Facile Access to 6-Substituted 1,4,5,7-Tetrahydropyrrolo[3,4-*b*]-pyridines *via* Hantzsch Type Dimethyl 4-Aryl-2-formyl-6-methyl-1,4-dihydropyridine-3,5-dicarboxylates

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Efficient assembly of 6-substituted 4-aryl-5-oxo-1,4,5,7-tetrahydropyrrolo[3,4-*b*]pyridines (**7a-f**) is described according to a Hantzsch type reaction from formyl-ester **4** by imination, borohydride reduction and intramolecular thermal amino-ester cyclization. The starting compound **4** was prepared in three steps from the readily available formyl derivative **1**, methyl 4,4-dimethoxy-3-oxobutanoate and methyl 3-aminocrotonate.

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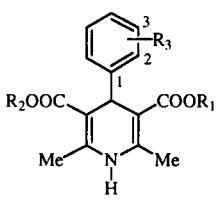
Because of their usefulness in the treatment of hypertension and other circulatory disorders [1], 4-arylsubstituted 1,4-dihydropyridines (1,4-DHPs) and their derivatives as synthetic targets for drugs have attracted considerable interest in recent years. These structures **A**, exemplified by Nifedipine $\mathbf{A_1}$, Nimodipine $\mathbf{A_2}$, Nitrendipine $\mathbf{A_3}$ and Nilvadipine $\mathbf{A_4}$, are now in clinical use due to their calcium antagonists effect [2-5]. 4-Arylsubstituted furo[3,4-*b*]-1,4-DHP, as compound **B** (X=O) [2,3-8] and 4-arylsubstituted thieno[3,4-*b*]-1,4-DHP **B** (X=S) [2,8] have been relatively unexplored in the literature. These structures have exhibited antithetical physiological properties compared to those of the simple corresponding 1,4-DHP diesters [9] and also are known as a calcium agonists that are the opposite of the Ca^{2+} ions modulators Nifedipine family (**A**) [2]. Contrary to that of the Nifedipine family, 4-arylsubstituted pyrrolo[3,4-*b*]-1,4-DHP as **B** (X=NR_5) [8,10,11], are relatively unknown in the literature and to our knowledge no biological activity concerning these structures has been reported. So, it appears interesting to study and evaluate the pyrrolo[3,4-*b*]-1,4-DHP system.

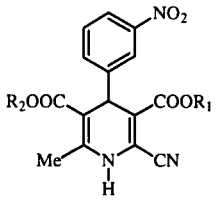
As a further development of our search on the synthetic utility and reactivity on polyheterocyclic systems containing a 1,4-dihydropyridine moiety fused to aza-heterocycles [12], we wish to present herein our approach to the synthesis of an efficient assembly of 6-substituted 4-aryl-5-oxo-1,4,5,7-tetrahydropyrrolo[3,4-*b*]pyridines (**7a-f**). The key step of this synthetic sequence is an intramolecular thermal amine-ester cyclization.

As shown in Chart 2, the requisite 2-formyl-1,4-dihydropyridine derivative **4**, used as the starting material, was chosen for its stability and easy preparation relative to the unstable 2-halomethyl-1,4-DHP derivatives [9]. The latter were lactonized under conventional halogenation of the methyl(or ethyl) 2-methyl-1,4-DHP-3,4-carboxylates parents to the corresponding 4-aryl-5-oxo-1,4,5,7-tetrahydrofuro[3,4-*b*]pyridine derivatives with bromine (or chlorine [6]) or by the use of the pyridinium bromide perbromide [9]. On the other hand, a lactamization was observed during bromination of 2-methyl-1,4-DHP-3-alkyl amide by pyridinium bromide perbromide with the addition of NBS as a radical initiator. This ring closure,

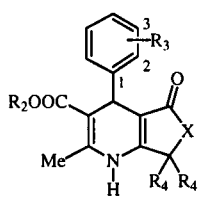
Chart 1



$\mathbf{A_1}$, $\mathbf{A_2}$, $\mathbf{A_3}$



$\mathbf{A_4}$



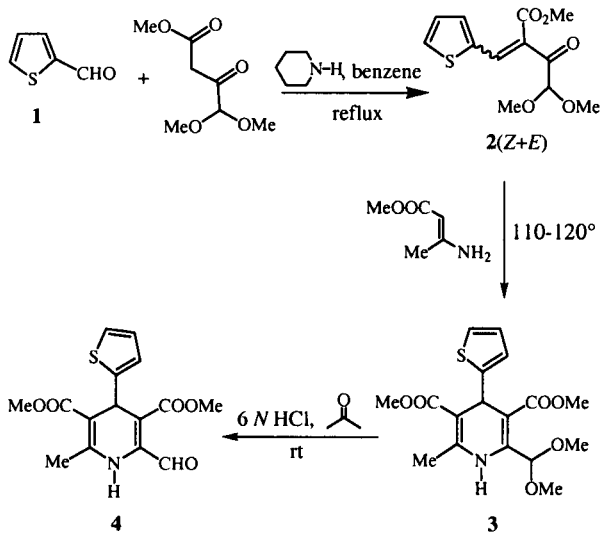
B: X=O, S, NR_5

$\mathbf{A_1}$: Nifedipine: R_1=Me, R_2=Me, R_3=2-NO_2
$\mathbf{A_2}$: Nimodipine: R_1=$(CH_2)_2OMe$, R_2=$CH(Me)_2$, R_3=3-NO_2
$\mathbf{A_3}$: Nitrendipine: R_1=Me, R_2=Et, R_3=3-NO_2
$\mathbf{A_4}$: Nilvadipine: R_1=Me, R_2=$CH(Me)_2$, R_3=3-NO_2

