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Rapid synthesis and biological evaluation of 1,4-dihydropyridine derivatives containing a benzothiazolyl moiety

Research Article

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Abstract: A series of N-(6-methylbenzothiazolyl)-2,3,5,6-tetrasubstituted-4-(aryl)-1,4-dihydropyridines were synthesized by reaction of 2-amino-6-methylbenzothiazole, aromatic aldehyde and active methylene compound in methanol by conventional, as well as, microwave irradiation (solvent free and solid support) methods. The microwave irradiation technique gives better yield and shorter reaction time. Among solid supported microwave irradiation better yields are obtained in acidic alumina as compared to silica, neutral alumina, and basic alumina. All compounds were tested for antibacterial and antifungal activities and results have been compared with standard drugs. Entomological activities were also tested. The results showed that a change in the substitution pattern in 1,4-dihydropyridine derivatives may cause a marked effect on their antimicrobial activity.

Keywords: *Benzothiazole • 1,4-Dihydropyridine • Antimicrobial activity • Microwave irradiation • Entomological activity*

1. Introduction

Dihydropyridine chemistry is of interest from the point of view of pure research on heterocyclic compounds and from a biological point of view [1]. Hantzsch 1,4-dihydropyridines (1,4-DHPs), a class of model compounds of the NADH coenzyme, have been extensively studied in view of the biological pertinence of these compounds to the NADH redox process [2]. Since the early 1980's the presence of a DHP ring in the structure of 1,4-DHP derivatives has been regarded as a prerequisite for calcium (Ca^{+2}) channel modulating properties [3]. So 1,4-DHPs classes of compounds are excellent starting synthons for the development of antitubercular agents [4-6]. As a result, newly synthesized generations of 1,4-DHPs possess different pharmacological activities such as anticancer [7], antidiabetic [8], antianginal [9], bronchodilating [10], neurotropic [11], antiallergic [12], anti-inflammatory [13], acaricidal, insecticidal, bactericidal, herbicidal [14] and other pharmacological activities [15]. These are used extensively in the treatment of angina pectoris, hypertension and arrhythmia [16] and some cardiovascular disorder. Several new derivatives of 1,4-DHP have been produced and pharmacologically evaluated in order to find drugs with better pharmacological properties [17]. So the pharmacology of 1,4-DHPs derivatives is at the eve of a novel boom.

Similarly, the benzothiazole ring is present in various marine and terrestrial natural compounds, which have useful biological activities [18-21]. As a consequence, benzothiazloes are bicyclic ring systems with multiple applications. Benzothiazoles comprise a class of therapeutic compounds that exert a wide and broad spectrum of biological activities such as antimicrobial [22,23], anticancer [24,25], antifungal [26], antihelmintic [27], antileishmanial [28] and anticonvulsant [29] activities. 2-(4-aminophenyl) benzothiazole [30,31]

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comprises a novel mechanistic class of antitumor agents. Conventional method of synthesis apparently suffer from disadvantages such as prolonged refluxing, use of volatile organic solvents, waste effluent and low to moderate yields, cumbersome workup procedure, create pollution to the environment and lack selectivity in the presence of other functional groups.

In light of growing eco-consciousness of energy, and economic and environmental issues over the recent decade have compelled the synthetic chemist to add a new twist to an old theme [32]. So microwave–induced organic reaction enhancement (MORE) chemistry can be termed 'eco-chemistry' because it is easy, effective, economic, eco-friendly and is believed to be a step towards green chemistry. We report a novel environmentally benign approach using a facile, microwave synthesis of title compounds carried out by a solvent free method, and various solid supports like silica gel, alumina basic, alumina neutral, and alumina acidic. In view of the biological importance associated with 1,4-DHPs and benzothiazole and the benefits offered by microwave heating, it was thought worthwhile to synthetise of N-(6-methylbenzothiazolyl)-2,3,5,6-tetrasubstituted-4-(Aryl)-1,4-dihydropyridines followed by antimicrobial susceptibility testing (AST) against *Lactobacillus spp*., *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Micrococcus leutius*, *Kocuria rosea*, *Aspergillus niger*, *Aspergillus candidus* using standard methods and comparison with standard drugs. All the synthesized derivatives were also screened for their entomological activities.

2. Experimental procedures

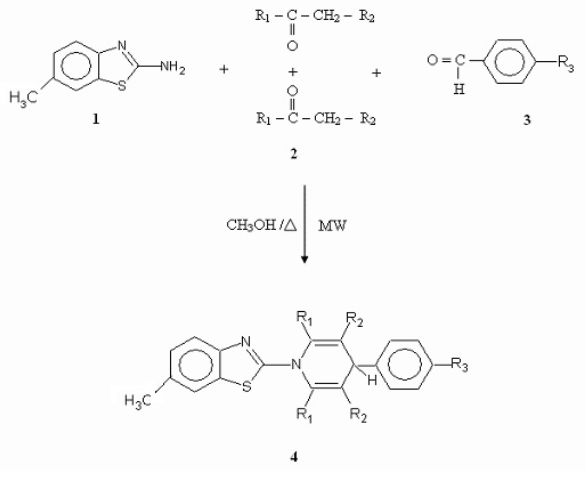
2.1. General Procedures

Reagent grade chemicals were used without further purification. The substrates and solvents were used as received. All the melting points are taken in open capillaries as uncorrected. The purity of the synthesized compounds was checked by Thin Layer Chromatographic studies. IR spectra were scanned on FT IR Perkin Elmer (Spectrum RX1) spectrophotometer (υ in cm^{-1}) using a KBr disc. ^1H NMR sprectra wereere recorded in $CDCl_3$ with tetramethylsilane (TMS) as the internal standard at 300 MHz on a Bruker DRTX-300 spectrophotometer. The chemical shifts are reported as parts per million (ppm). Fast atom bombardment mass spectra (FABMS) were recorded at room temperature on a Jeol SX-102/DA-6000 mass spectrophotometer/data system using Argon/Xenon (6 kV, 10mA) as the FAB gas. The accelerating potential was 10kV. Microwave synthesis was carried out in a "Q-pro-M Modified Microwave system". The elemental analysis of the compounds was performed on a Carlo Erba-1108 elemental analyzer.

