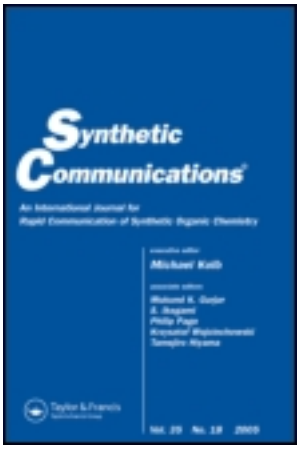

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Synthesis of Novel Asymmetrical 1,4-Dihydropyridine Derivatives

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Synthesis of Novel Asymmetrical 1,4-Dihydropyridine Derivatives

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Abstract: Asymmetrical 1,4-dihydropyridine esters **3a** and **3i**–**k** were synthesized from the symmetrical precursor **1** through the intermediate 2-bromomethyl derivative **2**. Then, compound **3a** was subjected to a different transformation for preparation of 1,4-dihydropyridine derivatives **3b**–**h**.

Keywords: Calcium channel blockers, 1,4-dihydropyridines, Hantzsch esters, Hantzsch synthesis

INTRODUCTION

The 1,4-dihydropyridine Ca^{2+} channel blockers are clinically significant antihypertensive drugs[1–3]and have been immensely valuable as molecular tools with which to probe structural and functional aspects of Ca^{2+} channel function.[4,5]

Most of the 1,4-dihydropyridines were prepared via the Hantzsch procedure,[6] employing all the components in different combinations (Scheme 1). This procedure is simple, and isolation of the product is generally straightforward. It works moderately well for symmetrical dihydropyridines, but the yield of the desired products decreases very rapidly for asymmetrically substituted dihydropyridines.[7] In this work we synthesized some new derivatives of asymmetrically substituted 1,4-dihydropyridine

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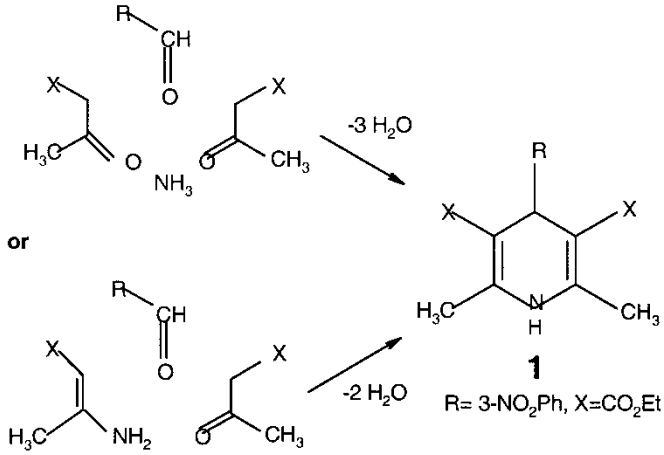


Scheme 1. Hantzsch synthesis of 1,4-DHPs.

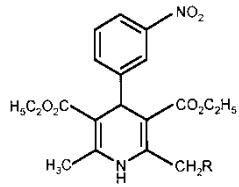
rings. The compounds **3a** and **3i–k** were synthesized by using nucleophilic attack of thiourea, 2-mercapto-4,6-dimethyl pyrimidine, 6-methyl-2-thiouracil, and sodium azide on the 2-bromomethyl-l,4-dihydropyridine **2**. The others were obtained by different transformation of isothiouronium salt **3a**.

RESULTS AND DISCUSSION

Synthesis was started by Hantzsch reaction of ethyl acetoacetate with 3-nitrobenzaldehyde and ammonia in refluxing ethanol, which afforded the 1,4-dihydropyridine **1** in 58% yield. Reaction of **1** with l. l equivalents of pyridinium bromide perbromide in dichloromethane/pyridine at $-20^{\circ}C$ for 45 min afforded the crude product **2** as a yellow gum. We have already published the synthesis of **2** in high yield[8] by modifying the literature methods.[7,9,10] Without further purification this brominated adduct was coupled with a range of nucleophiles at different conditions to give 2-substituted 1,4-dihydropyridines **3a** and **3i–k** (see Table 1).

