MICROWAVE SYNTHESIS OF NEW BIOLOGICALLY IMPORTANT 1,4-DIHYDROPYRIDINES CONTAINING BENZOTHIAZOLE MOIETY

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2,3,5,6-Tetrasubstituted-4-aryl-1-(6-ethoxybenzothiazol-2-yl)-1,4-dihydropyridines were synthesized by the reaction of 2-amino-6-ethoxybenzothiazole, an aromatic aldehyde and an active methylene compound in methanol by conventional or microwave irradiation method (solvent-free or with solid support). All compounds were tested for antibacterial and antifungal activities and the results were compared with standard drugs. Their acaricidal and antifeedant activities were also tested.

Keywords: Benzothiazole; 1,4-Dihydropyridine; Microwave synthesis; Antimicrobial activity; Acaricidal activity; Antifeedant activity.

Dihydropyridine chemistry is of interest from the view point of research on heterocyclic compounds and also from a biological point of view[1]. Hantzsch 1,4-dihydropyridines (1,4-DHPs), a class of model compounds of NADH coenzyme, have been extensively studied in view of their biological importance in NADH redox processes[2]. Since the early 1980's the presence of the DHP ring in the structure of 1,4-DHP derivatives has been regarded as a prerequisite for introduction of calcium (Ca^{2+}) channel[3]. So, 1,4-DHPs are excellent starting synthons for development of antitubercular agents[4–6]. As a result, newly synthesized 1,4-DHPs possess different pharmacological activities such as anticancer[7], antidiabetic[8], antianginal[9], bronchodilating[10], neurotropic[11], acaricidal, insecticidal, bactericidal and herbicidal[12,13]. They are extensively used in the treatment of angina pectoris, hypertension and arrhythmia[14] and of some cardiovascular disorder. Several new 1,4-DHP de-

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rivatives have been prepared and pharmacologically evaluated in order to find drugs with better pharmacological properties[15]. So, the pharmacology of 1,4-DHP derivatives is on the eve of a novel boom.

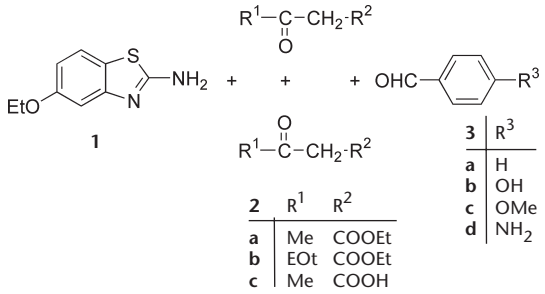
Similarly, benzothiazole rings are present in various marine or terrestrial natural compounds, which have useful biological activities[16–19]. In addition benzothiazoles are a class of therapeutic compounds that exert a broad spectrum of biological activities such as antimicrobial[20,21], anticancer[22,23], antifungal[24], antihelmintic[25], antileishmanial[26], anticonvulsant[27] anti-inflammatory[28] and insecticidal[29–31] activities. 2-(4-Aminophenyl)benzothiazoles[32,33] comprise novel mechanistic antitumor agents. Based on the above evidence revealing that both 1,4-DHP and benzothiazole moieties show enhanced biological effects, we have designed a synthetic strategy that leads to both moieties in the same molecule. The inclusion of these two rings in the same molecule may enhance the bioactivity of the compound. 2-Amino-6-ethoxybenzothiazole was treated with active methylene compounds (ethyl acetoacetate, diethyl malonate, acetylacetone) and aromatic aldehydes (benzaldehyde, 4-hydroxybenzaldehyde, 4-(dimethylamino)benzaldehyde, 4-methoxybenzaldehyde) on steam bath for 2–3 h and refluxed in methanol for 10–15 h. The above described method apparently suffers from disadvantages such as prolonged refluxing, use of volatile organic solvents, low to moderate yields, cumbersome work-up, pollution of the environment and lack of selectivity in the presence of other functional groups.

