

## SYNTHESIS OF NEW UNSYMMETRICAL 1,4-DIHYDROPYRIDINE DERIVATIVES AS POTENTIAL ANTICANCER AGENTS

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### Abstract

The 1,4-dihydropyridine structure is a very versatile and drug feasible template allowing multiple structural modulations and the resulted molecules can exert potent and selective actions on a large spectrum of biological targets. As a continuation of our previous research focused on the 1,4-dihydropyridine scaffold we designed and synthesized some new methyl 5-alkyl/aryl-carbamoyl-2,6-dimethyl-4-(substituted-phenyl)-1,4-dihydropyridine-3-carboxylate derivatives. The obtained compounds were characterized by elemental, IR and NMR analyses and are proposed for antitumor evaluation.

### Rezumat

Structura 1,4-dihidropiridinică reprezintă un „tipar” medicamentos foarte versatil și fezabil, care permite multiple modulații structurale, moleculele rezultate putând exercita acțiuni puternice și selective la nivelul unui spectru larg de ținte biologice. Ca o continuare a cercetărilor noastre anterioare axate pe scheletul structural al 1,4-dihidropiridinelor, am proiectat și sintetizat noi derivați ai 5-alchil/aryl-carbamoil-2,6-dimetil-4-(fenil substituit)-1,4-dihidropiridin-3-carboxilatului de metil. Compușii nou obținuți au fost caracterizați prin analize elementală, IR și RMN și sunt propuși pentru evaluare antitumorală.

**Keywords:** 1,4-dihydropyridine, antitumor, Hantzsch reaction, privileged structures

### Introduction

The first 1,4-dihydropyridines were synthesized in 1881 by Hantzsch in the reaction that now bears his name, but the first derivative was clinically used in the early 1970s. Nifedipine is the first and a prototypical example of the 1,4-dihydropyridine calcium channel blockers class, compounds with major cardiovascular usefulness [20]. Since the discovery of nifedipine and the development of several calcium channel blockers, many other effects were recorded for the 1,4-dihydropyridines derivatives.

Some 1,4-dihydropyridines showed promising activity against *Leishmania* and *Trypanosoma* parasites, especially those containing diphenylpropyl and diphenylmethy-azetidin groups at position 4 of the 1,4-dihydropyridine ring [17]. A series of N-aryl-1,4-dihydropyridines were synthesized and screened for their antidyslipidemic and antioxidant activity exhibiting promising lipid and triglyceride lowering activity, associated with antioxidant effects [8]. Recent studies showed that 3,5-dicarbamoyl derivatives of 1,4-dihydropyridine have considerable anti-tubercular activity against *M. tuberculosis* H37Rv [2]. An important anti-tubercular activity was also demonstrated for unsymmetrical 1,4-dihydropyridines alkyl or aryl esters substituted in C-3 and containing a diethyl carbamoyl group at the C-5 [7]. A new series of thiosemicarbazide substituted 1,4-dihydropyridine derivatives were developed as anticoagulant agents [9]. The 1,4-dihydropyridine derivatives have a wide range of other beneficial biological effects, such as anticonvulsant, antidiabetic, analgesic, hypnotic and anti-inflammatory [1,6]. The multifunctional pharmacological usefulness of the 1,4-dihydropyridine nucleus renders it into the class of “*privileged structures*”, a term formally introduced by Evans to describe pluripotent chemical templates [3].

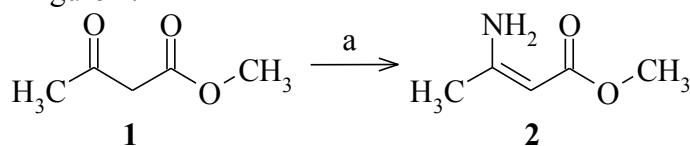
In our on-going project to find new potential antitumor substances [15,16] and as a continuation of our previous research focused on the 1,4-dihydropyridine structure [4-5,11-14,18] we capitalized the versatility of the 1,4-dihydropyridine scaffold and designed new methyl 5-alkyl/aryl-carbamoyl -2,6- dimethyl -4- (substituted-phenyl) -1,4- dihydropyridine -3 carboxylate derivatives. The potential uses of the 1,4-dihydropyridine moiety in the chemotherapy of cancer is well documented and is based on its ability to reverse the drug resistance in cancer treatment [10,21].