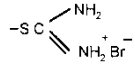
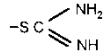
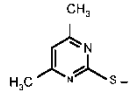
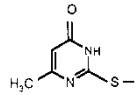
In spite of the low stability of **2**, which undergoes decomposition upon heating to yield the expected lactone. It reacts with thiourea, 2-mercapto-4,6-dimethyl pyrimidine, and sodium azide in refluxing ethanol in high to moderate yields. In the reaction of **2** with thiourea in refluxing ethanol for 5 h, evaporation of solvent, and recrystallization from EtOAc/Hex, isothiouronium salt **3a** is formed (entry 1). Transformation of isothiouronium salt **3a** into its isothiourea **3b**, as free base,was carried out by treatment of **3a** in CH_2C1_2/H_2O with Na_2CO_3 with vigorous stirring at room temperature (entry 2). Because the isothioureido group may easily be introduced and isothiourea is easily transformed, the process is particularly flexible and

Table 1. Compounds of **3**



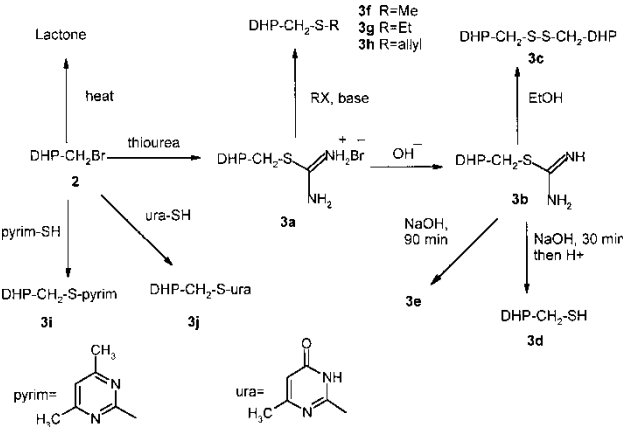
(DHP-CH_2-R)

3

Entry	Product	R	Yield (%)	Mp (°C)
1	3a		80	199.5[a]
2	3b		60	126–127
3	3c	-SSDHP	30	184–185
4	3d	-SH	45	143[a]
5	3f	-S CH_3	47	119–120
6	3g	-S $(CH_2)_5$ CH_3	55	Oil
7	3h	-S $CH_2CH = CH_2$	49	125–126.5
8	3i		80	177–178
9	3j		31	204–206
10	3k	-N_3	60	122–123

[a]It decomposes at the melting point.

adaptable to different synthetic procedures. During purification of **3b** by recrystallization from protic solvents such as ethanol, it decomposes to a thiol derivative that it is oxidized and converted to disulfide derivative **3c** (entry 3). Hydrolysis of ethanolic solution of **3b** into thiol derivative **3d** was performed under an inert gas atmosphere in the presence of aqueous sodium hydroxide solution at room temperature for 30 min (entry 4). By increasing the reaction time (1.5 h), the only product of this reaction was thiolactone derivative **3e**, which resulted from the nucleophilic attack of intermediate thiolate anion on adjacent ester group (Scheme 2). Additionally, to prepare the diasteromeric salts of **3b**, the mixture of **3b** and (1S)-(+)-camphor-10-sulfonic acid in CH_3CN was refluxed for 4 h but the product obtained was the thiol derivative **3d**. Conversely, reaction of isothiouronium salt **3a** with electrophilic species RX (methyl iodide, 1-bromo hexane, and allyl bromide) in the presence of base produces S-alkylated derivatives **3f**, **3g**, and **3h** respectively (Scheme 2). 2-Mercapto-4,6-dimethyl pyrimidine was



Scheme 2.

