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Research Article

Antimicrobial Activity of Some Derivatives of 1,4-Dihydropyridines

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Hantzsch reported the synthesis of functionalized 1,4- dihydropyridines via three-component condensation of an aromatic aldehyde, ketoester, and ammonium hydroxide. This multicomponent reaction is of much importance due to excellent pharmacological properties of dihydropyridines. In this account, we synthesized some halo- and nitrophenyl dihydropyridines and evaluated their antimicrobial activity. The minimum inhibitory concentration (MIC) was determined by microdilution technique in Mueller Hinton broth. The MICs were recorded after 24 hours of incubation at 37°C. These results showed that these compounds exhibited significant to moderate activities against both Gram-(+) and Gram-(−) organisms.

1. Introduction

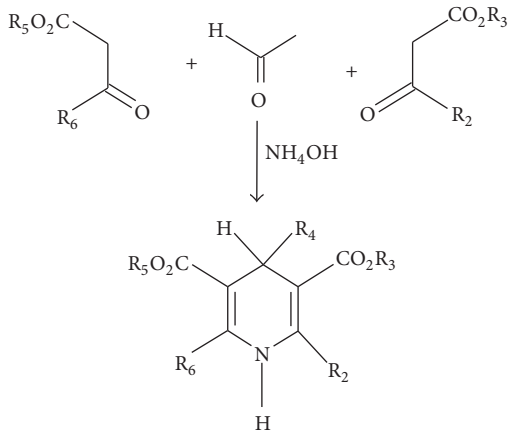
Antimicrobial drugs are the greatest contributions in the present century to therapeutics. It is essential to investigate newer drugs with lesser resistances. Systematic studies among various pharmaceutical compounds have revealed that any drug may possess diverse functions. Drugs belonging to different pharmacological classes such as vasodilators, antihypertensive [1–4], antiinflammatory [5], anaesthetics [6], anti-ischemic [7], and calcium channel modulators of the nifedipine type [8] may have useful activity in completely different spheres of medicine. Amlodipine and lacidipine, dihydropyridine Ca^{++} channels blockers, are used orally for the treatment of hypertension. Previous papers suggested that amlodipine can also inhibit the proliferation of different cancer cells [9, 10]. It has also been reported that lacidipine [11] and some 3-chlorophenyl [12], nitrophenyl 1,4-dihydropyridine [13] derivatives are cytotoxic towards *trypanosoma cruzi* through respiratory chain inhibition. Amlodipine and lacidipine both contain a phenyl-1,4-dihydropyridine ring which is absent in verapamil and diltiazem. In view of these observations, it was decided to synthesize a new series of 1,4-dihydropyridine derivatives (V-1 to V-9) and screen them for their level of antimicrobial activity.

2. Experimental

2.1. General Procedure for Synthesis of Substituted 1,4-Dihydropyridines (V-1 to V-9) . The mixture of aryl aldehyde (1 mole), β-ketoester (2 mole), and ammonium hydroxide (8 mL) was refluxed together in ethanol for about 5–18 hours (Scheme 1). Then the reaction mixture was cooled and recrystallized with ethyl alcohol.

Synthesis of 3,5-Diethyl-2,6-dimethy-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (V-1). The reaction mixture consisting of m-nitrobenzaldehyde (0.1 mol), ethyl acetoacetate (0.2 mol), and ammonium hydroxide (8 mL) in ethanol (60 mL) was heated at reflux for 5 hours. The obtained solid was filtered off, washed with warm water and recrystallized using ethyl alcohol. The above procedure was followed for the synthesis of compounds V-2 and V-5.

Synthesis of 3-Ethyl-5-(1,1-dimethyl ethyl)-2,6-dimethyl-4-(3-chlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (V-6). The reaction mixture consisting of chlorobenzaldehyde (0.025 mol), ethyl acetoacetate (0.025 mol), t-butyl acetoacetate (0.025 mol), and ammonium hydroxide (2 mL) in ethanol (15 mL) was heated at reflux for 11 hours.



Scheme 1: Synthesis of 1,4-dihydropyridines.

The obtained solid was filtered off, washed with warm water, and recrystallized using ethyl alcohol. The above procedure was followed for the synthesis of compounds V-8 and V-9.

Synthesis of 3,5-Di(1,1-dimethyl ethyl)-2,6-dimethyl-4-(3-chlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (V-3). The reaction mixture consisting of m-chlorobenzaldehyde (0.02 mol), t-butyl acetoacetate (0.04 mol), and ammonium hydroxide (1.6 mL) in ethanol (12 mL) was heated at reflux for 8 hours. The obtained solid was filtered off, washed with warm water, and recrystallized using ethyl alcohol. The above procedure was followed for the synthesis of compound V-7 (see Table 1).

Synthesis of 3,5-Di(1,1-dimethyl ethyl)-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate V-4). The reaction mixture consisting of m-nitrobenzaldehyde (0. 016 mol), t-butyl acetoacetate (0.032 mol), and ammonium hydroxide (1.33 mL) in ethanol (10 mL) was heated at reflux for 10 hours. The obtained solid was filtered off, washed with warm water, and recrystallized using ethyl alcohol.

