-dicarboxamide (6d)

Yield 55 %, m.p. 243-245 °C, IR (KBr): 1655 (NHC=O), ^{1}HNMR (DMSO-d_6) δ: 9.66 (s,2H, N-H), 8.44 (s, 1H, N_1-H DHP), 7.63 (d, 4H, aromatic), 7.33 (d, 4H, aromatic), 7.11 (m, 3H, aromatic), 6.94 (s, 1H, C_4-H imidazole), 6.88 (d, 2H, aromatic) 5.09 (s, 1H, C_4-H DHP), 4.64 (s, 2H, CH_2), 3.30 (s, 3H, N-CH_3), 2.10 (s, 6H, 2,6 CH_3). Mass: m/z (%) 649 (M^+, 3%), 508 (45), 427 (50), 286 (70), 271 (100), 261 (25), 201 (32). Anal. Calcd. For $C_{32}H_{29}N_5O_4S$: C, 59.08; H, 4.49; N, 10.76; Found: C, 59.25; H, 4.42; N, 10.82.

Physical data for compounds 6a-6k are shown in Table 1.

Antimicrobial activities and enhancing effect of the synthesized compounds

A disc diffusion method was used to assay the different antibiotics for bactericidal activity against test strains on Müeller-Hinton agar plates. The standard antibiotics discs (amoxicillin 25 µg, penicillin G 10 U, piperacillin 100 µg) were purchased from Mast Company.(UK). To screen the enhancing effects of new compounds, amoxicillin paper disc (25 µg) was further impregnated with compounds 6a-k at the final content of 500 µg/discs. A single colony of test strain was grown overnight in Müeller -Hinton liquid medium on a rotary shaker (200 rpm) at 35 °C. The inocula were prepared by diluting the overnight cultures with 0.9% NaCl to a 0.5 McFarland standard and were applied to the plates along with the standard and prepared discs containing different amount of compounds 6a-k. An amoxicillin resistant clinical isolate of *S. aureus* was used as the test strain. After incubation at 35 °C for 18 h, the zones of inhibition were measured. The assays were performed in triplicate. The combined antibacterial effect of different contents (100, 200, 300, 400, 500 µg/disc) of the most potent compound (6d) and penicillin G, piperacillin and amoxicillin was further investigated using a similar disc diffusion method against *S. aureus*.

The diameters of inhibition zones produced by effective compounds (6a,d,i,k), in presence and absence of antibiotic were recorded. The increase in the surface area (πr^2) due to the combination effects was statistically evaluated by determining Student's t-test for its level of significance.

RESULTS

Chemistry

1,4-dihydropyridine analogs described here were synthesized following the synthetic routes outlined in Scheme 1. The reaction of appropriate amine (compound 1**)** with 2,2,6-trimethyl-4H-1,3-dioxine-4-one (compound 2**)** resulted the corresponding acetoactamide (compound 3a-k) (76-92% yield) (12). Oxidation of compound 4 with manganese (IV) oxide in chloroform afforded the desired aldehyde (compound 5) in 90% yield (13,14). Classical Hantzsch condensation in which the compound 5 was reacted with N-aryl actoacetamide (3a-k) and ammonium acetate in ethanol resulted symmetrical dihydro-pyridine analogues 6a-k**.** The structure of all compounds was confirmed by IR, ^{1}H NMR and mass spectroscopy (Table 1.)