#### **Materials and Methods**

All starting materials and solvents were purchased from common commercial suppliers and were used without purification unless otherwise noted. The melting points were measured in open capillary tubes on an Electrothermal 9100 apparatus and are uncorrected. The elemental analyses were performed on a Perkin Elmer CHNS/O Analyser Series II 2400 apparatus. The IR spectra were recorded on a JASCO FT/IR-4200 spectrometer with an ATR PRO450-S accessory. The NMR spectra were recorded on a Gemini 300BB instrument at room temperature, operating at 300 MHz for  $^1\text{H}$  and 75.075 MHz for  $^{13}\text{C}$ . The chemical shifts are presented as  $\delta$  values in ppm units downfield to tetrametylsilane (TMS), used as internal standard. The coupling constants values are reported in hertz and

the splitting patterns are abbreviated as follows: s, singlet; d, doublet; t, triplet; m, multiplet; b, broad.

**The synthesis of methyl-3-aminocrotonate (2).** In a three-neck round-bottom flask, the methyl acetoacetate (23.2 g, 0.2 mol) was heated while stirring at 50-55°C. Over an interval of two hours, a 25% ammonia solution (16.5 mL) was slowly added using a dropping funnel, keeping the reaction temperature at 55°C. After the ammonia was fully added, the reaction mixture was still heated at 55°C for another hour and subsequently diluted with water (20 mL) and cooled at 10°C. After two hours the resulted solid was filtered and washed with cold water. Methyl-3-aminocrotonate resulted as a white substance, mp 80-2°C, yield 70%. The reaction is presented in Figure 1.



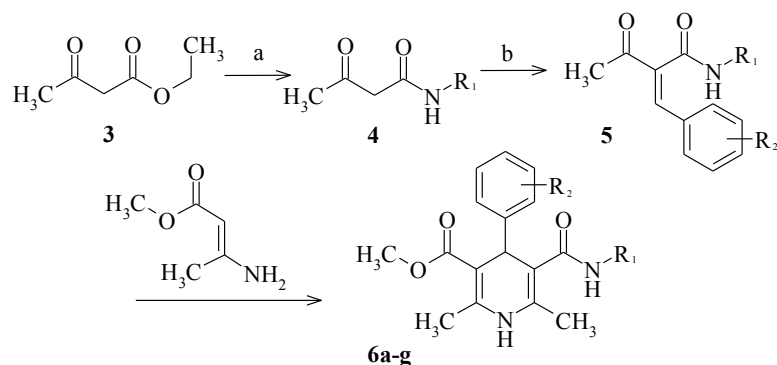
**Figure 1**

Synthesis of methyl-3-aminocrotonate. Reagents: (a) 25% NH<sub>3</sub> (aq), 55°C.

**The synthesis of N-substituted-acetoacetamide (4).** A mixture of ethyl acetoacetate (13 g, 0.1 mol), xylene (50 mL) and pyridine (0.1 mL) was refluxed under stirring, while gradually adding a solution of xylene (30 mL), pyridine (0.1 mL) and the suitable substituted amine (0.1 mol). The resulting ethanol was distilled as the reaction was completed and then the xylene was removed by distillation. The mixture was cooled on ice and the precipitate was filtered and recrystallized from xylene.

**The synthesis of N-R<sub>1</sub>-2-(R<sub>2</sub>-benzylidene-3-oxo-butanamide derivatives (5).** A mixture of isopropanol (12 mL), a substituted benzaldehyde (0.1 mol), the suitable N-substituted acetoacetamide, benzoic acid (10 mg) and piperidine (30 mg) was stirred at room temperature for 15-20 hours, cooled and afterwards filtered. The obtained N-R<sub>1</sub>-2-(R<sub>2</sub>-benzylidene-3-oxo-butanamides were recrystallized from isopropanol.

**The synthesis of the new methyl 4-(R<sub>2</sub>-phenyl)-5-(R<sub>1</sub>-carbamoil)-2,6-dimethyl-1,4-dihydropyridine-3-carboxylate (6a-g).** Methyl-3-aminocrotonate (0.1 mol) and the 2-benzylidene-3-oxobutanamide derivative (0.1 mol) were dissolved in isopropyl alcohol and refluxed for 5 hours. The mixture was cooled and the 1,4-dihydropyridine derivatives were filtered and purified by recrystallization from an ethanol water mixture (9:1). The general synthesis method is outlined in Figure 2.