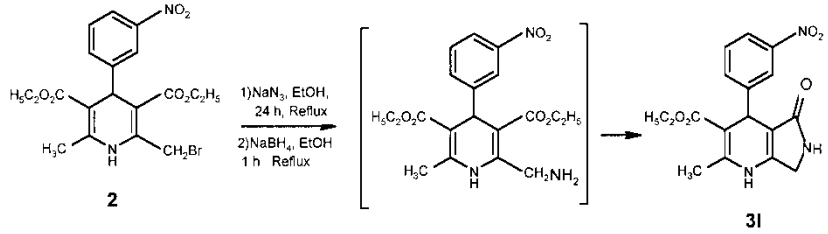
reacted easily with **2** in refluxing ethanol to give **3i** in high yield without any base (entry 8). However, reaction of 6-methyl-2-thiouracil with **2** needs basic conditions (entry 9).

The reaction of **2** with sodium azide in refluxing ethanol for 24 h gave **3 k** (entry 10). The reduction of **3 k** with $NaBH_4$ in refluxing ethanol for 1 h afforded the lactam derivative **31**, which resulted from the nucleophilic attack of in situ–obtained amin derivative on an adjacent ester group (Scheme 3).

EXPERIMENTAL

S-[(6-Methyl-3,5-dicarboethoxy-4-(3-nitrophenyl)1,4-dihydropyridin-2-yl)-methyl]-isothiouronium bromide 3a

A mixture of 2-bromomethyl-3,5-dicarboethoxy-4-(3-nitrophenyl)-6-methyl-l,4-dihydropyridine[8] (obtained from 1.34 mmol of **1**), thiourea (0.11 g,



Scheme 3.

1.47 mmol), and ethanol (40 ml) was heated to reflux for 5 h and then evaporated. Recrystallization of crude product from EtOAc/Hex furnished **3a** (0.56 g, 80%) as yellow crystals.

IR (KBr) $\bar{\nu} = 3500-2600$ (broad s), 1700 (s), 1662 (s), 1653 (s), 1528 (s), 1349 (s) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): $\delta = 1.13$ (m, 6H, 2 × CH_3 ester), 2.50 (s, 3H, CH_3-6), 4.02 (m, 4H, 2 × CH_2 ester), 4.54 (s, 2H, CH_2-2), 4.98 (s, 1H, CH-4), 7.60–8.04 (m, 4H, ArH), 9.35 (br s, 4H, NH), 10.04 (br s, 1 H, NH) ppm.

S-[(6-Methyl-3,5-dicarboethoxy-4-(3-nitrophenyl)1,4-dihydropyridin-2-yl)-methyl]-isothiourea 3b

Sodium bicarbonate (0.08 g, 0.94 mmol) was added to the miture of **3a** (0.5 g, 0.94 mmol) in CH_2Cl_2/H_2O (2 : 1, 15 ml) at room temperature and under vigorous stirring. After 30 min stirring at room temperature, the organic phase was separated, washed with water, dried over Na_2SO_4, and evaporated. Recrystallization of crude product from Et_2O furnished **3b** (0.25 g, 60%) as yellow crystals.

IR (KBr) $\bar{\nu} = 3416$ (s), 3319 (s), 3205 (m), 3066 (w), 2978 (w), 1696 (s), 1679 (s), 1637 (s), 1518 (s), 1348 (s) cm^{-1}, ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.22$ (t, $J = 8$ Hz, 6H, 2 × CH_3 ester), 2.30 (s, 3H, CH_3-6), 4.01–4.14 (m, 4H, 2 × CH_2 ester), 4.40 (AB quartet, $J = 14$ Hz, 2H, CH_2-2), 5.09 (s, 1H, CH-4), 7.37 (t, $J = 8$ Hz, 1H, ArH), 7.65 (d, $J = 8$ Hz, 1H, ArH), 8.00 (m, 1H, ArH), 8.15 (m, 1H, ArH), 10.04 (br s, 1H, NH); anal, calcd. for $C_{20}H_{24}N_4O_6S$: C, 53.57; H, 5.35; N, 12.50. Found: C, 53.44; H, 5.60; N, 12.64.