Incresing growing energy demands, economic and environmental issue over the recent decade has compelled the synthetic chemist to add a new twist to an old theme[34]. The 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 now report a novel environmental approach using a facile microwave synthesis of the title compounds carried out by the solvent-free method, and various solid supports like silica gel, basic alumina, neutral alumina and acidic alumina. Hence, with a view to further assess the pharmacological profile of benzothiazole and 1,4-DHPs, and benefits associated with microwave synthesis, it was thought worthwhile to synthesize some new compounds by incorporating the 2-amino-6-ethoxybenzothiazole and 1,4-DHP moieties in a single molecule. The present work deals with the synthesis of 2,3,5,6-tetrasubstituted-4-aryl-1-(6-ethoxybenzothiazol-2-yl)-1,4-dihydropyridines followed by antimicrobial susceptibility test (AST) against *Lactobacillus* sp., *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Micrococcus leutius*, *Kocuria rosea*, *Aspergillus niger*, *Aspergillus candidus* using standard

methods and comparison with standard drugs. All the synthesized compounds were also screened for their acaricidal and antifeedant activities.

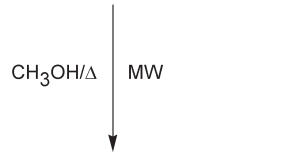
RESULTS AND DISCUSSIONS

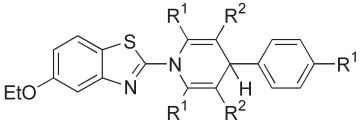
2-Amino-6-ethoxybenzothiazole (**1**) was synthesized by the reported methods[35,36]. 2,3,5,6-Tetrasubstituted-4-aryl-1-(6-ethoxybenzothiazol-2-yl)-1,4-dihydropyridines **4** were synthesized by the reaction of equimolar quanti-



2	R^1	R^2
a	Me	COOEt
b	EOt	COOEt
c	Me	COOH

3	R^3
a	H
b	OH
c	OMe
d	NH_2





4	R^1	R^2	R^3
a	Me	COOEt	NMe_2
b	OEt	COOEt	NMe_2
c	Me	COOEt	OMe
d	Me	COOEt	OH
e	OEt	COOEt	OH
f	OEt	COOEt	H
g	Me	COMe	OMe
h	Me	COOEt	H
i	Me	COMe	OH
j	Me	COMe	H
k	Me	COMe	NMe_2
l	OEt	COOEt	OMe

SCHEME 1
Synthesis of 2,3,5,6-tetrasubstituted-4-aryl-1-(6-ethoxybenzothiazol-2-yl)-1,4-dihydropyridines **4**

ties of **1** and aromatic aldehyde **3** with 2 equivalents of active methylene compound **2**. The mixture was heated without solvent on steam bath for 2–3 h. After elimination of water, methanol (25 ml) was added and the reaction mixture was refluxed for 10–15 h. In view of a long reaction time, moderate yields (Table I), tedious work-up and requirement for large quantities of solvent, a more versatile yet simplified procedure was designed. The procedure consists of reacting 2-amino-6-ethoxybenzothiazole, an aromatic aldehyde and an active methylene compound reacted without using any solvent with or without solid support using microwave synthesis[37]. The strategy worked well affording the desired product in improved yields and in a significantly lower reaction time (Tables I and II). In microwave-promoted reactions solid support like silica gels, basic alumina, neutral alumina and acid alumina have also been used. It was found that acid alumina is the best solid support for the present purpose. The synthesized compounds were characterized by their analytical and IR, ^{1}H NMR and mass spectral data.

TABLE I
Synthesis of 2,3,5,6-tetrasubstituted-4-aryl-1-(6-ethoxybenzothiazol-2-yl)-1,4-dihydropyridines **4**

Compd.	R^1	R^2	R^3	M.p. °C	Conventional heating		Microwave heating	
					time, h	yield, %	time, s	yield, %
4a	Me	COOEt	NMe_2	155	20.0	53	180	65
4b	OEt	COOEt	NMe_2	170	20.0	55	190	70
4c	Me	COOEt	OMe	90	20.0	53	180	72
4d	Me	COOEt	OH	130	20.0	56	200	70
4e	OEt	COOEt	OH	125	20.0	58	170	72
4f	OEt	COOEt	H	136	20.0	60	190	75
4g	Me	COMe	OMe	134	20.0	60	180	75
4h	Me	COOEt	H	98	20.0	50	180	65
4i	Me	COMe	OH	110	20.0	57	130	67
4j	Me	COMe	H	158	20.0	56	180	68
4k	Me	COMe	NMe_2	98	20.0	52	170	68
4l	OEt	COOEt	OMe	152	20.0	56	160	67

EXPERIMENTAL

Reagent grade chemicals were used without further purification. The chemicals and solvents were used as received. All the melting points were measured in open capillaries and are uncorrected. The purity of the synthesized compounds was checked by thin layer chromatography. IR spectra were scanned at FT IR Perkin–Elmer (Spectrum RX1) spectrophotometer (ν_{max} in cm^{-1}) using KBr discs. ^1H NMR was 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 in ppm (δ-scale), coupling constants, *J* in Hz. 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, 10 mA) as the FAB gas. The accelerating potential was 10 kV. Microwave (MW) synthesis was carried out in a Q-pro-M Modified Microwave system. Elemental analysis of compounds was performed on a Carlo Erba-1108 elemental analyzer.