R_2 = Me, Et, i-Pr
R_3 = H, 2-$OCHF_2$, 2-OBn, 2-Cl, 2-NO_2, 2-OMe, 2-Me, 3-CF_3, 3-Br
R_4 = H, Me; R_5 = H, Ph

leading to a pyrrolo[3,4-*b*]-1,4-DHP as **B** (X=NPh with R_2=Et, R_3=2-$OCHF_2$ and R_4=H) [9], proceeded *via* an intramolecular condensation of the 2-bromomethyl-1,4-DHP-3-alkyl amide intermediate. Others examples of pyrrolo[3,4-*b*]-1,4-dihydropyridines as **B** (X=NH with R_2=Me, R_3=H, 2-Cl or 3-NO_2 and R_4=Me) have been described from 5,5-dimethyltetramic acid in four steps [11]. The key step in this synthetic sequence was the construction of the DHP nucleus *via* an intermediate Michael adduct.

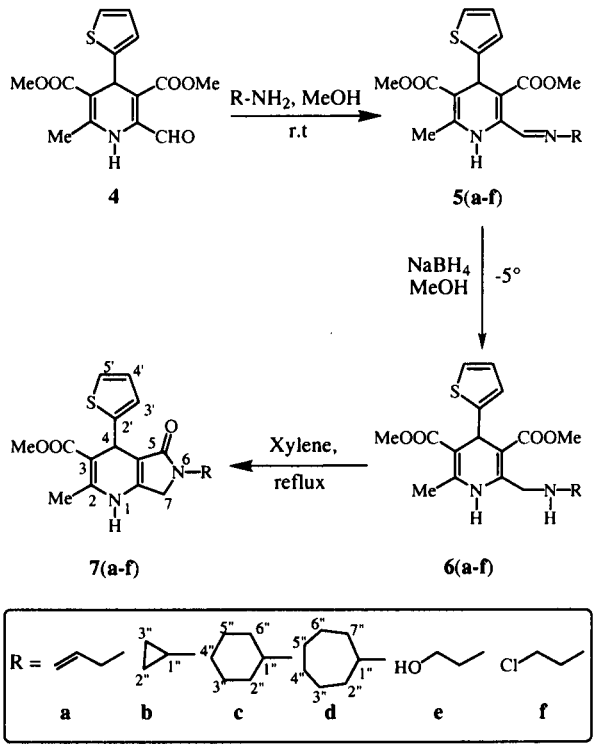
Chart 2



The 2-formyl-1,4-dihydropyridine derivative **4** is readily available by acid hydrolysis of the corresponding 2-dimethoxymethyl derivative **3**, which was prepared in two steps from thiophene-2-carboxaldehyde (**1**). Thus, condensation of **1** with methyl 4,4-dimethoxy-3-oxobutanoate gave the olefin **2** as a *Z/E* mixture and the thermal cyclization leading to **4** occurred in the presence of methyl 3-aminocrotonate. The overall yield of this synthesis was 73% calculated from the starting formyl derivative **1**.

As depicted in Chart 3, the condensation of primary amines with the 2-formyl-1,4-dihydropyridine derivative **4** proceeded in anhydrous methanol at room temperature and gave the expected imines **5a-f** in a range of 70 to 86% yields. Reduction of imines **5a-f** using sodium borohydride in methanol at -5° yield amines **6a-f** in good yields (88 to 99%). The amines **6c,d** could be isolated as pure product but amines **6a,b,e,f** were accompanied with their corresponding lactams **7a,b,e,f** (these observations were based on ^{1}H NMR analysis of the crude product). The mixture of **6** and **7** was used for the next step without further purification. Because of the low solubility of the 2-(*N*-cyclopropylimine)-1,4-dihydropyridine derivative **5b**, in methanol the reduction of this derivative into **6b** was accomplished by the addition of dichloromethane as a co-solvent.

Chart 3



Refluxing 2-aminomethyl-1,4-dihydropyridine derivatives **6a-f** in dry toluene led to the expected pyrrolo[3,4-*b*]-1,4-DHP lactams **7a-f** in yields of 49 to 65%. Using xylene instead of toluene shortened the reaction time and, in case of the less reactive amines **6c,d**, increased the yield. Cyclization occurred *via* intramolecular nucleophilic attack of the nitrogen atom on the carbonyl function of the ester group.