2.2. General procedure for the synthesis of N-(6-methylbenzothiazolyl)-2,3,5,6-tetrasubstituted-4-(aryl)-1,4-dihydropyridines

2.2.1. Conventional Method

A reaction mixture of 2-amino-6-methylbenzothiazole (0.1 mol), aromatic aldehyde (0.1 mol) and active methylene compound (0.2 mol) was heated (without solvent) on a steam bath for 2-3 hours. After elimination of water, methanol (25 mL) was added directly to the reaction mixture and refluxed for 10-15 hours. Then, the reaction mixture was poured into the ice water, the solid mass separated, and was extracted with diethyl ether (50 mL) and dried over magnesium sulphate, and finally recrystallised from methanol (Scheme 1, Table 1)



Scheme 1. Synthesis of N-(6-methylbenzothiazolyl)-2,3,5,6-tetrasubstituted–4-(aryl)-1,4-dihydropyridines (R_1 = CH_3, OC_2H_5; R_2 = C_2H_5OCO, CH_3CO; R_3 = H, $N(CH_3)_2$, OCH_3, OH, m-NO_2)

2.2.2. Microwave method

A reaction mixture of 2-amino-6-methylbenzothiazole (0.01 mol), aromatic aldehyde (0.01 mol) and active methylene compound (0.02 mol) were combined in a round bottom flask. The round bottom flask was placed in a microwave oven, irradiated under a low power 160 Watt, and monitored by TLC using Benzene: DMF (7:3). To ensure the reproducibility, every reaction is carried out five times in the microwave. The reaction mixture was cooled at room temperature and extracted with diethyl ether (10 mL), dried over magnesium sulphate, yielded pure product, and was recrystallised from methanol (Table 1).

2.2.2.1. Solid supported microwave synthesis

A mixture of 2-amino-6-methylbenzothiazole (0.01 mol), aromatic aldehyde (0.01 mol) and active methylene compound (0.02 mol) were placed in a round bottom flask with solid support alumina (acidic /basic /neutral (1.3 g)) and silica gel. Everything was mixed thoroughly in a mortar then the reaction mixture was transferred to a round bottom flask and irradiated under a low power 160 Watt in microwave oven at 30 seconds intervals of specified times. Upon completion of reaction as monitored by TLC using Benzene: DMF (7:3). To ensure the reproducibility every reaction is carried out five times in the microwave. The reaction mixture was cooled at room temperature and extracted with diethyl ether (10 mL), dried over magnesium sulphate, which gave pure product. The products were then recrystallised from methanol (Table 2).

2.2.2.2. Spectral and microanalysis data of (4a-4o)

N-(6-methylbenzothiazolyl)-3,5-dicarbethoxy-2,6-dimethyl-4-(p-dimethylaminophenyl)-1,4-dihydropyridine (4a): ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.31 (s, 3H, Benzothiazole, CH_3), 2.24 (s, 6H, dihydropyridine (DHP), CH_3), 4.90 (s, 1H, DHP), 6.46-8.11 (m, 7H, Ar-H), 1.29 (t, J=7.2 Hz, 6H, DHP, CH_2CH_3), 4.17 (q, J=7.2 Hz, 4H, DHP, CH_2), 2.82 (s, 6H, $N(CH_3)_2$), ^{13}C-NMR (300MHz, $CDCl_3$) δ 126.3, 135.5, 125.8, 155.8, 133.3, 124.6, 171.7, 22.9, 99.0, 134.9, 127.5, 109.3, 35.9, 18.5, 25.4, 17.3, 59.8, 13.6, 161.0, 61.8, 59.2, 129.3, 115.4, 146.4, 113.1, 129.6, 119.5, 16.5 IR (cm^{-1}): v_{max} 1063, 1108, 1150, 1586, 1532, 1452, 2996, 1664, 1628,1698; Accurate MS m/z: Calc: 519.66, Found: 519.57, Elemental Anal. Calcd. (CHNS) for $C_{29}H_{33}N_3O_4S$: C, 67.02, H, 6.41, N, 8.09, S, 6.16, Found: C, 66.98, H, 6.36, N, 8.05, S, 6.12.

N-(6-methylbenzothiazolyl)-3,5-dicarbethoxy-2,6-diethoxy-4-(p-dimethylaminophenyl)-1,4-dihydropyridine (4b): ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.51 (s, 3H, Benzothiazole, CH_3), 4.92 (s, 1H, DHP), 6.45-8.12 (m, 7H, Ar-H), 1.27 (t, J=7.2 Hz, 6H, DHPCOOCH$_2$CH$_3$), 4.15 (q, J=7.1 Hz, 4H, DHPCOOCH$_2$), 2.80 (s, 6H, $N(CH_3)_2$), 1.21 (t, J=7.2 Hz, 6H, DHP OCH$_2$CH$_3$), 4.01 (q, J=7.2 Hz, 4H, DHPOCH$_2$) ^{13}C-NMR (300MHz, $CDCl_3$) δ 126.5, 134.5, 122.8,

Table 1. Preparation of N-(6-methylbenzothiazolyl)-2,3,5,6-tetrasubstituted-4-(aryl)-1,4- dihydropyridines.