TABLE II
Microwave synthesis of 2,3,5,6-tetrasubstituted-4-aryl-1-(6-ethoxybenzothiazol-2-yl)-1,4-dihydropyridines (**4a–4l**) – the effect of solid supported

Compd.	Silica		Alumina					
			basic		neutral		acid	
	time, s	yield, %	time, s	yield, %	time, s	yield, %	time, s	yield, %
4a	200	60	240	53	100	72	60	82
4b	210	65	270	58	120	79	50	91
4c	200	67	250	50	90	78	40	93
4d	220	66	280	55	100	79	70	92
4e	190	67	255	57	100	80	60	93
4f	200	70	240	58	100	85	60	95
4g	230	70	240	58	120	87	80	98
4h	210	59	260	53	100	78	60	97
4i	210	62	270	54	120	79	90	92
4j	220	63	250	52	100	76	60	90
4k	200	60	250	48	100	76	60	90
4l	190	63	250	50	100	74	60	89

Synthesis of 2,3,5,6-Tetrasubstituted-4-aryl-1-(6-ethoxybenzothiazol-2-yl)-1,4-dihydropyridines. General Procedure

A. Conventional method. A mixture of 2-amino-6-ethoxybenzothiazole (**1**; 0.1 mol), an aromatic aldehyde **3** (0.1 mol) and an active methylene compound **2** (0.2 mol) was heated without solvent on steam bath for 2–3 h. After evaporations of water, methanol (25 ml) was added and the reaction mixture was refluxed for 10–15 h. Then the reaction mixture was poured into ice water, the insoluble portion was separated, extracted with diethyl ether (50 ml) and dried over anhydrous magnesium sulfate, and the residue after evaporation was recrystallized from methanol (Scheme 1, Table I).

B. Microwave method. A mixture of 2-amino-6-ethoxybenzothiazole (**1**; 0.01 mol), an aromatic aldehyde **3** (0.01 mol) and an active methylene compound **2** (0.02 mol) was placed in a microwave oven, microwave-irradiated with a low power and monitored by TLC in benzene–DMF (7:3). The reaction mixture was cooled to room temperature, extracted with diethyl ether (10 ml) and the extract was dried over anhydrous magnesium sulfate. The crude product was recrystallized from methanol (Table I).

C. Solid-supported microwave synthesis. A mixture of 2-amino-6-ethoxybenzothiazole (**1**; 0.01 mol), an aromatic aldehyde **3** (0.01 mol), an active methylene compound **2** (0.02 mol), alumina (acid/basic/neutral) and silica gel was mixed thoroughly in a mortar. Then the mixture was placed in a flask which was irradiated in microwave oven for 30-s intervals at predetermined times. On completion of the reaction as monitored by TLC in benzene–DMF (7:3), the reaction mixture was cooled to room temperature and extracted with diethyl ether (10 ml). The extract dried over anhydrous magnesium sulfate gave pure product which was recrystallized from methanol (Table II).

4-[4-(Dimethylamino)phenyl]-1-(6-ethoxybenzothiazol-2-yl)-3,5-bis(ethoxycarbonyl)-2,6-dimethyl-1,4-dihydropyridine (**4a**). ^{1}H NMR: 1.29 t, 6 H, J = 7.2 (DHP $CH_2C\mathbf{H}_3$); 1.33 t, 3 H, J = 7.2 (benzothiazole $OCH_2C\mathbf{H}_3$); 2.22 s, 6 H (DHP CH_3); 2.86 s, 6 H ($N(CH_3)_2$); 3.97 q, 2 H, J = 7.1 (benzothiazole $OC\mathbf{H}_2CH_3$); 4.18 q, 4 H, J = 7.2 (DHP CH_2); 4.90 s, 1 H (DHP); 6.46–8.11 m, 7 H (Ar-H). IR: 1063, 1108, 1150, 1452, 1532, 1586, 1628, 1664, 2996. MS, *m/z*: calculated 549.68, found 549.67. For $C_{30}H_{35}N_3O_5S$ calculated: 65.55% C, 6.42% H, 7.64% N, 5.83% S; found: 65.40% C, 6.41% H, 7.60% N, 5.84% S.