The structure of all compounds was proved by elemental analysis and spectral measurements. The ^{1}H NMR spectra of all synthetized derivatives of 1,4-DHPs display a proton signal of δ = 5.01 to 5.43 ppm, which is characteristic of the hydrogen at C-4 of the 1,4-DHP ring [3,5]. Generally, 1,4-DHPs **5a-f** and **6c,d** exhibit a H-4 hydrogen signal at lower field in comparison to the corresponding lactams **7a-f**. In the ^{1}H NMR spectra of 2-aminomethyl-1,4-DHPs **6c,d** and related lactams **7a-f**, the methylene hydrogens (CH_2-NR-CO) appear as an AB system (two doublets) at δ = 3.70 to 4.18 ppm, with a coupling constant of about 18 Hz typical of *gem* hydrogens. Likewise, the ^{13}C NMR spectra show the theoretical number of signals; the chemical shifts of all carbons were assigned by comparison with the ^{13}C NMR spectra of 2-formyl-1,4-dihydropyridine derivatives already published [3-5,13]. A characteristic signal in the ^{13}C NMR spectra of 1,4-dihydropyridine derivatives is that of the C-4 carbon of the pyridine ring at δ = 31.8 to 35.0 ppm. The C-4 carbon of 1,4-dihydropyridines **5a-f**

and **6c,d** is shifted downfield by 2.3 to 3.2 ppm as compared to the pyrrolo[3,4-*b*]-1,4-DHP lactams **7a-f**.

In summary we have presented a general approach (by intramolecular thermal amine-ester cyclization) to assemble the 6-substituted 4-aryl-5-oxo-1,4,5,7-tetrahydropyrrolo[3,4-*b*]pyridines (**7a-f**). The readily available formyl-ester **4**, used as the starting material, gave in two steps the amine-esters **6**, which were precursors for the cyclization reaction.

EXPERIMENTAL

All melting points were measured on a Boetius micro hot-stage and are uncorrected. The infrared spectra of solids (potassium bromide) were recorded on a Perkin Elmer FT-IR paragon 1000 spectrometer. The ^1H and ^{13}C NMR spectra were recorded on a Bruker AC-200 (200 MHz) instrument in deuteriochloroform or methylsulfoxide-d_6 for amides (**7a-f**) and chemical shifts (δ) are expressed in ppm relative to TMS as internal standard. Ascending thin layer chromatography was performed on pre-coated plates of silica gel 60 F 254 (Merck) and the spots visualized using an ultraviolet lamp or iodine vapor. Mass spectral measurements were recorded on a AEI MS 902 S spectrophotometer. The elemental analyses were carried out by the microanalysis laboratory of INSA, F-76130 Mt. St. Aignan, France.

Dimethyl 2-Formyl-6-methyl-4-(2-thienyl)-1,4-dihydropyridine-3,5-dicarboxylate (**4**).

A mixture of thiophene-2-carboxaldehyde (1) (1.12 g, 10 mmol), methyl 4,4-dimethoxy-3-oxo-butanoate (1.76 g, 10 mmol) and piperidine (0.09 g, 1 mmol) in benzene (10 ml) was refluxed with a Dean-Stark for 5 hours. The solvent was evaporated under reduced pressure to give an oil olefin **2**, which was used for the next step without any additional purification. To this oily residue **2**, methyl 3-aminocrotonate (1.15 g, 10 mmol), was added and the resulting mixture was stirred at 100-120° for 3 hours. After cooling, the viscous oil **3** was dissolved in acetone (37 ml) and 6 *N* hydrochloric acid (6.5 ml) was added dropwise. The solution was stirred at room temperature for 3 hours. The organic solvent was removed under reduced pressure and the residue was poured into water (10 ml) and neutralized with 10% solution of sodium hydrogenocarbonate. The water suspension was extracted twice with ethyl acetate (10 ml). The resulting organic layer was washed with water (5 ml), brine, dried over sodium sulfate and evaporated *in vacuo*. Recrystallization of the residue from dry ethanol gave **4** (2.34 g) in 73% yield, mp 152-154°; IR (KBr): 3344, 2947, 1705, 1639, 1487 cm^{-1}; ^1H NMR: δ 2.44 (s, 3H, CH_3), 3.72 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 5.45 (s, 1H, H_4), 6.82 (dd, 1H, $H_{3'}$, J = 3.6 and 1.2 Hz), 6.88 (dd, 1H, $H_{4'}$, J = 3.6 and 5.1 Hz), 7.12 (dd, 1H, $H_{5'}$, J = 5.1 and 1.2 Hz), 7.18 (br, 1H, N-H), 10.50 (s, 1H, CHO); ^{13}C NMR: δ 19.3 (CH_3), 35.1 (C_4), 51.3 (CH_3O), 52.2 (CH_3O), 102.0 (C_5), 114.5 (C_3), 124.0 ($C_{4'}$), 124.3 ($C_{5'}$), 126.8 ($C_{3'}$), 138.6 ($C_{2'}$), 144.9 (C_2), 148.4 (C_6), 165.9 (CO_2CH_3), 167.0 (CO_2CH_3), 186.6 (CH=O); EIMS, m/z : (M^+, 321).

Anal. Calcd. for $C_{15}H_{15}NO_5S$: C, 56.06; H, 4.70; N, 4.35; S, 9.98. Found: C, 56.01; H, 4.76; N, 4.33; S, 10.01.

General Procedure for the Preparation of Dimethyl 2-(*N*-substituted)iminomethyl-6-methyl-4-(2-thienyl)-1,4-dihydropyridine-3,5-dicarboxylates (**5a-f**).