Table 1. Physical data for compounds 6a-k

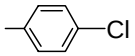
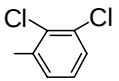
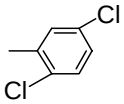
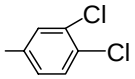
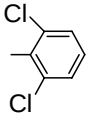
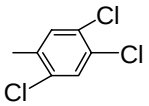
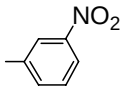
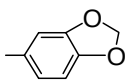
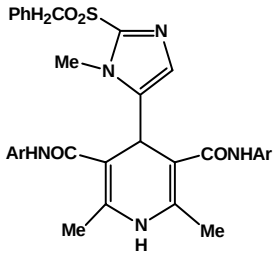
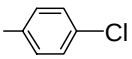
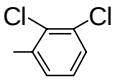
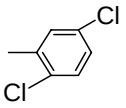
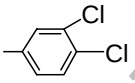
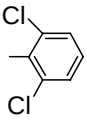
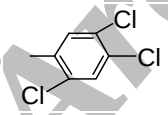
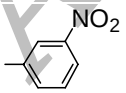
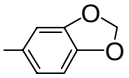
Compound No	Ar.	Yield (%)	m.p. (°C)	NMR
6a		52	201-203	9.50 (s, 2H, NH), 8.33 (s, 1H, N_1-H DHP), 7.59 (d, 4H, aromatic), 7.27 (t, 4H, H-aromatic), 7.07 (m, 3H, aromatic), 7.01 (m, 2H, aromatic), 6.96 (s, 1H, C_4-H imidazole), 6.89 (d, 2H, aromatic), 5.11 (s, 1H, C_4-H DHP), 4.63 (s, 2H, CH_2), 3.32 (s, 3H, N-CH_3), 2.10 (s, 6H, 2,6 CH_3).
6b		66	220-222	9.23 (s, 2H, N-H), 8.44 (s, 1H, N_1-H DHP), 7.59 (m, 2H, aromatic), 7.16 (m, 9H, aromatic), 6.97 (s, 1H, H-C_4 imidazole), 6.95 (m, 2H, aromatic), 5.15 (s, 1H,H-C_4 DHP), 4.66 (s, 2H, CH_2), 3.36 (s, 3H, N-CH_3), 2.15 (s, 6H, 2,6 CH_3).
6c		59	189-190	9.07 (s, 2H, N-H), 8.46 (s, 1H, N_1-H DHP), 7.55 (d, 2H, aromatic), 7.47 (d, 2H, aromatic), 7.30 (t, 2H, aromatic), 7.20 (m, 5H, aromatic), 7.01 (d, 2H, aromatic), 6.99 (s, 1H, C_4-H imidazole), 5.16 (s, 1H, - C_4-H DHP), 4.68 (s, 2H, CH_2),3.43 (s, 3H, N-CH_3), 2.19 (s, 6H, 2,6 CH_3).
6d		55	243-245	9.66 (s,2H, N-H), 8.44 (s, 1H, N_1-H DHP), 7.63 (d, 4H, aromatic), 7.33 (d, 4H, aromatic), 7.11 (m, 3H, aromatic), 6.94 (s, 1H, C_4-H imidazole), 6.88 (d, 2H, aromatic) 5.09 (s, 1H, C_4-H DHP), 4.64 (s, 2H, CH_2), 3.30 (s, 3H, N-CH_3), 2.10 (s, 6H, 2,6 CH_3).
6e		58	227-229	9.61 (s, 2H, NH), 8.33 (s, 1H, N_1-H DHP), 7.59 (d, 2H, aromatic), 7.27 (t, 2H, aromatic), 7.09 (m, 3H, aromatic), 7.01 (t, 2H, aromatic),6.96 (s, 1H, C_4-H imidazole), 6.89 (d, 2H, aromatic),5.11 (s, 1H, C_4 –H DHP), 4.63 (s, 2H, CH_2),3.32 (s, 3H, NCH_3), 2.10 (s, 6H, 2,6 CH_3).
6f		69	228-230	9.15 (s, 2H, NH), 8.64 (s, 1H, N_1-H DHP), 7.77 (d, J=2.0 Hz, 2H, aromatic), 7.52 (d, J=8.8 Hz, 2H, aromatic), 7.26 (dd, J=8.8 Hz, J=2.0 Hz, 2H, aromatic), 7.20(m, 3H, aromatic), 7.01 (d, 2H, aromatic), 6.99 (s, 1H, C_4-H imidazole), 5.13 (s, 1H, C_4-H DHP), 4.69 (s, 2H, CH_2), 3.43 (s, 3H, NCH_3), 2.20 (s, 6H, 2,6 CH_3).
6g		68	235-238	9.77 (s, 2H, NH), 8.56 (s, 1H, N_1-H DHP), 7.97 (s, 2H, aromatic), 7.53 (s, 4H, aromatic), 7.11(m, 3H, aromatic), 6.94 (s, 1H, C_4-H imidazole), 6.90 (d, 2H, aromatic), 5.06 (s, 1H, C_4-H DHP), 4.65 (s, 2H, CH_2), 3.32 (s, 3H, NCH_3), 2.10 (s, 6H, 2,6 CH_3).
6h		72	225-228	9.27 (bs, 2H, NH), 8.47 (bs, 1H, N_1-H DHP), 7.79 (m, 2H, aromatic), 7.53 (m, 3H, aromatic), 7.49 (d, 4H, aromatic), 7.30 (t, 2H, aromatic), 6.97 (s, 1H, C_4-H imidazole), 5.25 (s, 1H, C_4-H DHP), 4.68 (s, 2H, CH_2), 3.37 (s, 3H, N-CH_3), 2.15 (s, 6H, 2,6 CH_3).
6i		98	226-227	9.23 (s, 2H, NH), 8.67 (s, 1H, N_1-H DHP), 7.95 (s, 2H, aromatic), 7.89 (s,2H, aromatic), 7.20 (m, 3H, aromatic), 7.01 (d, 2H, aromatic), 6.98 (s, 1H, C_4-H imidazole), 5.11 (s, 1H, C_4-H DHP), 4.69 (s, 2H, CH_2), 3.43 (s, 3H, N-CH_3), 2.20 (s, 6H, 2,6 CH_3).
6j		51	237-240	9.93 (s, 2H, NH), 8.62 (s, 2H, aromatic), 7.83 (D, 4H, aromatic), 7.59 (m, 2H, aromatic), 7.13 (m, 3H, aromatic), 6.97 (s, 1H, C_4-H imidazole), 6.91 (m, 2H, aromatic), 5.14 (s, 1H, C_4-H DHP), 4.66 (s, 2H, CH_2), 3.32 (s, 3H, N-CH_3), 2.14 (s, 6H, 2,6 CH_3).
6k		85	221-223	9.42 (s, 2H, NH), 8.29 (s, 1H, N_1-H DHP), 7.28 (d, J=2.0 Hz, 2H, aromatic), 7.14 (m, 3H, aromatic),6.98 (dd, J=8.4 Hz, J=2.0 Hz, 2H, aromatic), 6.94 (s, 1H, C_4-H imidazole), 6.91 (m, 2H, aromatic), 6.82 (d, J=8.4 Hz, 2H, aromatic), 5.95 (s, 4H, O-CH_2-O), 5.06 (s, 1H, C_4-H DHP), 4.64 (s, 2H, CH_2), 3.32 (s, 3H, NCH_3), 2.06 (s, 6H, 2,6 CH_3).