4-[4-(Dimethylamino)phenyl]-2,6-diethoxy-1-(6-ethoxybenzothiazol-2-yl)-3,5-bis(ethoxycarbonyl)-1,4-dihydropyridine (**4b**). ^{1}H NMR: 1.21 t, 6 H, J = 7.2 (DHP OCH_2CH_3); 1.29 t, 6 H, J = 7.2 ($COOCH_2C\mathbf{H}_3$); 1.33 t, 3 H, J = 7.1 (benzothiazole OCH_2CH_3); 2.81 s, 6 H ($N(CH_3)_2$); 3.97 q, 2 H, J = 7.0 (benzothiazole OCH_2); 4.01 q, 4 H, J = 7.2 (DHP OCH_2); 4.16 q, 4 H, J = 7.1 ($COOC\mathbf{H}_2CH_3$); 4.93 s, 1 H (DHP); 6.46–8.11 m, 7 H (Ar-H). IR: 1062, 1105, 1151, 1450, 1530, 1583, 1622, 1652, 2995. MS, *m/z*: calculated 609.74, found 609.72. For $C_{32}H_{39}N_3O_7S$ calculated: 63.04% C, 6.45% H, 6.89% N, 5.26% S; found: 63.03% C, 6.42% H, 6.87% N, 5.25% S.

1-(6-Ethoxybenzothiazol-2-yl)-3,5-bis(ethoxycarbonyl)-4-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine (**4c**). ^{1}H NMR: 1.28 t, 6 H, J = 7.2 (DHP $CH_2C\mathbf{H}_3$); 1.33 t, 3 H, J = 7.0 (benzothiazole $OCH_2C\mathbf{H}_3$); 2.28 s, 6 H (DHP CH_3); 3.73 s, 3 H (Ar-OCH_3); 3.97 q, 2 H, J = 7.1 (benzothiazole $OC\mathbf{H}_2CH_3$); 4.18 q, 4 H, J = 7.2 (DHP $C\mathbf{H}_2CH_3$); 4.91 s, 1 H (DHP); 6.46–8.11 m, 7 H (Ar-H). IR: 1054, 1225, 1450, 1535, 1590, 1628, 1655. MS, *m/z*: calculated 536.64, found 536.62. For $C_{29}H_{32}N_2O_6S$ calculated: 64.91% C, 6.01% H, 5.22% N, 5.97% S; found: 64.87% C, 6.00% H, 5.20% N, 5.94% S.

1-(6-Ethoxybenzothiazol-2-yl)-3,5-bis(ethoxycarbonyl)-4-(4-hydroxyphenyl)-2,6-dimethyl-1,4-dihydropyridine (**4d**). ^{1}H NMR: 1.31 t, 6 H, *J* = 7.0 (DHP CH_3); 1.33 t, 3 H, *J* = 7.2 (benzothiazole $OCH_2C\mathbf{H}_3$); 2.14 s, 6 H (DHP CH_3); 3.97 q, 2 H, *J* = 7.1 (benzothiazole $OC\mathbf{H}_2CH_3$); 4.19 q, 4 H, *J* = 6.9 (DHP CH_2); 4.94 s, 1 H (DHP); 5.01 s, 1 H (OH); 6.48–8.14 m, 7 H (Ar-H). IR: 1056, 1136, 1227, 1451, 1536, 1627, 1662, 1694, 2973, 3650. MS, *m/z*: calculated 522.16, found 522.15. For $C_{28}H_{30}N_2O_6S$ calculated: 64.35% C, 5.79% H, 5.36% N, 6.13% S; found: 64.34% C, 5.78% H, 5.34% N, 6.14% S.

2,6-Diethoxy-1-(6-ethoxybenzothiazol-2-yl)-3,5-bis(ethoxycarbonyl)-4-(4-hydroxyphenyl)-1,4-dihydropyridine (**4e**). ^{1}H NMR: 1.24 t, 6 H (DHP $OCH_2C\mathbf{H}_3$); 1.29 t, 6 H, *J* = 7.2 (DHP $COOCH_2C\mathbf{H}_3$); 1.33 t, 3 H, *J* = 7.1 (benzothiazole $OCH_2C\mathbf{H}_3$); 3.97 q, 2 H, *J* = 7.1 (benzothiazole $OC\mathbf{H}_2CH_3$); 4.02 q, 4 H (DHP OCH_2); 4.19 q, 4 H, *J* = 7.2 (DHP $COOCH_2$); 4.90 s, 1 H (DHP); 5.01 s, 1 H (OH); 6.47–8.12 m, 7 H (Ar-H). IR: 1055, 1137, 1228, 1452, 1538, 1593, 1594, 1624, 1650, 1689, 2975, 3575. MS, *m/z*: calculated 582.67, found 582.65. For $C_{30}H_{34}N_2O_8S$ calculated: 61.84% C, 5.88% H, 4.81% N, 5.50% S; found: 61.82% C, 5.86% H, 4.80% N, 5.49% S.