To a solution of 2-formyl-1,4-dihydropyridine derivative **4** (0.642 g, 2 mmol) in dry methanol (10 ml) was added primary amine (2 mmol) and the mixture was stirred at room temperature overnight. After 10 minutes of refluxing with charcoal, the reaction mixture was filtered off and allowed to cool. The formed precipitate product **5** was isolated by filtration and dried.

Dimethyl 2-Allyliminomethyl-6-methyl-4-(2-thienyl)-1,4-dihydropyridine-3,5-dicarboxylate (**5a**).

This compound was obtained in 70% yield by recrystallization from a mixture of ethanol and water, mp 83-85°, IR (KBr): 3331 (N-H), 2945 (C-H), 1697 (C=O) cm^{-1}; ^1H NMR: δ 2.42 (s, 3H, CH_3), 3.72 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 4.20-4.34 (m, 2H, CH_2-CH=), 5.17-5.24 (m, 2H, C=CH_2), 5.43 (s, 1H, H_4), 5.96-6.01 (m, 1H, -CH=), 6.82 (dd, 1H, $H_{3'}$, J = 3.3 and 1.2 Hz), 6.86 (dd, 1H, $H_{4'}$, J = 3.3 and 5.1 Hz), 7.08 (dd, 1H, $H_{5'}$, J = 5.1 and 3.3 Hz), 7.87 (s, 1H, N-H), 9.04 (s, 1H, CH=N); ^{13}C NMR: δ 19.4 (CH_3), 34.9 (C_4), 51.1 (OCH_3), 51.6 (OCH_3), 62.2 (CH_2N), 101.9 (C_5), 108.8 (C_3), 116.9 (=CH_2), 123.5 ($C_{4'}$), 123.7 ($C_{5'}$), 126.6 ($C_{3'}$), 134.7 (-CH=), 139.6 (C_2), 145.5 (C_6), 149.8 ($C_{2'}$), 155.1 (CH=N), 166.8 (CO_2CH_3), 167.5 (CO_2CH_3); EIMS, m/z : (M^+, 360).

Anal. Calcd. for $C_{18}H_{20}N_2O_4S$: C, 59.98; H, 5.59; N, 7.77; S, 8.90. Found: C, 60.09; H, 5.54; N, 7.81; S, 8.86.

Dimethyl 2-Cyclopropyliminomethyl-6-methyl-4-(2-thienyl)-1,4-dihydropyridine-3,5-dicarboxylate (**5b**).

This compound was obtained in 80% yield, mp 173-174°, IR (KBr): 3351 (N-H), 2949 (C-H), 1699 (C=O) cm^{-1}; ^1H NMR: δ 0.98-1.00 (m, 4H, $H_{2''-3''}$), 2.40 (s, 3H, CH_3), 3.05-3.19 (m, 1H, $H_{1''}$), 3.71 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 5.42 (s, 1H, H_4), 6,81 (dd, 1H, $H_{3'}$, J = 3.3 and 1.2 Hz), 6,85 (dd, 1H, $H_{4'}$, J = 3.3 and 5.1 Hz), 7,07 (dd, 1H, $H_{5'}$, J = 5.1 and 1.2 Hz), 7.74 (s, 1H, N-H), 9.17 (s, 1H, CH=N); ^{13}C NMR: δ 10.1 ($C_{2''-3''}$), 19.5 (CH_3), 34.8 (C_4), 41.3 ($C_{1''}$), 51.1 (OCH_3), 51.6 (OCH_3), 101.9 (C_5), 107.5 (C_3), 123.4 ($C_{4'}$), 123.6 ($C_{5'}$), 126.5 ($C_{3'}$), 139.7 (C_2), 145.6 (C_6), 150.1 ($C_{2'}$), 151.5 (CH=N), 166.9 (CO_2CH_3), 167.6 (CO_2CH_3); EIMS, m/z : (M^+, 360).

Anal. Calcd. for $C_{18}H_{20}N_2O_4S$: C, 59.98; H, 5.59; N, 7.77; S, 8.90. Found: C, 60.13; H, 5.62; N, 7.86; S, 8.97.

Dimethyl 2-Cyclohexyliminomethyl-6-methyl-4-(2-thienyl)-1,4-dihydropyridine-3,5-dicarboxylate (**5c**).

This compound was obtained in 80% yield, mp 170-171°, IR (KBr): 3360 (N-H), 2934 (C-H), 1693 (C=O) cm^{-1}; ^1H NMR: δ 1.28-1.82 (m, 10H, $H_{2''-3''-4''-5''-6''}$), 2.44 (s, 3H, CH_3), 3.27-3.40 (m, 1H, $H_{1''}$), 3.71 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 5.42 (s, 1H, H_4), 6.81 (d, 1H, $H_{3'}$, J = 3.3 and 1.2 Hz), 6.87 (dd, 1H, $H_{4'}$, J = 3.3 and 5.1 Hz), 7.09 (d, 1H, $H_{5'}$, J = 5.1 and 1.2 Hz), 7.95 (s, 1H, N-H), 9.02 (s, 1H, CH=N); ^{13}C NMR: δ 19.5 (CH_3), 24.5 ($C_{4''}$), 25.4 ($C_{3''-5''}$), 33.9 ($C_{2''-6''}$), 34.9 (C_4), 51.1 (OCH_3), 51.7 (OCH_3), 68.1 ($C_{1''}$), 101.7 (C_5), 108.1 (C_3), 123.5 ($C_{4'}$), 123.7 ($C_{5'}$), 126.6 ($C_{3'}$), 139.9 (C_2), 145.8 (C_6), 150.0 ($C_{2'}$), 151.1 (CH=N), 166.9 (CO_2CH_3), 167.5 (CO_2CH_3); EIMS, m/z : (M^+, 402).