Compounds	R_1	R_2	R_3	M.P. °C	Conventional heating		Microwave (Neat reaction)	
					Time (h)	Yield (%)	Time (Sec)	Yield (%)
4a	Me	O=COEt	p-N(Me)$_2$	176-177	20.0	50	180	60
4b	OEt	O=COEt	p-N(Me)$_2$	165-167	20.0	52	190	69
4c	Me	O=COEt	p-OMe	178-179	20.0	56	210	70
4d	Me	O=COEt	p-OH	206-208	20.0	48	220	70
4e	Oet	O=COEt	p-OH	196-198	20.0	46	190	65
4f	Oet	O=COEt	H	209-210	20.0	44	190	68
4g	Me	COMe	p-OMe	193-194	20.0	45	200	68
4h	Me	O=COEt	H	207-208	20.0	50	200	68
4i	Me	COMe	p-OH	230-231	20.0	56	210	70
4j	Me	COMe	H	224-225	20.0	58	200	72
4k	Me	COMe	p-N(Me)$_2$	172-173	20.0	60	190	72
4l	Oet	O=COEt	p-OMe	182-183	20.0	55	210	69
4m	Me	O=COEt	m-NO$_2$	174-175	20.0	52	210	68
4n	Oet	O=COEt	m-NO$_2$	201-202	20.0	50	180	64
4o	Me	COMe	m-NO$_2$	220-221	20.0	52	200	68

Table 2. Comparitative study of synthesized compounds (**4a**- **4o**) under solid supported microwave irradiation.

Compounds	Solid supported microwave irradiation							
	Silica Gel		Alumina basic		Alumina neutral		Alumina acidic	
	Time (Sec)	Yield (%)	Time (Sec)	Yield (%)	Time (Sec)	Yield (%)	Time (Sec)	Yield (%)
4a	210	55	260	52	140	70	90	90
4b	220	58	270	55	150	80	100	95
4c	230	60	290	50	120	80	80	85
4d	260	55	300	55	120	82	80	87
4e	220	55	280	45	140	75	80	90
4f	220	60	280	46	150	80	100	92
4g	230	60	290	45	140	80	90	95
4h	230	60	290	50	140	80	90	93
4i	240	65	300	58	140	82	90	95
4j	230	62	280	60	120	83	80	94
4k	220	65	270	60	140	83	90	94
4l	240	62	260	55	150	85	90	98
4m	220	61	290	54	90	80	60	90
4n	190	60	220	54	90	80	60	92
4o	200	64	230	50	100	76	70	88

153.8, 131.3, 122.6, 169.7, 21.9, 99.0, 132.9, 126.5, 108.3, 27.9, 17.9, 24.4, 10.3, 16.6, 58.8, 12.6, 16.0, 161.8, 128.3, 116.4, 145.4, 111.1, 127.6, 117.5, 14.1, 15.5, 57.4, 14.2 IR (cm^{-1}): v_{max} 1062, 1105, 1151, 1583, 1530, 1450, 2995, 1652, 1622, 1704; Accurate MS m/z: Calc: 579.71, Found: 579.23., Elemental Anal. Calcd. (CHNS) for $C_{31}H_{37}N_3O_6S$: C, 64.22, H, 6.44, N, 7.25, S, 5.53, Found: C, 64.18, H, 6.37, N, 7.21, S, 5.47.

N-(6-methylbenzothiazolyl)-3,5-dicarbethoxy-2,6-dimethyl-4-(p-methoxyphenyl)-1,4-dihydropyridine (4c): ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.31 (s, 3H, Benzothiazole, CH_3), 2.27 (s, 6H,DHP, CH_3), 4.90 (s, 1H, DHP), 6.45-8.12 (m, 7H, Ar-H), 1.27 (t, J=7.2 Hz, 6H, DHP, CH_3), 4.19 (q, J=7.2 Hz, 4H, DHP, CH_2), 3.72 (s, 3H, Ar-OCH_3), ^{13}C-NMR (300MHz, $CDCl_3$) δ 126.3, 134.3, 151.8, 130.3, 122.6, 167.7, 20.9, 99.0, 134.9, 127.5, 109.3, 32.9, 18.5, 25.4, 11.3, 17.3, 59.8, 13.6, 161.0, 61.8, 129.3, 115.4, 146.4, 113.1, 129.6, 119.5, 15.1, 46.6 IR (cm^{-1}): v_{max} 1054, 1225, 1535, 1450, 1590, 1655, 1680, 1628; Accurate MS m/z: Calc: 522.62, Found: 522.16, Elemental Anal. Calcd. (CHNS) for $C_{28}H_{30}N_2O_5S$: C, 66.38, H, 5.97, N, 5.53, S, 6.33, Found: C, 66.28, H, 5.90, N, 5.46, S, 6.30.

N-(6-methylbenzothiazolyl)-3,5-dicarbethoxy-2,6-dimethyl-4-(p-hydroxyphenyl)-1,4-dihydropyridine (4d): ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.33 (s, 3H, Benzothiazole, CH_3), 2.14 (s, 6H,DHP, CH_3), 4.92 (s, 1H, DHP), 6.48-8.14 (m, 7H, Ar-H), 1.30 (t, J=7.0 Hz, 6H, DHP, CH_3), 4.21 (q, J=6.9 Hz, 4H, DHP, CH_2), 5.02 (s, 1H, Ar-OH), ^{13}C-NMR (300MHz, $CDCl_3$) δ 126.1, 134.2, 125.7, 155.6, 132.3, 124.6, 171.7, 99.0, 134.9, 127.5, 109.3, 35.9, 18.5, 25.4, 11.3, 17.3, 59.8, 13.6, 161.0, 129.3, 115.4, 146.4, 113.1, 129.6, 128.4, 125.5, 20.7 IR (cm^{-1}): v_{max} 1056, 1227, 1136, 1694, 1536, 1451, 2973, 3650, 1662, 1627, 1694; Accurate MS m/z: Calc: 508.59, Found: 508.16, Elemental Anal. Calcd. (CHNS) for $C_{27}H_{28}N_2O_5S$: C, 65.83, H, 5.73, N, 5.69, S, 6.51, Found: C, 65.79, H, 5.67, N, 5.62, S, 6.48.

