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Antimicrobial Screening of 2-Methyl-3-Acyl-4-Aryl-2,6,6 and / or 2,7,7-Trimethyl-1,4,5,6,7,8-Hexahydroquinoline Derivatives

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Introduction

1,4-Dihydropyridine (DHP) derivatives attract more interest in recent years because of their wide variety of biological and pharmacological activities, such as vasodilator, antihypertensive, anti-ischemic, bronchodilator, anticonvulsant, antioxidant and antiradical[1-3]. They represent the most important group of calcium-channel modulating agents and nifedipine is the prototype of this group[4] (Figure 1).

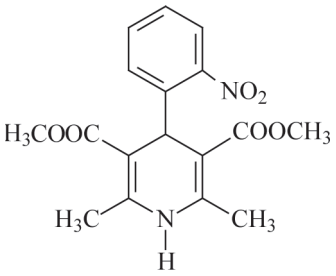

Figure 1
Nifedipine

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At the beginning DHPs were developed as cardiovascular agents, but later some of them were used for different therapeutic indications[5-7]. Recent studies have shown that substitution of carboxylate ester with carboxamide group reduces calcium channel blocking activity, but at the same time provides them significant antimicrobial properties[8,9].

Sirisha et all showed that the compounds having pyrrolyl and 4-methylphenyl groups in four position of the 1,4-DHP ring possess promising antimicrobial activity. These compounds exhibit a significant antitubercular activity in comparison with the first line drug pyrazinamide[9].

The antimicrobial evaluation of 1,4-dihydropyridine-3,5-dicarboxamide derivatives with lipophilic groups was also reported[10]. New 1,4-DHP derivatives containing diethyl carbamoyl and ester substituents on C-3 and C-5, and phenyl or substituted phenyl on C-4 position have also been reported as potential antimicrobial agents [11-13].

According to these studies, the antimicrobial activities of some 1,4-DHP derivatives having the structure of methyl(ethyl) 2,6,6- or 2,7,7-trimethyl-5-oxo-4-(difluorosubstituted phenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate and N,N-diethyl-2,6,6- or 2,7,7-trimethyl-5-oxo-4-(difluorosubstituted phenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxamide, were screened. These compounds were synthesized and their effects on calcium channels were investigated in our previous study [14].

Experimental

Chemistry

The compounds in this study were synthesized before according to the following procedures[14].

Synthesis of methyl(ethyl) 2,6,6- or 2,7,7-trimethyl-5-oxo-4-(difluorosubstituted phenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylates (3a-u)

A mixture of methyl(ethyl) aminocrotonate (1 mmol), 4,4(5,5)-dimethyl-1,3-cyclohexanedione (1 mmol) and the appropriate aromatic aldehyde (1 mmol) were refluxed in 20 mL methanol. The solvent was evaporated

and the residue was crystallized from ethanol.

Synthesis of N,N-diethyl-2,6,6- or 2,7,7-trimethyl-5-oxo-4-(difluorosubstituted phenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxamides (4a-j)

N,N-diethylaminoacetoacetamide (1 mmol), 4,4(5,5)-dimethyl-1,3-cyclohexanedione (1 mmol), appropriate aromatic aldehyde (1 mmol) and 1 mL ammonia were refluxed in 20 mL methanol. The reaction mixture was poured into ice-water and the precipitate was crystallized from appropriate solvents.

Microbiology

Antibacterial screening

The antimicrobial activity of the compounds **3a-u** and **4a-j** were screened against the bacteria; *Escherichia coli* (ATCC 25922), *Enterococcus faecalis* (ATCC 29212), *Pseudomonas aeruginosa* (ATCC 27853), *Staphylococcus aureus* (ATCC 29213) and the fungi; *Candida albicans* (ATCC 90028), *C. krusei* (ATCC 6258), *C. parapsilosis* (ATCC 90018) by using ciprofloxacin and fluconazole as reference compounds. Antimicrobial activities were determined as minimum inhibitory concentration (MIC) values. MICs were determined by broth microdilution method reported by the CLSI[15,16]. Antibacterial activity test was performed in Mueller-Hinton Broth (Difco, USA). RPMI-1640 medium with L-glutamine (ICN-Flow, USA) buffered with 3-(*N*-morpholino)propanesulphonic acid (MOPS) (ICN-Flow, USA) was used as the culture medium for antifungal activity test in 37°C. The inoculum densities were approximately 5x10 cfu/mL and 0.5-2.5x10 cfu/mL for bacteria and fungi, respectively. The MIC values were recorded as the lowest concentrations of the substances that had no visible turbidity. In microbiological studies, all compounds were dissoved in dimethyl sulphoxide.