2,6-Diethoxy-1-(6-ethoxybenzothiazol-2-yl)-3,5-bis(ethoxycarbonyl)-4-phenyl-1,4-dihydropyridine (**4f**). ^{1}H NMR: 1.20 t, 6 H, *J* = 7.2 (DHP OCH_2CH_3); 1.26 t, 6 H, *J* = 7.1 (DHP $COOCH_2C\mathbf{H}_3$); 1.33 t, 3 H, *J* = 7.0 (benzothiazole $OCH_2C\mathbf{H}_3$); 3.97 q, 2 H, *J* = 6.9 (benzothiazole $OC\mathbf{H}_2CH_3$); 4.00 q, 4 H, *J* = 7.2 (DHP OCH_2); 4.17 q, 4 H, *J* = 7.1 (DHP $COOCH_2$); 4.94 s, 1 H (DHP); 6.47–8.12 m, 8 H (Ar-H). IR: 1058, 1210, 1380, 1458, 1546, 1597, 1628, 1670, 2975. MS, *m/z*: calculated 566.67, found 566.65. For $C_{30}H_{34}N_2O_7S$ calculated: 63.59% C, 6.05% H, 4.94% N, 5.66% S; found: 63.58% C, 6.04% H, 4.92% N, 5.65% S.

3,5-Diacetyl-1-(6-ethoxybenzothiazol-2-yl)-4-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine (**4g**). ^{1}H NMR: 1.33 t, 3 H, *J* = 7.1 (benzothiazole $OCH_2C\mathbf{H}_3$); 2.18 s, 6 H (DHP CH_3); 2.30 s, 6 H (DHP $COCH_3$); 3.73 s, 3 H (Ar-OCH_3); 3.97 q, 2 H, *J* = 7.0 (benzothiazole $OC\mathbf{H}_2CH_3$); 4.96 s, 1 H (DHP); 6.47–8.12 m, 7 H (Ar-H). IR: 1053, 1226, 1450, 1535, 1596, 1622, 1662. MS, *m/z*: calculated 476.59, found 476.54. For $C_{27}H_{28}N_2O_4S$ calculated: 68.05% C, 5.92% H, 5.88% N, 6.73% S; found: 68.04% C, 5.91% H, 5.87% N, 6.72% S.

1-(6-Ethoxybenzothiazol-2-yl)-3,5-bis(ethoxycarbonyl)-2,6-dimethyl-4-phenyl-1,4-dihydropyridine (**4h**). ^{1}H NMR: 1.26 t, 6 H, *J* = 7.2 (DHP CH_3); 1.33 t, 3 H, *J* = 7.1 (benzothiazole $OCH_2C\mathbf{H}_3$); 2.33 s, 6 H (DHP CH_3); 3.97 q, 2 H, *J* = 7.1 (benzothiazole $OC\mathbf{H}_2CH_3$); 4.15 q, 4 H (DHP CH_2); 4.95 s, 1 H (DHP); 6.46–8.10 m, 8 H (Ar-H). IR: 1058, 1209, 1378, 1450, 1545, 1595, 1628, 1668, 2973. MS, *m/z*: calculated 506.62, found 506.60. For $C_{28}H_{30}N_2O_5S$ calculated: 66.38% C, 5.97% H, 5.43% N, 6.83% S; found: 66.37% C, 5.96% H, 5.52% N, 6.82% S.