N-(6-methylbenzothiazolyl)-3,5-dicarbethoxy-2,6-diethoxy-4-(p-hydroxyphenyl)-1,4 dihydropyridine (4e): ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.30 (s, 3H, Benzothiazole, CH_3), 4.90 (s, 1H, DHP), 6.45-8.12 (m, 7H, Ar-H), 1.27 (t, J=7.2 Hz, 6H, DHP, $COOCH_2CH_3$), 4.17 (q, J=7.2 Hz, 4H, DHP, $COOCH_2$), 5.05 (s, 1H, Ar-OH), 1.21 (t, 6H, DHP, OCH_2CH_3), 4.00 (q, 4H, DHP, OCH_2) ^{13}C-NMR (300MHz, $CDCl_3$) δ 126.3, 135.5, 122.8, 151.8, 130.3, 122.7, 168.7, 20.9, 16.6, 99.0, 134.9, 127.5, 109.3, 25.4, 11.3, 17.6, 59.8, 13.6, 161.0, 61.8, 129.3, 115.4, 146.4, 113.1, 129.6, 119.5, 16.5, 58.4, 20.9 IR (cm^{-1}): v_{max} 1055, 1228, 1137, 1594, 1538, 1452,1593, 2975, 3575, 1650, 1624, 1689; Accurate MS m/z: Calc: 568.64, Found: 568.18, Elemental Anal. Calcd. (CHNS) for $C_{29}H_{32}N_2O_7S$: C, 63.02, H, 5.84, N, 5.07, S, 5.79, Found: C, 62.98, H, 5.83, N, 5.02, S, 5.71.

N-(6-methylbenzothiazolyl)-3,5-dicarbethoxy-2,6-diethoxy-4-(phenyl)-1,4-dihydropyridine (4f): ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.34 (s, 3H, Benzothiazole, CH_3), 4.93 (s, 1H, DHP), 6.42-8.12 (m, 8H, Ar-H), 1.26 (t, J=7.1 Hz, 6H, DHP, $COOCH_2CH_3$), 4.15 (q, J=7.1 Hz, 4H, DHP, $COOCH_2$), 1.21 (t, J=7.2 Hz, 6H, DHP, OCH_2CH_3), 4.03 (q, J=7.2 Hz, 4H, DHP, OCH_2). ^{13}C-NMR (300MHz, $CDCl_3$) δ 126.3, 135.1, 124.8, 155.4, 131.3, 171.7, 22.8, 99.0, 134.7, 127.4, 109.2, 28.9, 18.9, 25.4, 11.3, 17.6, 59.8, 13.6, 161.0, 61.8, 129.3, 115.4, 146.4, 113.1, 129.6, 119.5, 15.1, 16.5, 14.8 IR (cm^{-1}): v_{max} 1058, 1210, 1380, 1597, 1546, 1458, 2975, 1628, 1684; Accurate MS m/z: Calc: 522.64, Found: 522.19, Elemental Anal. Calcd. (CHNS) for $C_{29}H_{32}N_2O_6S$: C, 64.90, H, 6.01, N, 5.22, S, 5.96, Found: C, 64.87, H, 6.00 N, 5.19, S, 5.91.

N-(6-methylbenzothiazolyl)-3,5-diacetyl-2,6-dimethyl-4-(p-methoxyphenyl)-1,4-dihydropyridine (4g): ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.50 (s, 3H, Benzothiazole, CH_3), 2.17 (s, 6H, DHP, CH_3), 4.95 (s, 1H, DHP), 6.47-8.12 (m, 7H, Ar-H), 2.29 (s, 6H, DHP, $COCH_3$), 3.72 (s, 3H, Ar-OCH_3), ^{13}C-NMR (300MHz, $CDCl_3$) δ 126.5, 134.3, 122.8, 151.8, 130.3, 168.7, 20.9, 16.6, 99.0, 127.5, 109.3, 32.9, 18.9, 125.4, 17.6, 11.3, 27.0, 199.5, 27.6, 129.3, 115.1, 146.7, 115.1, 118.5, 15.9, 46.6 IR (cm^{-1}): v_{max} 1053, 1226, 1535, 1450, 1596, 1622, 1682; Accurate MS m/z: Calc: 462.56, Found: 462.16, Elemental Anal. Calcd. (CHNS) for $C_{26}H_{26}N_2O_3S$: C, 69.93, H, 5.87, N, 6.27 S, 7.17, Found: C, 69.88, H, 5.85, N, 6.21, S, 7.14.

N-(6-methylbenzothiazolyl)-3,5-dicarbethoxy-2,6-dimethyl-4-(phenyl)-1,4-dihydropyridine (4h): ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.50 (s, 3H, Benzothiazole, CH_3), 2.30 (s, 6H, DHP, CH_3), 4.93 (s, 1H, DHP), 6.46-8.10 (m, 8H, Ar-H), 1.25 (t, J=7.2 Hz, 6H, DHP, CH_3), 4.12 (q, 4H, DHP, CH_2), ^{13}C-NMR (300MHz, $CDCl_3$) δ 126.3, 135.5, 155.8, 133.3, 124.6, 171.7, 22.9, 99.0, 134.9, 127.5, 109.3, 35.9, 18.5, 25.4, 11.3, 17.3, 59.8, 13.6, 161.0, 61.8, 129.3, 115.4, 146.4, 129.6, 128.4, 125.5, 20.9 IR (cm^{-1}): v_{max} 1058, 1209, 1378, 1595, 1545, 1450, 2973, 1628, 1678; Accurate MS m/z: Calc: 492.17, Found: 492.59, Elemental Anal. Calcd. (CHNS) for $C_{27}H_{28}N_2O_4S$: C, 68.04, H, 5.93, N, 5.88, S, 6.71, Found: C, 68.01, H, 5.87, N, 5.82, S, 6.65.