Anal. Calcd. for $C_{21}H_{26}N_2O_4S$: C, 62.66; H, 6.51; N, 6.96; S, 7.97. Found: C, 62.49; H, 6.47; N, 6.78; S, 7.83.

Dimethyl 2-Cycloheptyliminomethyl-6-methyl-4-(2-thienyl)-1,4-dihydropyridine-3,5-dicarboxylate (**5d**).

This compound was obtained in 76% yield, mp 186-187° IR (KBr): 3356 (N-H), 2930 (C-H), 1696 (C=O) cm^{-1}; ^1H NMR: δ 1.22-1.82 (m, 12H, $H_{2''-3''-4''-5''-6''-7''}$), 2.43 (s, 3H, CH_3), 3.48-3.51 (m, 1H, $H_{1''}$), 3.71 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 5.42 (s, 1H, H_4), 6.81 (d, 1H, $H_{3'}$, J = 3.3 and 1.2 Hz), 6.86 (dd, 1H, $H_{4'}$, J = 3.3 and 5.1 Hz), 7.08 (dd, 1H, $H_{5'}$, J = 5.1 and 1.2 Hz), 7.94 (s, 1H, N-H), 8.96 (s, 1H, CH=N); ^{13}C NMR: δ 19.5 (CH_3), 24.5 ($C_{4''-5''}$), 28.4 ($C_{3''-6''}$), 35.0 (C_4), 36.1 ($C_{2''-7''}$), 51.1 (OCH_3), 51.6 (OCH_3), 70.7 ($C_{1''}$), 101.8 (C_5), 108.3 (C_3), 123.4 ($C_{4'}$), 123.7 ($C_{5'}$), 126.5 ($C_{3'}$), 140.1 (C_2), 145.7 (C_6), 150.1 ($C_{2'}$), 151.1 (CH=N), 166.9 (CO_2CH_3), 167.6 (CO_2CH_3); EIMS, m/z : (M^+, 416).

Anal. Calcd. for $C_{22}H_{28}N_2O_4S$: C, 63.44; H, 6.78; N, 6.73; S, 7.70. Found: C, 63.18; H, 6.89; N, 6.67; S, 7.81.

Dimethyl 2-[(2-Hydroxyethyl)iminomethyl]-6-methyl-4-(2-thienyl)-1,4-dihydropyridine-3,5-dicarboxylate (**5e**).

This compound was obtained in 86% yield, mp 123-125°, IR (KBr): 3339 (N-H), 2951 (C-H), 1698 (C=O) cm^{-1}; ^1H NMR: δ 2.25 (s, 1H, OH), 2.41 (s, 3H, CH_3), 3.71 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.86 (t, 2H, CH_2, J = 5.5 Hz), 4.80 (t, 2H, CH_2, J = 5.5 Hz), 5.42 (s, 1H, H_4), 6.81 (dd, 1H, $H_{3'}$, J = 3.3 and 1.2 Hz), 6.85 (dd, 1H, $H_{4'}$, J = 3.3 and 5.1 Hz), 7.08 (d, 1H, $H_{5'}$, J = 5.1 and 1.2 Hz), 7.85 (s, 1H, N-H), 9.04 (s, 1H, CH=N); ^{13}C NMR: δ 19.4 (CH_3), 34.9 (C_4), 51.2 (OCH_3), 51.7 (OCH_3), 62.1 (CH_2), 62.2 (CH_2), 101.9 (C_5), 109.1 (C_3), 123.5 ($C_{4'}$), 123.8 ($C_{5'}$), 126.6 ($C_{3'}$), 139.4 (C_2), 145.6 (C_6), 149.8 ($C_{2'}$), 156.3 (CH=N), 166.8 (CO_2CH_3), 167.6 (CO_2CH_3); EIMS, m/z : (M^+, 364).

Anal. Calcd. for $C_{17}H_{20}N_2O_5S$: C, 56.03; H, 5.53; N, 7.69; S, 8.80. Found: C, 56.20; H, 5.47; N, 6.73; S, 8.68.

Dimethyl 2-[(2-Chloroethyl)iminomethyl]-6-methyl-4-(2-thienyl)-1,4-dihydropyridine-3,5-dicarboxylate (**5f**).