3,5-Diacetyl-1-(6-ethoxybenzothiazol-2-yl)-4-(4-hydroxyphenyl)-2,6-dimethyl-1,4-dihydropyridine (**4i**). ^{1}H NMR: 1.33 t, 3 H, *J* = 7.2 (benzothiazole $OCH_2C\mathbf{H}_3$); 2.21 s, 6 H (DHP CH_3); 2.31 s, 6 H (DHP $COCH_3$); 3.97 q, 2 H, *J* = 7.1 (benzothiazole $OC\mathbf{H}_2CH_3$); 4.96 s, 1 H (DHP); 5.00 s, 1 H (OH); 6.48–8.14 m, 7 H (Ar-H). IR: 1054, 1137, 1207, 1450, 1535, 1590, 1628, 1660, 1691, 2975, 3573. MS, *m/z*: calculated 462.56, found 462.52. For $C_{26}H_{26}N_2O_4S$ calculated: 67.51% C, 5.67% H, 6.06% N, 6.93% S; found: 66.50% C, 5.60% H, 6.04% N, 6.91% S.

3,5-Diacetyl-1-(6-ethoxybenzothiazol-2-yl)-2,6-dimethyl-4-phenyl-1,4-dihydropyridine (**4j**). ^{1}H NMR: 1.33 t, 3 H (benzothiazole $OCH_2C\mathbf{H}_3$); 2.16 s, 6 H (DHP CH_3); 2.30 s, 6 H (DHP $COCH_3$); 3.97 q, 2 H (benzothiazole $OC\mathbf{H}_2CH_3$); 4.96 s, 1 H (DHP); 6.47–8.12 m, 8 H (Ar-H). IR: 1056, 1209, 1375, 1455, 1543, 1594, 1628, 1667, 2974. MS, *m/z*: calculated 446.56, found 446.52. For $C_{26}H_{26}N_2O_3S$ calculated: 69.93% C, 5.87% H, 6.27% N, 7.18% S; found: 69.90% C, 5.80% H, 6.24% N, 7.15% S.

3,5-Diacetyl-4-[4-(dimethylamino)phenyl]-1-(6-ethoxybenzothiazol-2-yl)-2,6-dimethyl-1,4-dihydropyridine (**4k**). ^{1}H NMR: 1.33 t, 3 H, *J* = 7.1 (benzothiazole $OCH_2C\mathbf{H}_3$); 2.28 s, 6 H (DHP CH_3); 2.30 s, 6 H (DHP $COCH_3$); 2.85 s, 6 H ($N(CH_3)_2$); 3.97 q, 2 H, *J* = 7.1 (benzothiazole $OC\mathbf{H}_2CH_3$); 4.93 s, 1 H (DHP); 6.47–8.12 m, 7 H (Ar-H). IR: 1063, 1103, 1150, 1451, 1528, 1582, 1622, 1656, 2994. MS, *m/z*: calculated 489.63, found 489.60. For $C_{28}H_{31}N_3O_3S$ calculated: 68.69% C, 6.38% H, 8.58% N, 6.55% S; found: 68.60% C, 6.32% H, 8.54% N, 6.52% S.

2,6-Diethoxy-1-(6-ethoxybenzothiazol-2-yl)-3,5-bis(ethoxycarbonyl)-4-(4-methoxyphenyl)-1,4-dihydropyridine (**4l**). ^{1}H NMR: 1.22 t, 6 H, *J* = 7.2 (DHP OCH_2CH_3); 1.30 t, 6 H, *J* = 7.2 (DHP $COOCH_2CH_3$); 1.33 t, 3 H, *J* = 7.0 (benzothiazole $OCH_2C\mathbf{H}_3$); 3.73 s, 3 H (Ar-OCH_3); 3.97 q, 2 H, *J* = 6.9 (benzothiazole $OC\mathbf{H}_2CH_3$); 4.00 q, 4 H, *J* = 6.9 (DHP OCH_2); 4.19 q, 4 H, *J* = 7.1 (DHP $COOCH_2$); 4.95 s, 1 H (DHP); 6.47–8.12 m, 7 H (Ar-H). IR: 1053, 1136, 1224, 1450, 1534, 1590, 1622, 1653, 1701, 2973. MS, *m/z*: calculated 596.70, found 596.65. For $C_{31}H_{36}N_2O_8S$: 62.40% C, 6.08% H, 4.69% N, 5.37% S; found: 62.35% C, 6.02% H, 4.65% N, 5.32% S.