N-(6-methylbenzothiazolyl)-3,5-diacetyl-2,6-dimethyl-4-(p-hydroxyphenyl)-1,4-dihydropyridine (4i): ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.30 (s, 3H, Benzothiazole, CH_3), 2.20 (s, 6H, DHP, CH_3), 4.93 (s, 1H, DHP), 6.44-8.12 (m, 7H, Ar-H), 2.30 (s, 6H, DHP, $COCH_3$), 5.01 (s, 1H, Ar-OH), ^{13}C-NMR (300MHz, $CDCl_3$) δ 126.5, 134.3, 122.8, 151.8, 130.3, 168.7, 20.9, 16.6, 99.0, 127.5, 109.3, 32.9, 18.9, 125.4, 17.6, 11.3, 27.0, 199.5, 27.6, 129.3, 115.1, 146.7, 118.5, 15.9 56.0 IR (cm^{-1}): v_{max} 1054, 1207, 1137, 1535, 1590, 1450, 2975, 3573, 1660, 1628, 1691; Accurate MS m/z: Calc: 448.14, Found: 448.54, Elemental Anal. Calcd. (CHNS) for $C_{25}H_{24}N_2O_3S$: C, 69.42, H, 5.59, N, 6.48, S, 7.41, Found: C, 69.37, H, 5.52, N, 6.42, S, 7.38.

N-(6-methylbenzothiazolyl)-3,5-diacetyl-2,6-dimethyl-4-(phenyl)-1,4-dihydropyridine (4j): ^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.22 (s, 3H, Benzothiazole, CH_3), 2.14 (s, 6H, DHP, CH_3), 4.95 (s, 1H, DHP), 6.47-8.12 (m, 8H, Ar-H), 2.29 (s, 6H, DHP, $COCH_3$),). ^{13}C-NMR (300MHz, $CDCl_3$) δ 126.5, 134.2, 121.8, 151.7, 130.2, 168.6, 20.8, 16.5, 99.0, 1334.8, 127.6, 110.3, 32.8, 124.4, 17.6, 11.3, 122.4, 27.6, 128.3, 115.2, 146.7, 129.3, 118.5, 16.0, 46.4 IR (cm^{-1}): v_{max} 1056, 1209, 1375, 1594, 1543, 1455, 2974, 1628, 1694, 1667; Accurate MS m/z: Calc: 432.15, Found: 432.54, Elemental Anal. Calcd. (CHNS) for $C_{25}H_{24}N_2O_2S$: C, 72.09, H, 5.81, N, 6.73, S, 7.68, Found: C, 72.02, H, 5.78, N, 6.70, S, 7.62.

N-(6-methylbenzothiazolyl)-3,5-diacetyl-2,6-dimethyl-4-(p-dimethylaminophenyl)-1,4-dihydropyridine (4k): ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.31 (s, 3H, Benzothiazole, CH_3), 2.27 (s, 6H, DHP, CH_3), 4.92 (s, 1H, DHP), 6.47-8.12 (m, 7H, Ar-H), 2.31 (s, 6H, DHP, $COCH_3$), 2.84 (s, 6H, $N(CH_3)_2$), ^{13}C-NMR (300MHz, $CDCl_3$) δ 126.5, 134.3, 122.7, 151.89, 130.3, 122.6, 168.7, 20.9, 16.6, 99.0, 134.9, 127.5, 109.3, 32.9, 18.9, 125.4, 17.6, 11.3, 199.5, 27.6, 129.3, 115.1, 146.7, 129.2, 119.5, 15.8, 16.2 IR (cm^{-1}): v_{max} 1063, 1103, 1150, 1582,1528, 1451, 2994, 1622, 1656, 1687; Accurate MS m/z: Calc: 475.19, Found: 475.61, Elemental Anal. Calcd. (CHNS) for $C_{27}H_{29}N_3O_2S$: C, 70.56, H, 6.36, N, 9.15, S, 6.96, Found: C, 70.52, H, 6.32, N, 9.10, S, 6.92.

N-(6-methylbenzothiazolyl)-3,5-dicarbethoxy-2,6-diethoxy-4-(p-methoxyphenyl)-1,4-dihydropyridine (4l): ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.32 (s, 3H, Benzothiazole, CH_3), 4.98 (s, 1H, DHP), 6.47-8.12 (m, 7H, Ar-H), 1.29 (t, J=7.2 Hz, 6H, DHP, $COOCH_2CH_3$), 4.17 (q, 4H, DHP, $COOCH_2$), 3.72 (s, 3H, Ar-OCH_3), 1.21 (t, 6H, DHP, OCH_2CH_3), 4.02 (q, 4H, DHP, OCH_2). ^{13}C-NMR (300MHz, $CDCl_3$) δ 126.3, 135.4, 124.8, 155.9, 133.3, 124.5, 171.7, 22.9, 99.0, 134.9, 127.5, 109.3, 29.9, 18.9, 25.4, 11.3, 17.6, 59.8, 13.6, 161.0, 61.8, 129.3, 115.4, 146.7, 113.2, 119.6, 15.2, 16.7, 58.4, 46.7 IR (cm^{-1}): v_{max} 1053, 1224, 1136, 1534, 1590, 1450, 2973, 1701, 1622, 1653, 1701; Accurate MS m/z: Calc: 582.20, Found: 582.67, Elemental Anal. Calcd. (CHNS) for $C_{30}H_{34}N_2O_7S$: C, 63.58, H, 6.05, N, 4.95, S, 5.65, Found: C, 63.52, H, 6.01, N, 4.91, S, 5.62.

N-(6-methylbenzothiazolyl)-3,5-dicarbethoxy-2,6-dimethyl-4-(m-nitrophenyl)-1,4-dihydropyridine (4m): ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.31 (s, 3H, Benzothiazole, CH_3), 2.12 (s, 6H,DHP, CH_3), 4.90 (s, 1H, DHP), 6.48-8.14 (m, 3H, Ar-H), 7.70-8.01 (m, 4H, Ar-H), 1.28 (t, J=7.0 Hz, 6H, DHP, CH_3), 4.20 (q, J=6.9 Hz, 4H, DHP, CH_2)). ^{13}C-NMR (300MHz, $CDCl_3$) δ 126.5, 134.3, 122.8, 151.8, 130.3, 168.7, 70.2, 154.3, 127.5, 109.3, 29.5, 18.9, 17.6, 11.3, 58.3, 14.8, 171.0, 59.2, 13.6, 161.0, 61.7, 137.7, 129.2, 128.4, 20.9, 16.2, 15.9, IR (cm^{-1}): v_{max} 1056, 1227, 1136, 1694, 1536, 1451, 2973, 1514, 1390, 3650, 1662, 1627, 1694; Accurate MS m/z: Calc: 507.15, Found: 507.58, Elemental Anal. Calcd. (CHNS) for $C_{27}H_{27}N_3O_6S$: C, 62.17, H, 5.22, N, 8.06, S, 6.15, Found: C, 62.15, H, 5.20, N, 8.02, S, 6.12.