Results and Discussion

In this study twenty alkyl 5-oxo-4-(difluorosubstituted phenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylates and ten N,N-diethyl-5-

oxo-4-(difluorosubstituted phenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxamide derivatives were synthesized according to the Hantzsch reaction (Figure 2). The sythesized compounds were published before with their calcium channel modulating effects. The synthesized compounds and their antibacterial activities are given in Table 1 and 2.

The screening data indicate that compund **3a** show the best antibacterial activity in ester analogs against *S. aureus* among the synthesized compounds. All the studied compounds were found to be more effective against *C. parapsilosis* than the other tested fungi strains. Compounds **4i** and **4j** have more potent activity in amide derivatives against *C. parapsilosis* than the other compounds.

Conclusion

Thirty 1,4-DHP derivatives were screened for antimicrobial activity against bacteria and fungi. The results were determined as minimum inhibitory concentration (MIC) values comparing to ciprofloxacin and fluconazole. The results indicated that substitution of carboxylate ester with carboxamide group provides antimicrobial properties especially against *C.parapsilosis*.

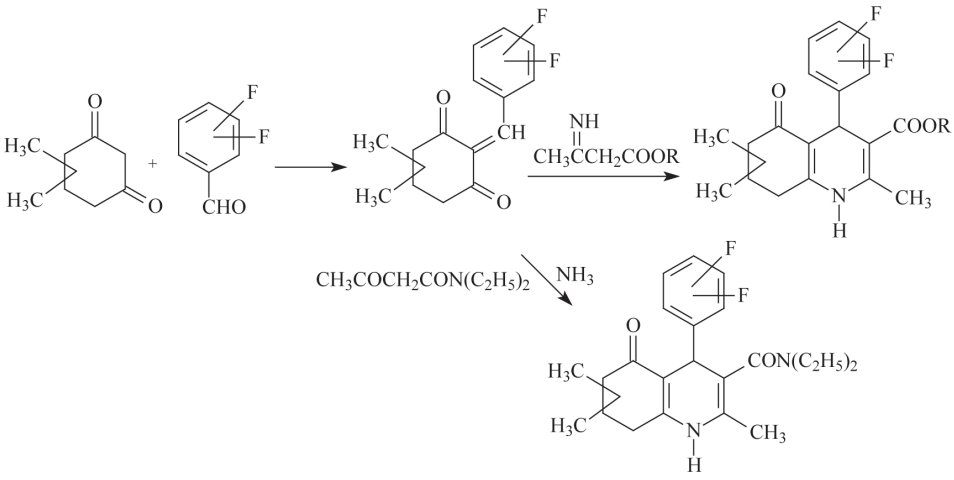
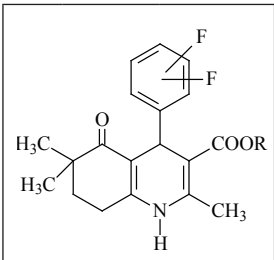
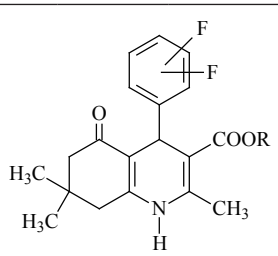


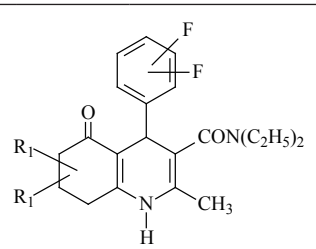
Figure 2
Synthesis of the compounds

TABLE I

Synthesized compounds







	Ar	R		Ar	R		Ar	R_1
3a	2,3-F_2	CH_3	**3**k	2,3-F_2	CH_3	4a	2,3-F_2	6,6-dimethyl
3b	2,4-F_2	CH_3	**3**l	2,4-F_2	CH_3	4b	2,4-F_2	6,6-dimethyl
3c	2,5-F_2	CH_3	**3**m	2,5-F_2	CH_3	4c	2,5-F_2	6,6-dimethyl
3d	2,6-F_2	CH_3	**3**n	2,6-F_2	CH_3	4d	2,6-F_2	6,6-dimethyl
3e	3,4-F_2	CH_3	**3**o	3,4-F_2	CH_3	4e	3,4-F_2	6,6-dimethyl
3f	2,3-F_2	C_2H_5	**3**p	2,3-F_2	C_2H_5	4f	2,3-F_2	7,7-dimethyl
3g	2,4 F_2	C_2H_5	**3**r	2,4 F_2	C_2H_5	4g	2,4 F_2	7,7-dimethyl
3h	2,5-F_2	C_2H_5	**3**s	2,5-F_2	C_2H_5	4h	2,5-F_2	7,7-dimethyl
3i	2,6-F_2	C_2H_5	**3**t	2,6-F_2	C_2H_5	4i	2,6-F_2	7,7-dimethyl
3j	3,4-F_2	C_2H_5	**3**u	3,4-F_2	C_2H_5	4j	3,4-F_2	7,7-dimethyl

TABLE II

Antibacterial activity of the synthesized compounds (MIC in μg/mL).