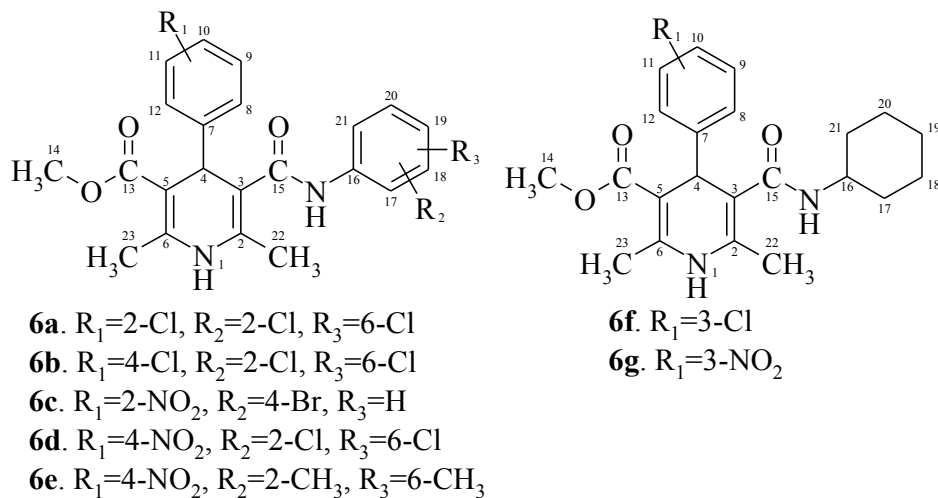


**Figure 2**

Synthesis of the new 1,4-dihydropyridine derivatives. Reagents: (a)  $R_1$ -NH<sub>2</sub>, C<sub>6</sub>H<sub>4</sub>(CH<sub>3</sub>)<sub>2</sub>, C<sub>5</sub>H<sub>5</sub>N; (b)  $R_2$ -C<sub>6</sub>H<sub>4</sub>CHO, C<sub>3</sub>H<sub>7</sub>OH, C<sub>5</sub>H<sub>11</sub>N, C<sub>6</sub>H<sub>5</sub>COOH.

### Results and Discussion

Following the aforementioned synthesis procedure, we obtained 7 new **4-(R<sub>2</sub>-phenyl)-5-(R<sub>1</sub>-carbamoyl)-2,6-dimethyl-1,4-dihydropyridine-3-carboxylates**, solid crystalline, white or yellow compounds that were characterized by NMR and IR spectra. The compound's purity was certified by elemental analyses, the results being within  $\pm 0.4$  of the calculated values. In the following there are presented the reaction yield, melting point, elemental composition and the spectral data for the new compounds **6a-g**.



**Figure 3**

Designing the new 1,4-dihydropyridine derivatives

**Methyl 4-(2-chlorophenyl)-5-((2,6-dichlorophenyl)carbamoyl)-2,6-dimethyl-1,4-dihydropyridine-3-carboxylate (6a).** Yield 51%, mp 196-7°C (ethanol).

Calculated for  $C_{22}H_{19}Cl_3N_2O_3$ : C, 56.73; H, 4.10; N, 6.01. Found: C, 56.88; H, 4.21; N, 5.86.

$^1H$ -NMR ( $CDCl_3$ ,  $\delta$  ppm, J Hz): 7.59 (s, 1H, NH); 7.38 (s, 1H, NH); 7.31 (dd, 7.7, 1.9, 1H, H-9); 7.07 (t, 8.9, 1H, H-11); 6.85-7.05 (m, 5H, H-10, H-12, H-18-20); 5.20 (s, 1H, H-4); 3.39 (s, 3H, H-14); 2.10 (s, 6H, H-22-23);

$^{13}C$ -NMR ( $CDCl_3$ ,  $\delta$  ppm, J Hz): 167.96 (C-13(15)); 166.37 (C-15(13)); 146.16 (Cq); 145.44 (Cq); 142.19 (Cq); 133.47 (C-17, C-21); 132.97 (Cq); 131.56 (CH); 131.18 (Cq); 129.18 (CH); 129.06 (CH); 128.32 (CH); 127.87 (CH); 127.34 (CH); 105.80 (C-3(5)); 101.21 (C-5(3)); 50.47 (C-14); 39.96 (C-4); 18.97 (C-22(23)); 18.01 (C-23(22)).