N-(6-methylbenzothiazolyl)-3,5-dicarbethoxy-2,6-diethoxy-4-(m-nitrophenyl)-1,4 dihydropyridine (4n): ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.29 (s, 3H, Benzothiazole, CH_3), 4.90 (s, 1H, DHP), 6.45-8.12 (m, 3H, Ar-H), 7.90-8.10 (m, 4H, Ar-H), 1.26 (t, J=7.2 Hz, 6H, DHP, $COOCH_2CH_3$), 4.16 (q, J=7.2 Hz, 4H, DHP, $COOCH_2$), 1.21 (t, 6H, DHP, OCH_2CH_3), 4.00 (q, 4H, DHP, OCH_2) ^{13}C-NMR (300MHz, $CDCl_3$) δ 126.3, 134.2, 123.8, 153.8, 132.3, 124.6, 167.7, 70.1, 153.3, 127.4, 109.4, 30.5, 18.9, 17.6, 11.3, 17.3, 58.3, 14.8, 171.0, 59.2, 13.6, 161.0, 61.7, 137.7, 129.2, 128.4, 20.9, 16.2, 15.9, IR (cm^{-1}): v_{max} 1055, 1228, 1137, 1594, 1538, 1452,1593, 2975,1520, 1380, 3575, 1650, 1624, 1689; Accurate MS m/z: Calc: 582.19, Found: 582.65, Elemental Anal. Calcd. (CHNS) for $C_{29}H_{31}N_3O_8S$: C, 59.77, H, 5.54, N, 7.22, S, 5.49, Found: C, 59.74, H, 5.47, N, 7.19, S, 5.47.

N-(6-methylbenzothiazolyl)-3,5-diacetyl-2,6-dimethyl-4-(m-nitrophenyl)-1,4-dihydropyridine (4o): ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.30 (s, 3H, Benzothiazole, CH_3), 2.20 (s, 6H, DHP, CH_3), 4.93 (s, 1H, DHP), 6.44-8.12 (m, 3H, Ar-H), 7.80-8.01 (m, 4H, Ar-H), 2.30 (s, 6H, DHP, $COCH_3$), ^{13}C-NMR (300MHz, $CDCl_3$) δ 126.5, 134.3, 122.8, 151.8, 130.3, 122.6, 168.7, 20.9, 16.6, 99.0, 134.9, 127.5, 109.3, 32.9, 18.9, 25.4, 17.6, 11.3, 27.0, 129.2, 131.7, 128.4, 128.2, 126.4, 20.9, IR (cm^{-1}): v_{max} 1054, 1207, 1137, 1535, 1590, 1450, 2975, 1505, 1390, 3573, 1660, 1628, 1691; Accurate MS m/z: Calc: 461.14, Found: 461.54, Elemental Anal. Calcd. (CHNS) for $C_{25}H_{23}N_3O_4S$: C, 65.06, H, 5.03, N, 9.11, S, 6.93, Found: C, 65.02, H, 5.502, N, 9.09, S, 6.87.

2.3. Antimicrobial Assay

All the synthesized compounds were tested for their antibacterial activity against various bacteria, *Lactobacillus sp*., *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Micrococcus leutius*, *Kocuria rosea* and antifungal activity against fungi *Aspergillus niger* and *Aspergillus candidus* using paper disc method. Muller Hinton Agar (Hi-Media Pvt. Ltd. Mumbai, India) was used to culture the test bacteria and Potato Dextrose Agar was used to culture fungi. The microbial culture were grown at 37^{0}C for 8 hours and then appropriately diluted with sterile 0.8% saline solution. The concentration of test drugs was kept 200 µg mL^{-1} in DMF. Standard drugs Novobiocine, Gentamycin, Kanamycin, Amikacin (for antibacterial) and Ampicilline (for antifungal) were used for comparison. The antimicrobial activity was evaluated by measuring the zone of growth inhibition around disc of test organism (Table 3).

2.4. Antifeedant activity

The antifeedant activity of these compounds was also carried out by leaf dip method [41,42], using fourth instars larvae of Spodoptera litura. The leaf discs of about 25 cm^2 were prepared and dipped for thirty seconds in various concentrations of the test compounds. Now air-dried the leaf discs to evaporate the excess acetone and the leaf discs offered for feeding. The insects were allowed to feed for 24 h. After 24 h leaf area uneaten was measured by using leaf area meter. The difference between leaf area provided and the leaf area uneaten is taken as amount of leaf area consumed. The feeding inhibition was calculated and used for calculation of effective concentration (EC_{50}/LD_{50}) using Maximum likelihood programmer (MLP) 3.01. The results of antifeedant activity are summarized in Table 4.

2.5. Acaricidal activity

The acaricidal activity of these compounds was carried out by leaf dip method [41,42]. Leaf discs of Mulberry (5 cm^2 diameter) were dipped in different concentration

Table 3. Antimicrobial activities of compounds **4a**-**4o**.