Bis-[(6-Methyl)-3,5-dicarboethoxy-4-(3-nitrophenyl)1,4-dihydropyridin-2-yl)-methyl]-disulfide 3c

After preparation of **3b** recrystallization was performed in EtOH and **3c** was obtained in 30% yield.

IR (KBr) $\bar{\nu} = 3320$ (s), 3100 (m), 2985 (m), 1700 (s), 1355 (s) cm^{-1}; ^1H NMR (400 MHz, $CDC1_3$): $\delta = 1.17$ (t, $J = 8$ Hz, 12H, 4 × CH_3 ester), 2.22 (s, 6H, CH_3-6, CH_3-6′), 3.99–4.06 (m, 12H, 4 × CH_2 ester, CH_2-2, CH_2-2′), 5.06 (s, 2H, H-4, H-4′), 6.77 (br s, 2H, NH), 7.29–8.10 (m 8H, ArH ppm; anal. calcd. for $C_{38}H_{42}N_4O_{12}S_2$: C, 56.29; H, 5.22; N, 6.91. Found: C, 56.0; H, 5.30; N, 6.82.

2-Mercaptomethyl-3,5-dicarboethoxy-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine 3d

An aqueous solution of NaOH (32%, 0.5 ml) was added to a stirred solution of **3a** (0.5 g, 0.94 mmol) in ethanol/water (1 : 1, 25 ml) under an argon

atmosphere. After 30 min stirring, at rt and evaporating the solvent, the residue was partitioned between CH_2C1_2 and 2 M HCI, and the organic layer washed with water, dried over Na_2SO_4, and evaporated. The crude product was purified by column chromatography on silica gel using EtOAc/Hex 3 : 2 as eluent. An appropriate fraction ($R_f = 0.75$) was obtained (0.17 g, 45%) as a yellow solid.

IR (KBr) $\bar{\nu} = 3340$ (s), 3050 (w), 2963–2850 (m), 2510 (w), 1700 (s), 1650 (s), 1529 (s), 1497 (s), 1373 (s), 1261 (s), 1214 (s), 1095 (s), 801 (s) cm^{-1}; ^1H NMR (400 MHz, $CDC1_3$): $\delta = 1.22$ (t, $J = 8$ Hz, 6H, 2 × CH_3 ester), 2.02 (m, 1H, SH), 2.39 (s, 3H, CH_3-6), 3.80 (m, 1H, H-2), 3.95 (m, 1H, H-2), 4.08 (m, 4H, 2 × CH_2 ester), 5.09 (s, 1H, CH-4), 6.56 (s, 1H, NH), 7.38 (t, $J = 8$ Hz, 1H, ArH), 7.63 (d, $J = 8$ Hz, 1H, ArH), 8.00 (d, $J = 8$ Hz, 1H, ArH), 8.12 (s, 1 H, ArH) ppm.

Thiolactone Derivative 3e

The experimental procedure is the same as for **3d**, only the reaction time was increased to 90 min. The compound **3e** ($R_f = 0.15$ in EtOAc/Hex 3 : 2) was obtained in 57% yield.

Mp 171–172°C; IR (KBr) $\bar{\nu} = 3320$ (s), 3080 (w), 2963–2850 (m), 1700 (s), 1645 (s), 1520 (m), 1490 (s), 1350 (s) 1261 (s), 1100 (s), 800 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.13$ (t, $J = 7.2$ Hz, 3H, CH_3 ester), 2.43 (s, 3H, CH_3-6), 3.87 (AB quartet, $J = 20$ Hz, 2H, CH_2-2), 4.03 (q, $J = 7.2$ Hz, 2H, CH_2 ester), 5.09 (s, 1H, CH-4), 7.38 (s, 1H, NH), 7.43 (t, $J = 8$ Hz, 1H, ArH) 7.68 (d, $J = 8$ Hz, 1H, ArH), 8.04 (m, 1H, ArH) ppm; anal. calcd. for $C_{17}H_{16}N_2O_5S$: C, 60.00; H, 4.70; N, 8.23. Found: C, 60.40; H, 4.86; N, 8.63.