FT-IR ( $\nu$ ,  $cm^{-1}$ ): 3301 (NH), 3251 (CONH), 2958 ( $CH_3$ ), 1656 ( $CH_3OCO$ ), 1601 (CONH), 1228 ( $CH_3OCO$ ).

**Methyl 4-(4-chlorophenyl)-5-((2,6-dichlorophenyl)carbamoyl)-2,6-dimethyl-1,4-dihydropyridine-3-carboxylate (6b).** Yield 41%, mp 199-200°C (ethanol).

Calculated for  $C_{22}H_{19}Cl_3N_2O_3$ : C, 56.73; H, 4.10; N, 6.01. Found: C, 57.02; H, 3.91; N, 6.19.

$^1H$ -NMR ( $CDCl_3$ ,  $\delta$  ppm, J Hz): 7.48 (s, 1H, NH); 7.22 (d, 8.5, 2H, H-9, H-11); 7.15 (d, 8.4, 2H, H-8, H-12); 7.10 (d, 8.4, 2H, H-18, H-20); 6.96 (t, 8.4, 1H, H-19); 4.83 (s, 1H, H-4); 3.52 (s, 3H, H-14); 2.21 (s, 3H, H-22(23)); 2.16 (s, 3H, H-22(23)).

$^{13}C$ -NMR ( $CDCl_3$  + DMSO- $d_6$ ,  $\delta$  ppm, J Hz): 167.71 (C-13(15)); 166.28 (C-15(13)); 145.60 (C-2(6)); 145.00 (C-6(2)); 132.77 (Cq), 132.71 (Cq), 132.04 (Cq), 129.05 (CH); 128.50 (CH); 128.32 (CH); 127.34 (Cq); 127.89 (C-19); 103.60 (C-3(5)); 101.21 (C-5(3)); 50.47 (C-14); 39.96 (C-4); 18.98 (C-22(23)); 14.01 (C-23(22)).

FT-IR ( $\nu$ ,  $cm^{-1}$ ): 3311 (NH), 3240 (CONH), 2932 ( $CH_3$ ), 1656 ( $CH_3OCO$ ), 1603 (CONH), 1223 ( $CH_3OCO$ ).

**Methyl 5-((4-bromophenyl)carbamoyl)-2,6-dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3-carboxylate (6c).** Yield 42%, mp 238-9°C (ethanol).

Calculated for  $C_{22}H_{20}BrN_3O_5$ : C, 54.34; H, 4.15; N, 8.64. Found: C, 54.28; H, 4.17; N, 8.86.

$^1H$ -NMR ( $CDCl_3$  + DMSO- $d_6$ ,  $\delta$  ppm, J Hz): 8.96 (s, 1H, NH); 8.09 (s, 1H, NH); 7.60 (m, 2H, H-9, H-12); 7.48 (m, 1H, H-11); 7.43 (d, 9.1, 2H, H-18, H-20); 7.25 (d, 9.1, 2H, H-17, H-21); 7.18 (m, 1H, H-10); 5.56 (s, 1H, H-4); 3.47 (s, 3H, H-14); 2.45 (s, 3H, H-22(23)); 2.20 (s, 3H, H-22(23)).

$^{13}C$ -NMR ( $CDCl_3$  + DMSO- $d_6$ ,  $\delta$  ppm, J Hz): 167.05 (C-13(15)); 165.54 (C-15(13)); 146.91 (C-2(6)); 146.87 (Cq); 145.74 (C-6(2)); 141.20 (C-8); 138.07 (Cq); 133.91 (C-11); 131.58 (C-12); 131.31 (C-18, C-20); 127.62 (C-10); 123.49 (C-9); 121.74 (C-17, C-21); 115.60 (C-19); 103.78 (C-3(5)); 101.48 (C-5(3)); 50.74 (C-14); 34.29 (C-4); 19.39 (C-22(23)); 18.99 (C-23(22)).