Antimicrobial Activity

All the synthesized compounds were tested for their antibacterial activity against *Lactobacillus* sp., *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Micrococcus leutius* and *Kocuria rosea* as well as antifungal activity against *Aspergillus niger* and *Aspergillus candidus* using the paper disc method. Muller–Hinton agar (Hi-Media Pvt. Ltd. Mumbai, India) was used to for culturing of the test bacteria and potato dextrose agar was used to culture fungi. The microbial cultures were grown at 37 °C for 8 h and then appropriately diluted with sterile 0.8% saline solution. The concentration of test drugs was kept 200 μg/ml in DMF. Standard drugs novobiocine, gentamycin, kanamycin and amikacin (for antibacterial tests), and ampicilline (for antifungal tests) were used for comparison. The antimicrobial activity was evaluated by measuring the growth zone inhibition around the disc of the tested organism (Table III).

Antifeedant Activity

The antifeedant activity of the compounds was measured by the leaf dip method[38,39], using fourth instars larvae of *Spodoptera litura*. The leaf discs of ca. 25 cm^2 area were prepared and dipped for 30 s in various concentrations of the test compounds. They were air-dried to evaporate the excess of acetone and the leaf discs offered for feeding. The insects were allowed to feed for 24 h. Then the uneaten leaf area was measured with a leaf area meter. The difference between leaf area provided and the leaf area uneaten is taken as the amount of the consumed leaf area. The feeding inhibition was calculated and used for calculation of effective concentration (EC_{50}/LD_{50}) using a maximum probability programmer (MPP) 3.01. The results of antifeedant activity are summarized in Table IV.

Acaricidal Activity

The acaricidal activity of the compounds was measured by the leaf dip method[38,39]. Mulberry leaf discs (5 cm^2 diameter) were dipped in different concentrations of compounds for 30 s. The leaf discs were dried to remove excess of acetone and placed on wet cotton in Petri dish. The adult female mites were released on the treated leaf discs and the mortality data were recorded after 48 h. Mites released on leaf treated only with acetone and Tween 20

emulsifier served as control. The mortality data were used for calculation of LC_{50}/LD_{50} using a programmer MPP 3.01. The results of acaricidal activity are summarized in Table V.

Statistical Analysis

Statistical analysis of the experimental data was performed using 'Probit analysis' to find out the LC_{50}/LD_{50} values, regression, chi-square and variance[40]. The data were analyzed by completely randomized, one-way analysis of variance (ANOVA) and the means were separated using Duncan's multiple range test[41] (DMRT).

TABLE III
Antimicrobial activity of 2,3,5,6-tetrasubstituted-4-aryl-1-(6-ethoxybenzothiazol-2-yl)-1,4-dihydropyridines (**4a–4l**)

Compd.	Antibacterial activity (inhibition zone, mm)					Antifugal activity	
	B1	B2	B3	B4	B5	F1	F2
4a	15	20.0	19.0	26.0	18.0	17.0	21.0
4b	16	23.0	18.0	28.0	20.0	20.0	22.0
4c	10	17.0	16.0	22.0	15.0	15.0	16.0
4d	7.0	13.0	12.0	16.0	12.0	13.0	12.0
4e	6.0	11.0	11.0	15.0	10.0	10.0	15.0
4f	10.0	1.08	17.0	22.0	15.0	15.0	17.0
4g	9.0	15.0	16.0	19.0	14.0	12.0	18.0
4h	13.0	19.0	18.0	24.0	16.0	16.0	17.0
4i	8.0	17.0	16.0	17.0	13.0	10.0	14.0
4j	8.0	14.0	13.0	17.0	13.0	14.0	18.0
4k	14.0	22.0	17.0	25.0	17.0	17.0	20.0
4l	7.0	12.0	15.0	16.0	12.0	11.0	17.0
Benzothiazole	5.0	6.0	4.0	7.0	5.0	6.0	4.0
Novobiocin	7.0	20.0	15.0	35.0	22.0	–	–
Gentamycin	19.0	24.0	22.0	35.0	24.0	–	–
Kanamycin	7.0	11.0	18.0	25.	22.0	–	–
Amikacin	16.0	25.0	18.0	32.0	24.0	–	–
Ampicilin	–	–	–	–	–	30.0	32.0
Blank	0.0	0.0	0.0	0.0	0.0	0.0	0.0

B1, *Lactobacillus* sp.; B2, *Pseudomonas aeruginosa*; B3, *Staphylococcus aureus*; B4, *Micrococcus leutius*; B5, *Kocuria rosea*; F1, *Aspergillus candidus*; F2, *Aspergillus niger*.