2-(Methyl thio)-methyl-3,5-dicarboethoxy-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine 3f

An aqueous solution of NaOH (32%, 1 ml) was added to a stirred solution of **3a** (1 g, 1.89 mmol) and methyl iodide (1.22 g, 4.54 mmol) in ethanol/water (1 : 1, 40 ml) under an argon atmosphere. After 3 h stirring at room temperature, the mixture was filtered. Recrystallization of the crude product from ethanol furnished compound **3f** in 47% yield.

IR (KBr) $\bar{\nu} = 3320$ (s), 3094 (w), 2980–2850 (m), 1676 (s), 1644 (m), 1620 (m), 1527 (s), 1494 (s), 1351 (s), 1289 (s), 1212 (s), 1101 (s) cm^{-1}; ^1H NMR (400 MHz, $CDC1_3$): $\delta = 1.16$ (t, $J = 7.2$ Hz, 6H, 2 × CH_3 ester), 1.99 (s, 3H, S-CH_3), 2.34 (s, 3H, CH_3-6), 3.86–4.07 (m, 6H, 2 × CH_2 ester, CH_2-2), 5.06 (s, 1H, H-4), 6.92 (s, lH, NH), 7.31 (t, $J = 7.6$ Hz, 1H, ArH) 7.57 (d, $J = 7.6$ Hz, IH, ArH), 7.94 (d, $J = 7.6$ Hz, 1H, ArH), 8.07 (s, 1H, ArH) ppm; anal. calcd. for $C_{20}H_{24}N_2O_6S$: C, 57.14; H, 5.71; N, 6.66. Found: C, 57.51; H, 5.83; N, 7.05.

2-(*n*-Hexyl thio)-methyl-3,5-dicarboethoxy-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine 3g

An aqueous solution of NaOH (32%, 1 ml) was added to a stirred solution of **3a** (1 g, 1.89 mmol) and 1-bromo hexane (0.74 g, 4.54 mmol) in ethanol/water (1:1, 40 ml) under an argon atmosphere. After 20 h stirring at room temperature, the mixture was diluted with water (10 ml) and extracted with CH_2C1_2 (20 ml). The organic phase was washed with 2 M HCl and water, dried over Na_2SO_4, and evaporated. The crude product was purified by preparative chromatography on silica gel using EtOAc/hexane 2:3 as eluent. An appropriate fraction ($R_f = 0.65$) was obtained as a yellow oil in 55% yield.

IR (neat) $\bar{\nu} = 3350$ (m), 3020 (w), 2962 (m), 1688 (s), 1529 (s), 1474 (s), 1351 (s), 1216 (s), 1100 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.77$ (t, $J = 7.2$ Hz, 3H, CH_3), 1.09–1.27 (m, 12H, 2 × CH_3 ester, 3 × CH_2), 1.42–1.49 (m, 2H, CH_2), 2.33 (s, 3H, CH_3-6), 2.39 (t, $J = 7.2$ Hz, 2H S-CH_2), 3.88–4.08 (m, 6H, 2 × CH_2 ester, CH_2-2), 5.06 (s, 1H, CH-4), 7.08 (s, lH, CH-4), 7.31 (t, $J = 8$ Hz, 1H, ArH), 7.56 (m, 1H, ArH), 7.93 (m, lH, ArH), 8.06 (m, lH, ArH) ppm; anal. calcd. for $C_{25}H_{32}N_2O_6S$: C, 61.22; H, 6.94; N, 5.71. Found: C, 60.96; H, 6.91; N, 6.03.