2.2. Spectral Data of Compound (V-1 to V-9). 3,5-Diethyl-2,6-dimethy-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate, V-1. IR (KBr cm^{-1}): 3344 (–NH str), 2988(C–H), 1705 (C=O, ester), 1526(–NO_2); ^{1}HNMR (400 MHz, $CDCl_3$): 8.12(s, 1H, NH), 7.98–8.01 (m, 4H Ph-ring), 5.09 (s, 1H, CH), 4.02–4.15 (m, 4H, $2CH_2$, ester group), 2.36 (s, 6H, $2CH_3$ ester group), 1.20–1.23 (t, 6H, $2CH_3$, methyl group); *m/z*: 252, (M = 100%).

3,5-Diethyl-2,6-dimethy-4-(3-chlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylate, V-2. IR (KBr cm^{-1}): 3322(–NH str), 2980(C–H), 1703 (C=O, ester), 620(–Cl); ^{1}HNMR (400 MHz, $CDCl_3$): 7.26 (s, 1H,NH), 7.08–7.18 (m, 4H, Ph-ring), 4.96 (s, 1H, CH), 4.04–4.14(m, 4H, $2CH_2$ ester group), 2.33 (s, 6H, $2CH_3$, methyl group), 1.20–1.24 (t, 6H, $2CH_3$, ester group); *m/z*: 252, (M = 100%).

3,5-Di(1,1-dimethylethyl)-2,6-dimethyl-4-(3-chlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylate, V-3. IR (KBr cm^{-1}): 3334(–NH str), 2973(C–H), 1698 (C=O, ester), 612(–Cl); ^{1}HNMR (400 MHz, $CDCl_3$): 7.26 (s, 1H, NH), 7.07–7.17 (m, 4H, Ph-ring), 4.88 (s, 1H, CH), 2.29 (s, 6H, $2CH_3$, methyl group), 1.40 (s, 18H, $2(CH_3)_3$); *m/z*: 152, (M = 100%).

3,5-Di(1,1-dimethylethyl)-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate, V-4. IR (KBr cm^{-1}): 3337 (–NH str), 2972 (C–H), 1699 (C=O, ester), 1528 (–NO_2); ^{1}HNMR (400 MHz, $CDCl_3$): 8.16 (s, 1H, NH), 7.99–8.01 (m, 4H, Ph-ring), 5.01(s, 1H, CH), 2.31 (s, 6H, $2CH_3$, methyl group), 1.39 (s, 18H, $2(CH_3)_3$, ester group); *m/z*: 108, (M = 100%).

3,5-Diethyl-2,6-dimethy-4-(2-chlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylate, V-5. IR (KBr cm^{-1}): 3332(–NH str), 2978(C–H), 1659 (C=O, ester), 623(–Cl); ^{1}HNMR (400 MHz, $CDCl_3$): 7.26 (s, 1H, NH), 7.09–7.23 (m, 4H, Ph-ring), 5.39 (s, 1H, CH), 4.04–4.10 (m, 4H, $2CH_2$ ester group), 2.27(s, 6H, $2CH_3$, ester group); *m/z*: 252, (M = 100%).

3-Ethyl-5-(1,1-dimethyl ethyl)-2,6-dimethyl-4-(3-chloro phenyl)-1,4-dihydropyridine-3,5-dicarboxylate, V-6. IR (KBr cm^{-1}): 3312 (–NH str), 2981(C–H), 1697 (C=O, ester), 682 (–Cl); ^{1}HNMR (400 MHz, $CDCl_3$): 7.26 (s, 1H, NH), 7.15–7.18 (m, 4H, Ph-ring), 4.96 (s, 1H, CH), 4.04–4.12 (m, 2H, CH_2, ester group), 2.33 (s, 6H, $2CH_3$, methyl group), 1.39 (s, 9H, $(CH_3)_3$, ester group) 1.22–1.24 (t,3H, CH_3, ester group); *m/z*: 224, (M = 100%).

3,5-Di(1,1-dimethyl ethyl)-2,6-dimethyl-4-(2-chlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylate, V-7. IR (KBr cm^{-1}): 3341 (–NH str), 2976 (C–H), 1699 (C=O, ester), 645 (–Cl); ^{1}HNMR (400 MHz, $CDCl_3$): 7.38 (s, 1H, NH), 7.22–7.26 (m, 4H, Ph-ring), 5.23 (s, 1H, CH), 2.22 (s, 6H, $2CH_3$, methyl group), 1.37 (s, 18H, $2(CH_3)_3$, ester group).