Table 2. Physical data and enhancement of antimicrobial activity of amoxicillin (25 µg/ml) against resistant *Staphylococcus aureus* by compounds 6a-6k (500 µg/disc).



Compound No.	Ar	Mean diameter of inhibition (mm) A In absence of amoxicillin	B In presence of amoxicillin	C Fold increase in area
6a		-	9 ± 0.5	0.65
6b		-	-	-
6c		-	-	-
6d		-	14 ± 1	3.00
6e		-	-	-
6f		-	-	-
6g		-	-	-
6h		-	-	-
6i		-	9 ± 1	0.65
6j		-	-	-
6k		-	8.5 ± 0.5	0.47

C: Mean surface area of the inhibition zone (mm^2) was calculated for amoxicillin as $(b^2-a^2)/a^2$ where a and b are the areas of inhibition zone for A and B, respectively. In the absence of bacterial growth inhibition zones, the discs diameter (7mm) was used to calculate the fold increase in columns A and B. The experiments were conducted in triplicate; data are mean ± SD.

Antibacterial assay

The combination effect of synthetic compounds (500 µg) with amoxicillin was firstly investigated against resistant *S. aureus* using the disc diffusion method. The diameter of inhibition zones (mm) around the

amoxicillin antibiotic discs with or without synthetic compounds against test strain are shown in Table 2. The results of the antibacterial evaluation of these compounds using disc diffusion assay indicated that none of the synthetic compounds have any antibacterial activity at tested concentration (500 µg/disc). In contrast, the antibacterial activity of amoxicillin against test strain increased in the presence of compounds 6a, 6d, 6i, 6k. Other synthetic compounds (at 500 µg) had no significant enhancing effect on the antibacterial activities of amoxicillin against *S. aureus*. The highest fold increases in area were observed for compound 6d against test strain (3 fold increase) and this compound was selected for further bioassay. The combination effect of compound 6d at different contents (100, 200, 300, 400, 500 µg/disc) was further investigated along with selected antibiotics from penicillin group (amoxicillin 25 µg, penicillin G 10 U, piperacillin 100 µg) (Table 3). This study indicates that the antibacterial activity of these antibiotics can be enhanced in the presence of compound 6d.

Table 3. The enhancing effect of the different contents of the compound 6d (100, 200, 300, 400 and 500 µg) on the antibacterial activity of selected antibiotics against a resistant clinical isolate of *Staphylococcus aureus*.