This compound was obtained in 84% yield, mp 98-100°, IR (KBr): 3357 (N-H), 2849 (C-H), 1698 (C=O) cm^{-1}; ^1H NMR: δ 2.43 (s, 3H, CH_3), 3.72 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 3.81 (t, 2H, CH_2, J = 6 Hz), 3.94 (t, 2H, CH_2, J = 6 Hz), 5.43 (s, 1H, H_4), 6.82 (dd, 1H, $H_{3'}$, J = 3.3 and 1.2 Hz), 6.87 (dd, 1H, $H_{4'}$, J = 3.3 and 5.1 Hz), 7.09 (dd, 1H, $H_{5'}$, J = 5.1 and 1.2 Hz), 7.77 (s, 1H, N-H), 9.06 (s, 1H, CH=N); ^{13}C NMR: δ 19.5 (CH_3), 34.9 (C_4), 43.6 (CH_2), 51.1 (OCH_3), 51.7 (OCH_3), 61.1 (CH_2), 101.9 (C_5), 109.4 (C_3), 123.6 ($C_{4'}$), 123.8 ($C_{5'}$), 126.6 ($C_{3'}$), 139.2 (C_2), 145.5 (C_6), 149.7 ($C_{2'}$), 156.7 (CH=N), 166.7 (CO_2CH_3), 167.5 (CO_2CH_3); EIMS, m/z : (M^+, 382).

Anal. Calcd. for $C_{17}H_{19}ClN_2O_4S$: C, 53.33; H, 5.00; N, 7.32; S, 8.37. Found: C, 53.41; H, 4.98; N, 7.30; S, 8.43.

General Procedure for the Synthesis of Dimethyl 2-(*N*-Substituted aminomethyl)-6-methyl-4-(2-thienyl)-1,4-dihydropyridine-3,5-dicarboxylates (**6a-f**).

To a solution of imine 5a-f (1.2 mmol) in dry methanol (50 ml) at -5° was added sodium borohydride in several portions during 10 minutes. The reaction was monitored by TLC by using a 2/1 mixture of isohexane and ethyl acetate as eluent. After the reaction was completed, the solvent was evaporated under reduced pressure. The residue was diluted with water (30 ml) and the suspension was extracted with ethyl acetate (2x20 ml). The organic layer was washed with water, brine, dried over sodium sulfate and evaporated. In the case of products **6c** and **6d**, the oily residue was treated with ether and the precipitated solid material was filtered by suction and recrystallized from dry ethanol. For other amines, the oily material was used for the next reaction without other purification.

Dimethyl 2-Cyclohexylaminomethyl-6-methyl-4-(2-thienyl)-1,4-dihydropyridine-3,5-dicarboxylate (**6c**).

This compound was obtained in 96% yield, mp 168-170°, IR (KBr): 3256 (N-H), 2930 (C-H), 1689 (C=O) cm^{-1}; ^1H NMR: δ 1.06-1.97 (m, 11H, $H_{1''-2''-3''-4''-5''-6''}$), 2.38 (s, 3H, CH_3), 3.70 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 3.98 (d, 1H, CH_2-N, J = 15,1 Hz), 4.08 (d, 1H, CH_2-N, J = 15,1 Hz), 5.35 (s, 1H, H_4), 6.77 (dd, 1H, $H_{3'}$, J = 3.3 and 1.2 Hz), 6.87 (dd, 1H, $H_{4'}$, J = 3.3 and 5.1 Hz), 7.09 (dd, 1H, $H_{5'}$, J = 5.1 and 1.2 Hz), 8.46 (br, 1H, N-H); ^{13}C NMR: δ 19.3 (CH_3), 24.8 ($C_{4'}$), 25.8 ($C_{3''-5''}$), 33.7 ($C_{2''-6''}$), 34.6 (C_4), 46.0 (CH_2N), 50.9 (OCH_3), 51.1 (OCH_3), 57.7 ($C_{1''}$), 100.0 (C_3), 103.3 (C_5), 122.7 ($C_{4'}$), 123.1 ($C_{5'}$), 126.4 ($C_{3'}$), 144.9 (C_6), 148.2 (C_2), 151.8 ($C_{2'}$), 167.6 (CO_2CH_3), 167.9 (CO_2CH_3); EIMS, m/z : (M^+, 404).

Anal. Calcd. for $C_{21}H_{28}N_2O_4S$: C, 62.35; H, 6.98; N, 6.93; S, 7.93. Found: C, 62.29; H, 6.90; N, 6.99; S, 7.80.

Dimethyl 2-Cycloheptylaminomethyl-6-methyl-4-(2-thienyl)-1,4-dihydropyridine-3,5-dicarboxylate (**6d**).

This compound was obtained in 89% yield, mp 174-175°, IR (KBr): 3285 (N-H), 2926 (C-H), 1698 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.33-1.89 (m, 12H, $H_{2''-3''-4''-5''-6''-7''}$), 2.38 (s, 3H, CH_3), 2.43 (m, 1H, $H_{1''}$), 3.70 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 3.97 (d, 1H, CH_2-N, J = 16 Hz), 4.04 (d, 1H, CH_2-N, J = 16 Hz), 5.35 (s, 1H, H_4), 6,77 (dd, 1H, $H_{3'}$, J = 3.3 and 1.2 Hz), 6.84 (dd, 1H, $H_{4'}$, J = 3.3 and 5.1 Hz), 7.04 (dd, 1H, $H_{5'}$, J = 5.1 and 1.2 Hz), 8.66 (br, 1H, N-H); ^{13}C NMR: δ 19.3 (CH_3), 23.9 ($C_{4''-5''}$), 28.3 ($C_{3''-6''}$), 34.5 (C_4), 34.8 ($C_{2''-7''}$), 46.5 (CH_2N), 50.9 (OCH_3), 51.0 (OCH_3), 59.9 ($C_{1''}$), 100.0 (C_3), 103.3 (C_5), 122.7 ($C_{4'}$), 123.1 ($C_{5'}$), 126.4 ($C_{3'}$), 144.9 (C_6), 148.2 (C_2), 151.9 ($C_{2'}$), 167.6 (CO_2CH_3), 167.9 (CO_2CH_3); EIMS, m/z : (M^+, 418).