	Antibacterial activity[a]					Antifungal activity[a]	
Compounds	**B1**	**B2**	**B3**	**B4**	**B5**	**F1**	**F2**
4a	+	++	++	++	++	+	+
4b	++	++	+++	++	++	+	+
4c	++	++	++	++	++	++	++
4d	++	++	++	++	++	++	++
4e	+	++	++	++	++	+	++
4f	+	++	++	++	++	+	+
4g	++	++	++	++	++	++	++
4h	+	+	++	++	++	+	++
4i	+	++	++	++	++	++	++
4j	+	+	++	++	++	+	+
4k	++	++	++	++	+++	+	+
4l	+	++	++	+++	++	++	++
4m	++	++++	++++	+++++	++++	++++	++++
4n	++	+++	+++	++++	+++	++	+++
4o	+++	++++	++++	++++	++++	+++	+++
Benzothiazole	+	+	-	+	+	+	+
Blank	-	-	-	-	-	-	-
Novobiocine	+	+++	+++	+++++	++++	-	-
Gentamycin	+++	++++	++++	+++++	++++	-	-
Kanamycin	+	++	+++	++++	++++	-	-
Amikacin	+++	++++	+++	+++++	++++	-	-
Ampicilline	.	-	-	-	-	+++++	+++++

[a] *Data represent zones of inhibition (mm) as follows:*
- no measurable activity; + 5-7 mm; ++ 7-14 mm; +++ 15-21 mm; ++++ 22-28 mm; +++++ >29 mm
B1 Lactobacillus spp.; B2 Pseudomonas aeruginosa; B3 Staphylococcus aureus; B4 Micrococcus leutius; B5 Kocuria rosea; F1 Aspergillus candidus; F2 = Aspergillus niger

for 30 seconds. Now air dried the leaf discs to remove the excess of acetone and placed over wet cotton in Petri plate. The adult female mites were released on treated leaf discs and mortality data were recorded after 48 hours. Mites released on leaf treated only with acetone and tween 20 emulsifier served as control. The mortality data was used for calculation of LC_{50}/LD_{50} using Maximum Likelihood Programmer (MLP) 3.01.The results of acaricidal activity are summarized in Table 5.

Table 4. Antifeedant activity of compounds **4a**-**4o**.

Compounds 4	Fiducial Limits	Slop ±	Chi. Sq. (3)	LC_{50}/LD_{50} at 24 h
4a	0.78–3.42	0.80±0.12	0.41 (3)	1.35
4b	0.64–1.74	1.01±0.11	0.65 (3)	0.97
4c	0.41–0.83	1.02±0.13	0.34 (3)	0.37
4d	0.60–1.42	1.05±0.13	1.03 (3)	0.85
4e	0.84–2.33	1.06±0.14	0.77 (3)	1.23
4f	0.68–2.42	0.96±0.14	0.21 (3)	1.13
4g	0.31–0.47	1.26±0.13	3.39 (3)	0.37
4h	0.33–0.64	1.00±0.10	0.67 (3)	0.42
4i	0.42–1.05	0.83±0.13	1.68 (3)	0.62
4j	0.46–0.77	1.50±0.15	2.56 (3)	0.57
4k	0.28–0.50	1.01±0.12	5.34 (3)	0.56
4l	0.24–0.55	0.95±0.12	0.25 (3)	0.36
4m	0.47-0.78	1.50±0.14	2.58 (3)	0.60
4n	0.34-0.56	1.02±0.12	5.37 (3)	1.01
4o	0.25-0.57	0.96±0.16	0.27 (3)	0.38

3. Results and discussions

Synthesis of title compounds by conventional methods suffer from long reaction time, moderate yields, tedious workup (Table 1), and requirement of large quantity of solvent associated with conventional method is another problem. A relatively more versatile yet simplified procedure was created, in which 2-amino-6-methylbenzothiazole, aromatic aldehydes and active methylene compounds could react without using any solvent (without, as well as, with solid support). Microwave synthesis has received attention as new strategy for organic synthesis due to the fact that many reactions seem to proceed with much alacrity under such conditions as opposed to the corresponding thermal-assisted reaction [33]. The strategy worked well, affording the desired product in improved yields and in significantly lower reaction time (Tables 1 and 2). In microwave promoted reactions, solid supports like silica gel, alumina basic, alumina neutral and alumina acidic has been used, and it is found that the acidic alumina is the best solid support in the present investigation. The structures of all the synthesized compounds **4a**-**4o** were established on the basis of spectroscopic and analytical data. The elemental analysis (C, N and H) found for all the condensed products were in close agreement with the calculated values, the infrared (IR) spectrum of compounds **4** display two characteristic bands at 1622 and 1698 cm^{-1} due to C=C, and CO_2 stretching, respectively. The ^1H nuclear magnetic resonance (NMR) spectrum of compounds **4** and its derivatives exhibit characteristic signals at δ 4.90-4.98 and δ 4.21 due to DHP proton and $DHPCOOCH_2$, respectively. Formation of compounds **4** was further confirmed on the basis of ^{13}C-NMR spectroscopy. Similarly the mass spectra of the 1,4-dihydropyridine derivatives revealed a molecular ion peak at m/z values corresponding to the molecular weight of the target compound. Thus on the basis of spectral data all the products **4a**-**4o** have been identified.

3.1. Antibacterial Activity

The antibacterial activity of all the synthesized compounds were tested *in-vitro* against pathogenic microbial strains, *Lactobacillus spp.*, *Pseudomonas aeruginosa, Staphylococcus aureus, Micrococcus lutius* and *Kocuria rosea* and the results were compared with some standard drugs like novobiocine, gentamycin, kanamycin and amkacin. In case of *Lactobacillus spp*. Compounds **4a**, **4m**, **4n** and **4o** exhibit higher

Table 5. Acaricidal activity of compounds **4a**-**4o**.