FT-IR ( $\nu$ ,  $\text{cm}^{-1}$ ): 3352 (NH), 3278 (CONH), 2945 ( $\text{CH}_3$ ), 1657 ( $\text{CH}_3\text{OCO}$ ), 1601 (CONH), 1216 ( $\text{CH}_3\text{OCO}$ ).

**Methyl 5-((2,6-dichlorophenyl)carbamoyl)-2,6-dimethyl-4-(4-nitrophenyl)-1,4-dihydropyridine-3-carboxylate (6d).** Yield 39%, mp 215-6°C (ethanol).

Calculated for  $\text{C}_{22}\text{H}_{19}\text{Cl}_2\text{N}_3\text{O}_5$ : C, 55.48; H, 4.02; N, 8.82. Found: C, 55.60; H, 4.11; N, 9.03.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ,  $\delta$  ppm, J Hz): 8.08 (d, 8.4, 2H, H-9, H-11); 7.51 (d, 8.4, 2H, H-8, H-12); 7.14 (s, 1H, NH); 7.06 (m, 3H, H-18-20); 5.08 (s, 1H, H-4); 3.61 (s, 3H, H-14); 2.30 (s, 3H, H-22(23)); 2.27 (s, 3H, H-22(23)).

$^{13}\text{C-NMR}$  ( $\text{CDCl}_3$  + DMSO- $d_6$ ,  $\delta$  ppm, J Hz): 167.75 (C-13(15)); 166.41 (C-15(13)); 153.91 (C-10); 146.51 (C-2(6)); 141.58 (C-6(2)); 138.17 (C-16); 133.17 (C-17, C-21); 132.61 (Cq); 128.01 (Cq); 128.84 (CH); 128.34 (CH); 128.01 (CH); 123.86 (C-9, C-11); 105.56 (C-3(5)); 100.89 (C-5(3)); 51.06 (C-14); 41.20 (C-4); 19.57 (C-22(23)); 18.51 (C-23(22)).

FT-IR ( $\nu$ ,  $\text{cm}^{-1}$ ): 3385 (NH), 3289 (CONH), 2953 ( $\text{CH}_3$ ), 1699 ( $\text{CH}_3\text{OCO}$ ), 1641 (CONH), 1203 ( $\text{CH}_3\text{OCO}$ ).

**Methyl 5-((2,6-dimethylphenyl)carbamoyl)-2,6-dimethyl-4-(4-nitrophenyl)-1,4-dihydropyridine-3-carboxylate (6e).** Yield 37%, mp 139-40°C (ethanol).

Calculated for  $\text{C}_{24}\text{H}_{25}\text{N}_3\text{O}_5$ : C, 66.19; H, 5.79; N, 9.65. Found: C, 66.06; H, 5.81; N, 9.83.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ,  $\delta$  ppm, J Hz): 7.94 (d, 8.2, 2H, H-9, H-11); 7.59 (s, 1H, NH); 7.40 (d, 8.2, 2H, H-8, H-12); 6.82 (m, 3H, H-18-20); 4.97 (s, 1H, H-4); 3.46 (s, 3H, H-14); 2.14 (s, 6H, H-22, H-23); 1.76 (s, 6H, H-17', H-21').

$^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ ,  $\delta$  ppm, J Hz): 167.70 (C-13(15)); 166.30 (C-15(13)); 154.63 (C-10); 147.09 (C-2(6)); 146.41 (C-6(2)); 139.35 (Cq); 135.17 (C-17, C-21); 134.44 (Cq); 128.84 (CH); 127.96 (C-8, C-12); 127.31 (Cq); 126.76 (CH); 123.61 (C-9, C-11); 106.54 (C-3(5)); 99.81 (C-5(3)); 50.85 (C-14); 41.56 (C-4); 19.60 (C-22', C-23'); 18.47 (C-22(23)); 18.30 (C-23(22)).

FT-IR ( $\nu$ ,  $\text{cm}^{-1}$ ): 3385 (NH), 3288 (CONH), 2931 ( $\text{CH}_3$ ), 1700 ( $\text{CH}_3\text{OCO}$ ), 1602 (CONH), 1224 ( $\text{CH}_3\text{OCO}$ ).