Anal. Calcd. for $C_{22}H_{30}N_2O_4S$: C, 63.13; H, 7.22; N, 6.69; S, 7.66. Found: C, 63.03; H, 7.12; N, 6.69; S, 7.61.

General Procedure for the Preparation of Methyl 6-Substituted 5-Oxo-2-methyl-4-(2-thienyl)-1,4,5,7-tetrahydropyrrolo[3,4-*b*]-pyridine-3-carboxylates (**7a-f**).

A stirred solution of 0.5 g of 2-aminomethyl-1,4-dihydropyridines **6a-f** in 10 ml of xylene was refluxed. Reaction time is dependent on the substituent in the aminomethyl group and is monitored by TLC by using a 2:1 mixture of dichloromethane:methanol as eluent. After cooling the precipitated product was filtered off, washed with ether and recrystallized from ethanol to yield the expected lactam **7**.

Methyl 6-Allyl-5-oxo-2-methyl-4-(2-thienyl)-1,4,5,7-tetrahydropyrrolo[3,4-*b*]pyridine-3-carboxylate (**7a**).

This compound was obtained in 50% yield after recrystallization from ethanol, mp 264-266°, IR (KBr): 3247 (N-H), 2990 (C-H), 1698 (C=O) cm^{-1}; ^1H NMR: δ 2.31 (s, 3H, CH_3), 3.66

(s, 3H, OCH_3), 3.70 (d, 1H, CH_2-N, J = 17.8 Hz), 3.81 (d, 1H, CH_2-N, J = 17.8 Hz), 3.90-3.95 (m, 2H, N-CH_2-CH=), 5.07-5.15 (m, 2H, C=CH_2), 5.24 (s, 1H, H_4), 5.72-5.74 (m, 1H, -CH=), 6.75-6.85 (m, 2H, $H_{3'-4'}$), 7.05 (dd, 1H, $H_{5'}$, J = 5.2 and 1.4 Hz), 8.31 (br, 1H, N-H); ^{13}C NMR: δ 19.9 (CH_3), 32.3 (C_4), 44.5 (CH_2), 47.4 (CH_2), 50.9 (OCH_3), 102.7 (C_3), 108.2 (C_{4a}), 117.3 (=CH_2), 123.4 ($C_{4'}$), 123.7 ($C_{5'}$), 126.7 ($C_{3'}$), 133.4 (-CH=), 146.1 (C_2), 148.2 (C_{7a}), 151.1 ($C_{2'}$), 168.1 (CO), 170.9 (CO); EIMS, m/z : (M^+, 330).

Anal. Calcd. for $C_{17}H_{18}N_2O_3S$: C, 61.80; H, 5.49; N, 8.48; S, 9.70. Found: C, 61.78; H, 5.46; N, 8.43; S, 9.72.

Methyl 6-Cyclopropyl-5-oxo-2-methyl-4-(2-thienyl)-1,4,5,7-tetrahydropyrrolo[3,4-*b*]pyridine-3-carboxylate (**7b**).

This compound was obtained in 49% yield after recrystallization from ethanol, mp 289-293°, IR (KBr): 3241 (N-H), 2950 (C-H), 1698 (C=O) cm^{-1}; ^{1}H NMR: δ 0.68-0.78 (m, 4H, $H_{2''-3''}$), 2.38 (s, 3H, CH_3), 2.61-2.65 (m, 1H, $H_{1''}$), 3.64 (s, 3H, OCH_3), 3.81 (d, 1H, CH_2-N, J = 17.7 Hz), 3.87 (d, 1H, CH_2-N, J = 17.7 Hz), 5.25 (s, 1H, H_4), 6.84-6.86 (m, 2H, $H_{3'-4'}$), 7.06 (dd, 1H, $H_{5'}$, J = 5.2 and 1.4 Hz), 8.43 (s, 1H, N-H); ^{13}C NMR: δ 20.1 (CH_3), 24.6 (CH_2), 32.1 (C_4), 44.7 (CH_2), 48.7 (CH), 51.1 (OCH_3), 102.8 (C_3), 109.7 (C_{4a}), 123.5 ($C_{4'}$), 123.6 ($C_{5'}$), 126.9 ($C_{3'}$), 146.2 (C_2), 147.9 (C_{7a}), 151.3 ($C_{2'}$), 168.5 (CO), 171.2 (CO); EIMS, m/z : (M^+, 330).

Anal. Calcd. for $C_{17}H_{18}N_2O_3S$: C, 61.80; H, 5.49; N, 8.48; S, 9.70. Found: C, 61.90; H, 5.48; N, 8.49; S, 9.67.

Methyl 6-Cyclohexyl-5-oxo-2-methyl-4-(2-thienyl)-1,4,5,7-tetrahydropyrrolo[3,4-*b*]pyridine-3-carboxylate (**7c**).