TABLE IV
Antifeedant activity of 2,3,5,6-tetrasubstituted-4-aryl-1-(6-ethoxybenzothiazol-2-yl)-1,4-dihydropyridines (**4a**–**4l**)

Compound	Fiducial limits	Slope		Chi-square (3)	LC_{50}/LD_{50} 24 h
4a	0.80–3.43	0.80	0.13	0.44 (3)	1.36
4b	0.65–1.70	1.02	0.12	0.66 (3)	0.98
4c	0.42–0.84	1.03	0.14	0.35 (3)	0.58
4d	0.60–1.41	1.06	0.14	1.04 (3)	0.86
4e	0.85–2.34	1.07	0.15	0.78 (3)	1.24
4f	0.70–2.43	0.94	0.14	0.22 (3)	1.14
4g	0.32–0.48	1.27	0.14	3.40 (3)	0.38
4h	0.34–0.65	1.00	0.13	0.68 (3)	0.43
4i	0.43–1.06	0.86	0.13	1.70 (3)	0.63
4j	0.47–0.78	1.50	0.16	2.57 (3)	0.58
4k	0.29–0.51	1.01	0.13	5.35 (3)	0.40
4l	0.25–0.56	0.96	0.13	0.26 (3)	0.39

CONCLUSIONS

Antibacterial activity. 2-Amino-6-ethoxybenzothiazole (**1**) shows very low activity against all the bacteria under study. However, 2,3,5,6-tetrasubstituted-4-aryl-1-(6-ethoxybenzothiazol-2-yl)-1,4-dihydropyridine derivatives **4** show enhanced activity comparable to standard drugs. Compounds **4a**, **4b** and **4k** show a good activity against *Lactobacillus* sp. Compounds **4a**, **4b** and **4k** exhibit a significant activity against *Pseudomonas aeruginosa*. Compounds **4a**, **4b** and **4h** exhibit a significant activity against *Staphylococcus aureus*. Compounds **4a**, **4b** and **4k** exhibit a significant activity against *Micrococcus leutius*. Compounds **4b**, **4h** and **4k** exhibit a significant activity against *Kocuria rosea* (Table III).

Antifungal activity. 2,3,5,6-Tetrasubstituted-4-aryl-1-(6-ethoxybenzothiazol-2-yl)-1,4-dihydropyridines **4** exhibit higher antifungal activities as compared to 2-amino-6-ethoxybenzothiazole (**1**). Compounds **4a**, **4b**, **4h** and **4k** exhibit a good antifungal activity against *Aspergillus candidus*, though lower than the standard drug ampicilline. Compounds **4a**, **4b**, **4g**, **4j** and **4k** exhibit good antifungal activities against *Aspergillus niger*, but are less active than the standard drug ampicilline.

Antifeedant activity. It is evident from LC_{50}/LD_{50} values given in Table IV. Compound **4g** has the lowest LC_{50}/LD_{50} value, hence possessing a higher contact toxicity against insect. The decreasing order of contact toxicity of compounds is **4g > 4l > 4k > 4h > 4c = 4j > 4i > 4d > 4b > 4f > 4e > 4a**.

Acaricidal activity. It is evident from LC_{50}/LD_{50} values given in Table V. Compound **4e** has the lowest LC_{50}/LD_{50} value, hence possessing a higher contact toxicity against insect. The decreasing order of contact toxicity of compounds is **4e > 4i = 4k > 4f > 4b > 4a = 4g = 4j > 4d > 4c > 4l > 4h**.

TABLE V
Acaricidal activity of 2,3,5,6-tetrasubstituted-4-aryl-1-(6-ethoxybenzothiazol-2-yl)-1,4-dihydropyridines (**4a–4l**)

Compound	Fiducial limits	Slope		Chi-square (3)	LC_{50}/LD_{50} 24 h
4a	0.11–0.32	0.78	0.88	1.70 (3)	0.18
4b	0.12–0.24	0.88	0.08	2.14 (3)	0.15
4c	0.16–0.36	0.09	0.09	8.28 (3)	0.23
4d	0.14–0.30	0.96	0.09	7.52 (3)	0.20
4e	0.06–0.10	1.24	0.10	14.27 (3)	0.08
4f	0.09–0.24	0.65	0.07	6.12 (3)	0.13
4g	0.12–0.30	0.80	0.08	6.91 (3)	0.18
4h	0.36–1.88	0.64	0.08	3.57 (3)	0.70
4i	0.07–0.20	0.64	0.06	8.43 (3)	0.11
4j	0.12–0.30	0.78	0.08	1.70 (3)	0.18
4k	0.08–0.17	0.81	0.7	9.10 (3)	0.11
4l	0.04–0.06	0.76	0.07	15.89 (3)	0.40

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