2-(Allyl thio)-methyl-3,5-dicarboethoxy-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine 3h

An aqueous solution of NaOH (32%, 1 ml) was added to a stirred solution of **3a** (1 g, 1.89 mmol) and allyl bromide (0.55 g, 4.54 mmol) in ethanol/water (1:1, 40 ml) under an argon atmosphere. After 1 h stirring at room temperature, the mixture was filtered. Recrystallization of the crude product from ethanol furnished compound **3h** as yellow needle crystals in 49% yield.

IR (KBr) $\bar{\nu} = 3319$ (s), 3091 (w), 2978–2850 (m), 1675 (s), 1639 (m), 1619 (m), 1527 (s), 1350 (s), 1288 (s), 1211 (s), 1101 (s) cm^{-1}; ^1H NMR (500 MHz, $CDC1_3$): $\delta = 1.16$ (t, $J = 6.8$ Hz, 6H, 2 × CH_3 ester), 2.35 (s, 3H, CH_3-6), 3.05 (d, $J = 7.2$ Hz, 2H, S-CH_2), 3.88–4.10 (m, 6H, 2 × CH_2 ester, CH_2-2), 4.93–5.02 (m, 2H,=CH_2), 5.06 (s, 1H, CH-4), 5.66–5.76 (m, 1H,=CH), 6.93 (s, lH, NH), 7.31 (t, $J = 6.8$ Hz, 1H, ArH), 7.57 (d, $J = 7.6$ Hz, 1H, ArH), 7.96 (m, 1H, ArH), 8.06 (m, lH, ArH) ppm; anal. calcd. for $C_{22}H_{26}N_2O_6S$: C, 59.19; H, 5.83; N, 6.27. Found: C, 58.83; H, 5.89; N, 6.42.

2-[(4,6-Dimethyl Pyrimidin-2-yl)thio-]-methyl-3,5-dicarboethoxy-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine 3i

A mixture of 2-bromomethyl-3,5-dicarboethoxy-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine (obtained from 2.3 mmol of **1**), 2-mercapto-4,6-

dimethyl pyrimidine (0.35 g, 2.5 mmol), and ethanol (20 ml) was heated to reflux for 0.5 h and then evaporated. The residue was partitioned between CH_2Cl_2 (30 ml) and saturated Na_2CO_3 solution, and the organic layer, was washed with water, dried over Na_2SO_4, and evaporated. Recrystallization of crude product from 2-propanol furnished **3i** 0.942 g, 80%) as yellow crystals.

IR (KBr) $\bar{\nu} = 3350$ (s), 3050 (m), 2982 (m), 1689 (s), 1647 (s), 1532 (s), 1348 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.23$ (m, 6H, $2 \times CH_3$ ester), 2.29 (s, CH_3-6), 2.50 (s, 6H, $2 \times CH_3$), 4.00–4.20 (m, 4H, $2 \times CH_2$ ester), 4.52 (AB quartet, $J = 18$ Hz, 2H, CH_2-2), 5.10 (s, 1H, CH-4), 6.83 (s, 1H, H-5 pyrimidine), 7.35–8.15 (m, 4H, ArH), 8.75 (br s,1H, NH) ppm; anal. calcd. for $C_{25}H_{28}N_4O_6S$: C, 58.58; H, 5.51; N, 10.93. Found: C, 58.60; H, 5.35; N, 11.00.

2-(6-Methyl-2-thiouracil-2-yl)-methyl-3,5-dicarboethoxy-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine 3j

A mixture of 6-methyl-2-thiouracil (0.04 g, 0.3 mmol), aq. NaOH (3 ml, 0.3 mmol), and MeOH (20 ml) was stirred at rt for 1 h. Then 2-bromomethyl-3,5-dicarboethoxy-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine (obtained from 0.8 mmol of **1**) was added and the mixture stirred at room temperature for 2 h. After evaporating the solvent, the residue was partitioned between CH_2C1_2 and 2M HCI, the organic layer was washed with water, dried over Na_2SO_4, and evaporated. Recrystallization of crude product from 2-propanol furnished **3j** (0.27 g, 31%) as yellow crystals.