Antibiotics	Mean diameter of inhibition (mm)		
	In absence of antibiotic	In presence of antibiotic	Fold increase in area
Amoxicillin (25 µg)			
100 µg	-	8 ± 0.5	0.30
200 µg	-	9 ± 0.5	0.65
300 µg	-	11 ± 0.0	1.47
400 µg	-	12 ± 1	1.94
500 µg	-	14 ± 1	3.00
Penicillin G (10 unit)			
100 µg	-	9 ± 0.0	0.65
200 µg	-	11 ± 0.5	1.47
300 µg	-	12.5 ± 0.5	2.19
400 µg	-	14 ± 0.5	3.00
500 µg	-	14 ± 1	3.00
Piperacillin (100 µg)			
100 µg	-	9 ± 0.5	0.65
200 µg	-	10 ± 0.0	1.04
300 µg	-	11 ± 0.5	1.47
400 µg	-	11 ± 0.5	1.47
500 µg	-	13 ± 0.5	2.45

DISCUSSION

Recently some natural products and synthetic compounds have been tested for enhancing the antimicrobial activities of different antibiotics (6-11). In this investigation the enhancing effects of new N, N′- diaryl- 2,6- dimethyl-4- (2-benzylsulfonyl-1-methylimidazol-5-yl)- 1,4- dihydropyridine-3,5-dicarboxamide analogs on the antibacterial activity of selected antibiotics have been screened against resistant *S. aureus*. The compound 6d showed the most potent enhancing effect on the antimicrobial activity of tested antibiotics (amoxicillin, penicillin, piperacillin)**.** At this time the reason of these enchantments and the reason for theses differences are not known and merits further study. Efflux transporter mediates bacterial resistance to different antibiotics [14] and we

can conclude that this compound may inhibit this efflux pump system. This is the first report of combination effect of some 1,4-dihydropyridine analogs with different antibiotics.

The comparison of new synthetic symmetrical amides activities indicates that presence of withdrawing substitutions especially on para position of phenyl ring in 3,5-diarylcarboxamide structure increases the enhancing effect of synthetic compounds with amoxicillin however presence of substitution on meta or ortho position reduces or eliminates the enhancing effect.

ACKNOWLEDGMENT

This study was supported by grants from the Research Council of Tehran University of Medical Sciences, Tehran, Iran and INSF (Iran National Science Foundation).

REFERENCES

1. Bennett PM. Plasmid encoded antibiotic resistance: acquisition and transfer of antibiotic resistance genes in bacteria. Br J Pharmacol. 2008;153:347-357.
2. Wright GD. Bacterial resistance to antibiotics: enzymatic degradation and modification. Adv Drug Deliver Rev. 2005;57:1451-1470.
3. Gibbons S. Plants as a source of bacterial resistance modulators and anti-infective agents. Phytochem Rev. 2005;4:63-68.
4. Renau TE, Hecker SJ, Lee VJ. Antimicrobial potentiation approaches: targets and inhibitors. Ann Rep Med Chem. 1998;33:121-130.
5. Wright GD. Resisting resistance: new chemical strategies for battling superbugs. Chem Biol. 2000;7:127-132.
6. Lak P, Amini M, Safavi M, Shafiee A, Shahverdi AR. Enhancement of the antibacterial activity of ciprofloxacin against *Staphylococcus aureus* by 3-alkyl ester and 3-aryl ester of hexahydroquinoline derivatives. Arzneim-Forsch/Drug Res. 2008;58:464-468.
7. Shahverdi AR, Fakhimi A, Zarrini G, Dehghan G, Iranshahi M. Galbanic acid from *ferula szowitsian* enhanced the antibacterial activity of penicillin G and cephalexin against *Staphylococcus aureus*. Biol Pharm Bull. 2007;30:1805-1807.
8. Braga LC, Leite AA, Xavier KG, Takahashi JA, Bemquerer MP, Chartone-Souza E, et al. Synergic interaction between pomegranate extract and antibiotics against *Staphylococcus aureus*. Can J Microbiol. 2005;51:541-547.
9. Gibbons S. Phytochemicals for bacterial resistance. Strengths, weaknesses and opportunities. Planta Med. 2008;74:594-602.
10. Liu LX, Durham DG, Richards RME. Vancomycin resistance reversal in *Enterococci* by flavonoids. J Pharm Pharmacol. 2001;53:129-132.
11. Shin S, Pyun MS, Anti-candida effects of estragole in combination with ketoconazole or amphotericin B. Phytother Res. 2004;8:827-830.
12. Clemens RJ, Hyatt JA. Acetoacetylation with 2,2,6-trimethyl-4H-1,3-dioxin-4-one: a convenient alternative to diketen. J Org Chem. 1985;50:2431-2435.
13. Inayama S, Mori T, Tanami T, Amano T. 5-(Imidazol-5-ylmethylene)-2,2-dimethyl-1,3-dioxane-4,6-dione derivatives. Jpn. Kokai Tokkyo Koho JP 6212, 763, 6PP; Chem. Abstr. 106, 156477d. 1987.
14. Shafiee A, Dehpour AR, Hadizadeh F. Syntheses and calcium channel antagonist activity of nifedipine analogues with methylsulfonylimidazolyl substituent. Pharmaceutica Acta Helvetiae. 1998;73:75-79