Compounds 4	Fiducial Limits	Slop ±	Chi. Sq. (3)	LC_{50}/LD_{50} at 24 h
4a	0.09–0.31	0.77±0.87	1.71 (3)	0.17
4b	0.11–0.23	0.88±0.09	2.13 (3)	0.14
4c	0.15–0.35	0.09±0.08	8.26 (3)	0.24
4d	0.13–0.30	0.95±0.08	7.51 (3)	0.10
4e	0.05–0.09	1.23±0.09	14.26 (3)	0.07
4f	0.09–0.23	0.64±0.05	6.11(3)	0.12
4g	0.14–0.30	0.80±0.07	6.90 (3)	0.17
4h	0.36–1.87	0.63±0.07	3.56 (3)	0.68
4i	0.06–0.19	0.63±0.05	8.42 (3)	0.10
4j	0.11–0.29	0.77±0.07	1.68 (3)	0.17
4k	0.07–0.16	0.80±0.5	9.09 (3)	0.26
4l	0.03–0.05	0.76±0.06	15. 87 (3)	0.38
4m	0.13-0.32	0.80±0.09	1.73 (3)	0.20
4n	0.07-0.20	0.89±0.05	9.15 (3)	0.15
4o	0.06-0.09	0.76±0.09	15.80 (3)	0.45

activity (Inhibition zone = 22-28 mm) while rest of the compounds, except **4e** (Inhibition zone = 5 mm) shows moderate activity. In case of *Pseudomonas aeruginosa* compounds **4m**, **4n**, **4o** show higher activity than the rest of the compounds. The inhibition of compounds **4a**, **4f**, **4m** and **4o** was higher in case of *Staphylococcus aureus* while rest of the were moderately active. In case of *Micrococcus lutius* and *Kocuria rosea* compounds **4m**, **4n**, **4o** and **4j** show higher efficacy than the rest of the compounds. The activity results clearly indicate that the compounds **4**, **4n** and **4o** along with **4a**, **4f** and **4j** show higher activity against the bacterial strains in comparison to the rest of the compounds. The presence of methyl and *m*-nitro groups, in **4m** and **4o**, play an important role in activity, while in compound **4n** presence of an ethoxy group, along with nitro group, justify the activity. It may be found that the nitro group present on the phenyl ring generally form complexes with metaloenzymes, particularly those which are responsible in basic physiology such as cytochrome oxidase. These compounds may react with the peptidoglycan layer of the bacterial cell wall and damage it by penetrating in such a manner that the phenyl ring gets entered inside the cell by puncturing it, followed by bacterial cell death [34]. Sometimes these compounds when present in low concentrations may cause bacteriostatic conditions which slow down the growth of bacteria (Table 3).

3.2. Antifungal Activity

The antifungal activity of all these compounds were carried out against two pathogenic fungal strains *Aspergillus niger* and *Aspergillus candidus* using Ampicilin as a standard. It was found that compounds **4m**, **4n** and **4o** show potent activity. Compound **4m** exhibit higher efficacy against both fungal strains. The higher efficacy of this compound may be due to the presence of nitrogen and sulphur content (containing a lone pair of electrons), presence of two methyl groups along with a nitro group on the phenyl ring. These compounds generally damage the fungal strains by puncturing the cell wall similar to the mechanism proposedfor bacteria. The water and lipid solubility also increases the activity due to presence of polar groups in the molecules [35] (Table 3).

3.3. Entomological Activity

The newly synthesized compounds were also screened out for their entomological activity (antifeedant and acraricidal) against *Spodoptera litura* (an insect which damages the Indian agriculture crops) and *Tetranychus urticae* of mites (damage house goods) respectively.

3.4. Antifeedant activity

The Antifeedant activity of the newly synthesized compounds was tested by a leaf dip method against larvae of *Spodoptera litura*. The results clearly indicate that the compounds show higher, moderate and less antifeedant activity against the larvae of the insect. Compounds **4c**, **4l**, **4g** and **4o** show higher activity, compounds **4m**, **4k**, **4j**, **4h** and **4a** show moderate activity while the rest of the compounds exhibit lower activity as seen by their LC_{50}/LD_{50} results. The results clearly show that the presence of methyl and methoxy groups onthe aromatic ring enhance the activity. The presence of $N(Me)_2$ group as R_3 in the side ring also plays an important role in activity. It may be found that these compounds may cause a spasm condition in insects by interacting with the active site of the enzyme responsible for nervous breakdown in insects [36] (Table 4).

3.5. Acaricidal Activity

The Acaricidal activity of these compounds was performed by the same method, as in the case of Antifeedant activity, against *Tetranychus urticae*, a species of mite using acetone as a standard. The results obtained clearly show that compound **4e** shows the highest acaricidal activity with respect to the other compounds. The higher activity of this compound is due to the presence of three polar groups in the molecules which enhances the water and lipid solubility of this compound. It is reported that the compounds which are easily soluble in polar solvent have higher activity against microbes and insect pests or mites [37]. Compounds **4b**, **4d**, **4f** and **4i** shows moderate activity and the rest of the compounds show lower to moderate activity against the mites. Besides solubility, the presence of a lone pair of electrons on the nitrogen and sulphur along with the phenyl ring, having varying side groups, may also be responsible for variation in activity (Table 5).

4. Conclusion

We have developed an economical, solvent free, very efficient microwave assisted protocol for the synthesis of N-(6-methylbenzothiazolyl)-2,3,5,6-tetrasubstituted-4-(aryl)-1,4-dihydropyridines which can be a viable alternative to their conventional synthesis. The synthetic protocol has the inherent potential for future drug synthesis. The 1,4-dihydropyridine derivatives (**4a**-**4o**) showed potent antimicrobial activity against various bacterial and fungal strains. The maximum antibacterial and antifungal activity was exhibited by **4m**, **4n** and **4o**. The presence of R_3 = *m*-NO_2 substituent on the phenyl ring along with a variation in solubility plays a significant role in determining the antimicrobial activity of the compounds in comparison to other substituents [38]. The ortho and meta electron withdrawing groups on the aromatic ring enhances the activity while anything at the para position reduces activity [39,40]. The compounds also show potent antifeedant and acaricidal activity against *Spodoptera litura* and *Tetranychus urticae*, respectively, where solubility of the compounds plays a significant role [37]. From the results, it is clear that these compounds would be better used in drug development to combat bacterial and fungal infections, and would be better used as pesticides in the future as well.

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