IR (KBr) $\bar{\nu} = 3208$, 3082, 1676, 1585, 1525, 1348 cm^{-1}; ^1H NMR (500 MHz, $CDC1_3$): $\delta = 1.23$ (m, 6H, $2 \times CH_3$ ester), 2.34 (s, 3H, CH_3-6), 2.41 (s, 3H, CH_3), 4.02–4.17 (m, 4H, $2 \times CH_2$ ester), 4.55 (d, $J = 14.5$ Hz, 1H, CH_2-2), 4.63 (d, $J = 14.5$ Hz, 1H, CH_2-2), 5.01 (s, 1H, CH-4), 6.16 (s, 1H, H-5 uracil), 7.39–8.15 (m, 4H, ArH), 8.53 (br s, 1H, NH), 13.01 (br s, IH, NH) ppm; anal. calcd. for $C_{24}H_{26}N_4O_7S$: C, 56.03; H, 5.05; N, 10.89. Found: C, 56.23; H, 5.01; N, 11.03.

2-Azidomethyl-6-methyl-3,5-dicarboethoxy-4-(3-nitrophenyl)-1,4-dihydropyridine 3k

A mixture of 2-bromomethyl-3,5-dicarboethoxy-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine (obtained from 2.67 mmol of **1**), sodium azide (0.18 g, 2.84 mmol) and ethanol (40 ml) was heated to reflux for 24 h and then evaporated. The residue was partitioned between CH_2C1_2 (20 ml) and 2 M HCl solution, and the organic layer was washed with water, dried over Na_2SO_4, and evaporated. Recrystallization of crude product from Et_2O furnished **3k** in 60% yield.

IR (KBr) $\bar{\nu} = 3354$ (s), 3050 (w), 2978–2850 (m), 2107 (s), 1693 (s), 1653 (m), 1625 (m), 1527 (s), 1487 (s), 1351 (s), 1273 (s), 1200 (s), 1099 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.22$ (m, 6H, $2 \times CH_3$ ester), 2.41 (s, 3H, CH_3-6), 4.09 (m, 4H, $2 \times CH_2$ ester), 4.82 (AB quartet, $J =$ Hz, 2H, CH_2-2), 5.10 (s, 1H, CH-4), 6.69 (s, 1H, NH), 7.39 (t, $J = 6.8$ Hz, lH, ArH), 7.62 (m, 1H, ArH), 8.03 (m, 1H, ArH), 8.12, (m, 1H, ArH) ppm; anal. calcd. for $C_{19}H_{21}N_5O_6$: C, 54.94; H, 5.06; N, 16.86. Found: C, 55.06; H, 5.10; N, 16.54.

Lactam Derivative 3l

A mixture of **3k** (0.1 g, 0.24 mmol), sodium borohydride (0.03 g, 0.96 mmol), and ethanol (20 ml) was heated to reflux for 1 h and then evaporated. The residue was partitioned between CH_2Cl_2 (20 m1) and 10% HCl solution, and the organic layer was washed with water, dried over Na_2SO_4, and evaporated. Recrystallization of crude product from CH_2C1_2/Hex furnished **31** in 54% yield.

Mp 225–227°C; IR (KBr) $\bar{\nu} = 3354$ (s), 3250 (m), 3060 (w), 2978–2850 (w), 1671 (s), 1524 (s), 1346 (s), 1203 (s), 1088 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.11$ (t, $J = 8$ Hz, 3H, CH_3 ester), 2.41 (s, 3H, CH_3-6), 3.83–4.14 (m, 4H, CH_2 ester and CH_2-2): 5.05 (s, lH, CH-4), 6.08 (s, lH, NH), 6.94 (s, lH, NH), 7.39 (t, $J = 8$ Hz, lH, ArH) 7.69 (d, $J = 8$ Hz, lH, ArH), 7.99 (d, $J = 8$ Hz, 1H, ArH), 8.10 (s, 1H, ArH) ppm.

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