Compounds	A	B	C	D	E	F	G
3a	>512	512	512	16	>512	>512	128
3b	>512	512	>512	512	>512	>512	>512
3c	>512	512	>512	512	>512	>512	>512
3d	>512	512	>512	512	>512	>512	>512
3e	>512	512	>512	512	>512	>512	256

3f	>512	512	>512	512	>512	>512	>512
3g	>512	512	512	512	>512	>512	256
3h	>512	512	>512	512	>512	>512	>512
3i	>512	>512	>512	512	>512	>512	128
3j	>512	>512	>512	512	512	>512	>512
3k	>512	>512	>512	512	>512	>512	256
3l	>512	>512	>512	512	>512	>512	512
3m	>512	>512	>512	512	>512	>512	>512
3n	>512	>512	>512	512	>512	>512	256
3o	>512	>512	>512	512	>512	>512	>512
3p	>512	>512	>512	512	>512	>512	>512
3r	>512	>512	>512	256	512	>512	256
3s	>512	>512	>512	>512	>512	>512	>512
3t	>512	>512	>512	>512	>512	>512	>512
3u	>512	>512	>512	512	>512	>512	>512
4a	>512	>512	>512	512	>512	>512	>512
4b	>512	>512	>512	512	>512	>512	>512
4c	>512	>512	>512	512	>512	>512	512
4d	>512	>512	>512	512	>512	>512	512
4e	>512	>512	>512	512	512	>512	128
4f	>512	>512	>512	512	512	>512	64
4g	>512	>512	>512	512	256	>512	64
4h	>512	>512	>512	512	>512	>512	128
4i	>512	>512	>512	512	>512	>512	32
4j	>512	>512	>512	512	>512	512	32
C*	0,015	0,25	0,25	0,125	-	-	-
F**	-	-	-	-	0,5	32	1

* **A:** *E.coli ATCC 25923,* ***B:*** *E.faecalis ATCC 29212,* **C:** *P.aeuruginosa ATCC 27853,* **D.** *S.aureus ATCC 25923,* **E:** *C.albicans ATCC 90028,* **F:** *C.crusei ATCC 6258,* **G:** *C.parapsilosis ATCC90018,* **C*:** *Ciprofloxazin,* F**: *Fluconazole*

Summary

In this study, thirty compounds having methyl(ethyl) 2,6,6- or 2,7,7-trimethyl-5-oxo-4-(difluorosubstituted phenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate and N,N-diethyl-2,6,6- or 2,7,7-trimethyl-5-oxo-4-(difluorosubstituted phenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxamide structure, have been screened for their antimicrobial activities. Antimicrobial activities were determined as minimum inhibitory concentration (MIC) values by broth microdilution method against bacteria and fungi.

Key words: 1,4-dihydropyridine, hexahydroquinoline, antimicrobial activity

Özet

2-Metil-3-Acil-4-Aril-2,6,6 ve/veya 2,7,7-Trimetil-1,4,5,6,7,8-Hekzahidrokinolin Türevlerinin Antimikrobiyal Etkilerinin Araştırılması

Bu çalışmada metil(etil) 2,6,6- veya 2,7,7-trimetil-5-okso-4-(difluorosübstitüe fenil)-1,4,5,6,7,8-hekzahidrokinolin-3-karboksilat ve N,N-dietil-2,6,6- veya 2,7,7-trimetil-5-okso-4-(difluorosübstitüe fenil)-1,4,5,6,7,8-hekzahidrokinolin-3-karboksamit yapısına sahip otuz bileşiğin antimikrobiyal aktivitesi taranmıştır. Bakteri ve funguslara karşı antimikrobiyal aktiviteleri broth mikrodilüsyon yöntemi kullanılarak minimum inhibitör konsantrasyonu (MIC) olarak saptanmıştır.

Anahtar kelimeler: 1,4-dihidropiridin, hekzahidrokinolin, antimikrobiyal aktivite

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