3-Ethyl-5-(1,1-dimethyl ethyl)-2,6-dimethyl-4-(2-chloro phenyl)-1,4-dihydropyridine-3,5-dicarboxylate, V-8. IR (KBr cm^{-1}): 3327(–NH str), 2981(C–H), 1678 (C=O, ester), 639 (–Cl); ^{1}HNMR (400 MHz, $CDCl_3$): 7.39 (s, 1H, NH), 7.22–7.26 (m, 4H„ Ph-ring), 4.76 (s, 1H, CH), 4.02–4.10 (m, 2H, CH_2, ester group), 2.27(s, 6H, $2CH_3$, methyl group), 1.38 (s, 9H, $(CH_3)_3$, ester group), 1.19–1.22 (t, 3H, CH_3, ester group); *m/z*: 252, (M = 100%).

3,5-Di(1,1-dimethyl ethyl)-2,6-dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate, V-9. IR (KBr cm^{-1}): 3342 (–NH str), 2975 (C–H), 1693 (C=O, ester), 1531 (–NO_2); ^{1}HNMR (400 MHz, $CDCl_3$): 7.52 (s, 1H, NH), 7.22–7.47 (m, 4H, Ph-ring), 5.44 (s, 1H, CH), 2.27 (s, 6H, $2CH_3$, methyl group), 1.36 (s, 18H, $2(CH_3)_3$, ester group).

Table 1: Analytical data of compounds V-1 to V-9.

Compound	Mol weight	Molecular formula	M.P (°C)	Tim (hr)	Yield (%)	Found % (Cald)			
						C	H	N	Cl
V-1	374	$C_{19}H_{22}N_2O_6$	165	5	48.12	60.93	5.91	7.46	—
						(60.96)	(5.88)	(7.48)	—
V-2	363.5	$C_{19}H_{22}NO_4Cl$	120	5	47.96	62.69	6.06	3.83	9.77
						(62.72)	(6.05)	(3.85)	(9.76)
V-3	419.5	$C_{23}H_{30}NO_4Cl$	176	8	18.10	65.74	7.17	3.32	8.48
						(65.79)	(7.15)	(3.33)	(8.46)
V-4	430	$C_{23}H_{30}N_2O_6$	188	10	10.18	64.15	6.98	6.50	—
						(64.18)	(6.97)	(6.51)	—
V-5	363.5	$C_{19}H_{22}NO_4Cl$	132	16	41.69	62.69	6.04	3.82	9.74
						(62.72)	(6.02)	(3.85)	(9.76)
V-6	391.5	$C_{21}H_{26}NO_4Cl$	108	11	20.22	64.39	6.62	3.72	9.05
						(64.36)	(6.64)	(3.75)	(9.06)
V-7	419.5	$C_{23}H_{30}NO_4Cl$	168	13	11.55	65.70	7.14	3.35	8.43
						(65.79)	(7.15)	(3.33)	(8.46)
V-8	391.5	$C_{21}H_{26}NO_4Cl$	112	13	12.30	64.39	6.62	3.74	9.03
						(64.36)	(6.64)	(3.75)	(9.06)
V-9	430	$C_{23}H_{30}N_2O_6$	109	15	11.81	64.16	6.99	6.50	—
						(64.18)	(6.97)	(6.51)	—

Table 2: Antibacterial activity of compounds V-1 to V-9 against Gram-(+) and Gram-(−) organisms.

S. no.	Compounds name	gm (−)			gm (+)
		E. coli	*K. aerogenes*	*NLF*	*S. aureus*
(1)	V-1	+	R	+	R
(2)	V-2	++	R	+++	R
(3)	V-3	R	+++	+	+++
(4)	V-4	++	++	R	R
(5)	V-5	R	R	R	+
(6)	V-6	R	R	R	+
(7)	V-7	+	R	R	++
(8)	V-8	R	R	R	R
(9)	V-9	R	R	R	R

Zone of inhibition was measured in mm. +++: strong activity, ++: good activity, +: moderate activity, R: resistant.

2.3. Antimicrobial Studies. *In vitro* antibacterial studies of the newly synthesized compounds V-1 to V-9 were screened for their *in vitro* antibacterial activity against *Escherichia coli, Klebsiella aerogenes, nonlactose fermenters,* and *Staphylococcus aureus* according to the disc diffusion method. The minimum inhibitory concentration (MIC) was determined by the serial dilution technique using acetone as solvent. The zone of inhibition is reported in the Table 2. Nutrient agar was employed as culture medium. The MIC calculated was 400 μ g/mL for compounds.

3. Results and Discussion

The synthesis of a series of 1,4-dihydropyridine derivatives (V-1) to (V-9) has been achieved by condensation of acetoacetic ester, aryl aldehyde, and ammonium hydroxide in ethanol. All the synthesized 1,4 dihydropyridines have given appreciable yield with satisfactory element analysis. The compounds V-1 to V-9 were evaluated for their *in vitro* antibacterial activity against Gram-(−) and Gram-(+) organisms. It is inferred from Table 2, out of nine synthesized compounds V-1 to V-9, compound V-2 was effective against Gram-(−) organism, that is, *E. coli* and *NLF.* Compound V-3 was effective against Gram-(−) and Gram-(+) organisms, that is, against *Klebsiella aerogenes* and *Staphylococcus aureus*, while compounds V-1 and V-4 were only effective against Gram-(−) *E. coli* and *NLF*.

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