**Methyl 4-(2-chlorophenyl)-5-(cyclohexylcarbamoyl)-2,6-dimethyl-1,4-dihydropyridine-3-carboxylate (6f).** Yield 45%, mp 250-1°C (ethanol).

Calculated for  $\text{C}_{22}\text{H}_{27}\text{ClN}_2\text{O}_3$ : C, 65.58; H, 6.75; N, 6.95. Found: C, 65.39; H, 6.81; N, 7.09.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ,  $\delta$  ppm, J Hz): 7.23 (t, 1.4, 1H, H-8); 7.18 (m, 3H, H-10-12); 5.88 (sl, 1H, NH); 5.19 (d, 7.9, 1H, NH); 4.70 (s, 1H, H-4); 3.70 (m, 1H, H-16); 3.62 (s, 3H, H-14); 2.28 (s, 3H, H-22(23)); 2.18 (s, 3H, H-22(23)); 0.90-1.80 (m, 10H, H-17-21).

$^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ ,  $\delta$  ppm, J Hz): 167.97 (C-13(15)); 167.39 (C-15(13)); 148.92 (C-2(6)); 145.71 (C-6(2)); 137.27 (Cq); 134.52 (Cq); 127.80 (CH); 127.01 (CH); 125.78 (CH); 123.77 (CH); 107.97 (C-3(5)); 100.98 (C-5(3)); 50.94 (C-14);

47.97 (C-16); 41.46 (C-4); 33.03 (CH<sub>2</sub>); 25.55 (CH<sub>2</sub>); 24.58 (CH<sub>2</sub>); 19.99 (C-22(23)); 18.20 (C-23(22)).

FT-IR (ν, cm<sup>-1</sup>): 3306 (NH), 3250 (CONH), 2932 (CH<sub>3</sub>), 1677 (CH<sub>3</sub>OCO), 1602 (CONH), 1224 (CH<sub>3</sub>OCO).

**Methyl 5-(cyclohexylcarbamoyl)-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylate (6g).** Yield 47%, mp 202-3°C (methanol).

Calculated for C<sub>22</sub>H<sub>27</sub>N<sub>3</sub>O<sub>5</sub>: C, 63.91; H, 6.58; N, 10.16. Found: C, 64.08; H, 6.77; N, 10.08.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, δ ppm, J Hz): 7.99 (t, 1.9, 1H, H-8); 7.89 (ddd, 7.8, 1.9, 1.1, 1H, H-10); 7.52 (ddd, 7.8, 1.9, 1.1, 1H, H-12); 7.30 (t, 7.8, 1H, H-11); 7.23 (s, 1H, NH); 5.42 (d, 8.1, 1H, CONH); 4.78 (s, 1H, H-4); 3.61 (m, 1H, H-16); 3.49 (s, 3H, H-14); 2.21 (s, 3H, H-22(23)); 2.04 (s, 3H, H-22(23)); 1.70-0.90 (m, 10H, H-17-21).

<sup>13</sup>C-NMR (CDCl<sub>3</sub>, δ ppm, J Hz): 167.94 (C-13(15)); 167.47 (C-15(13)); 149.44 (C-9); 148.39 (C-2(6)); 147.39 (C-6(2)); 136.90 (Cq); 133.90 (C-12); 129.06 (C-11); 122.36 (C-8); 121.43 (C-10); 107.83 (C-3(5)); 99.44 (C-5(3)); 50.84 (C-14); 48.07 (C-16); 41.50 (C-4); 33.02 (CH<sub>2</sub>); 25.43 (CH<sub>2</sub>); 24.74 (CH<sub>2</sub>); 19.47 (C-22(23)); 17.67 (C-23(22)).

FT-IR (ν, cm<sup>-1</sup>): 3315 (NH), 3269 (CONH), 2934 (CH<sub>3</sub>), 1678 (CH<sub>3</sub>OCO), 1601 (CONH), 1223 (CH<sub>3</sub>OCO).

## Conclusions

We have synthesized 7 new compounds, methyl 5-alkyl/aryl-carbamoyl-2,6-dimethyl-4-(substituted-phenyl)-1,4-dihydropyridine-3-carboxylate derivatives and confirmed their structure by spectrometric methods (FT-IR and NMR) coupled with elemental analyses. The compounds are presently under evaluation for antitumor activity and further investigations.

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