This compound was obtained in 56% yield by recrystallization from ethanol, mp 286-290°, IR (KBr): 3229 (N-H), 2855 (C-H), 1698 (C=O) cm^{-1}; ^{1}H NMR: δ 1.00-1.80 (m, 10H, $H_{2''-3''-4''-5''-6''}$), 2.28 (s, 3H, CH_3), 3.57 (s, 3H, OCH_3), 3.69-3.76 (m, 1H, $H_{1''}$), 3.88 (d, 1H, CH_2-N, J = 18.0 Hz), 4.01 (d, 1H, CH_2-N, J = 18.0 Hz), 5.01 (s, 1H, H_4), 6.72 (dd, 1H, $H_{3'}$, J = 3.4 and 1.4 Hz), 6,87 (dd, 1H, $H_{4'}$, J = 3.4 and 5.2 Hz), 7,23 (dd, 1H, $H_{5'}$, J = 5.2 and 1.4 Hz), 9.59 (s, 1H, N-H); ^{13}C NMR: δ 19.1 (CH_3), 25.0 ($C_{4''}$), 25.2 ($C_{3''-5''}$), 30.7 ($C_{2''-6''}$), 31.8 (C_4), 43.4 (C_7), 49.6 ($C_{1''}$), 50.7 (OCH_3), 100.6 (C_3), 107.8 (C_{4a}), 122.7 ($C_{4'}$), 123.7 ($C_{5'}$), 126.7 ($C_{3'}$), 146.8 (C_2), 147.6 (C_{7a}), 151.7 ($C_{2'}$), 167.5 (CO), 168.8 (CO); EIMS, m/z : (M^+, 372).

Anal. Calcd. for $C_{20}H_{24}N_2O_3S$: C, 64.49; H, 6.49; N, 7.52; S, 8.61. Found: C, 64.36; H, 6.53; N, 7.51; S, 8.50.

Methyl 6-Cycloheptyl-5-oxo-2-methyl-4-(2-thienyl)-1,4,5,7-tetrahydropyrrolo[3,4-*b*]pyridine-3-carboxylate (**7d**).

This compound was obtained in 65% yield after recrystallization from ethanol, mp 278-280°, IR (KBr): 3227 (N-H), 2930 (C-H), 1698 (C=O) cm^{-1}; ^{1}H NMR: δ 1.48-1.89 (m, 12H, $H_{2''-3''-4''-5''-6''-7''}$), 2.30 (s, 3H, CH_3), 3.66 (s, 3H, OCH_3), 3.75 (d, 1H, CH_2-N, J = 17.9 Hz), 3.86 (d, 1H, CH_2-N, J = 17.9 Hz), 4.01-4.11 (m, 1H, $H_{1''}$), 5.22 (s, 1H, H_4), 6.79-6.81 (m, 2H, $H_{3'-4'}$), 7.02 (dd, 1H, $H_{5'}$, J = 5.2 and 1.4 Hz), 8.79 (s, 1H, N-H); ^{13}C NMR: δ 19.9 (CH_3), 24.7 ($C_{2''-7''}$), 27.6 ($C_{3''-6''}$), 32.3 (C_4), 33.8 ($C_{4''-5''}$), 44.1 (CH_2N), 50.9 (OCH_3), 52.3 ($C_{1''}$), 102.3 (C_3), 108.3 (C_{4a}), 123.3 ($C_{4'}$), 123.6 ($C_{5'}$), 126.7 ($C_{3'}$), 146.6 (C_2), 148.2 (C_{1a}), 151.4 ($C_{2'}$), 168.2 (CO), 170.4 (CO); EIMS, m/z : (M^+, 386).

Anal. Calcd. for $C_{21}H_{26}N_2O_3S$: C, 65.26; H, 6.78; N, 7.25; S, 8.29. Found: C, 65.37; H, 6.69; N, 7.33; S, 8.37.

Methyl 6-(2-Hydroxyethyl)-5-oxo-2-methyl-4-(2-thienyl)-1,4,5,7-tetrahydropyrrolo[3,4-*b*]pyridine-3-carboxylate (**7e**).

This compound was obtained in 60% yield after recrystallization from ethanol, mp 274-275°, IR (KBr): 3233 (N-H), 2994 (C-H), 1694 (C=O) cm^{-1}; ^{1}H NMR: δ 2.29 (s, 3H, CH_3), 3.30 (t, 2H, CH_2, J = 5.7 Hz), 3.49 (t, 2H, CH_2, J = 5.7 Hz), 3.58 (s, 3H, OCH_3), 4.03 (d, 1H, CH_2-N, J = 18.3 Hz), 4.14 (d, 1H, CH_2-N, J = 18.3 Hz), 4.76 (s, 1H, OH), 5.02 (s, 1H, H_4), 6.73 (dd, 1H, $H_{3'}$, J = 3.4 and 1.4 Hz), 6.87 (dd, 1H, $H_{4'}$, J = 3.4 and 5.2 Hz), 7.23 (dd, 1H, $H_{5'}$, J = 5.2 and 1.4 Hz), 9.56 (s, 1H, N-H); ^{13}C NMR (DMSO-d_6): δ 19.1 (CH_3), 31.9 (C_4), 44.0 (CH_2), 48.1 (CH_2), 50.7 (OCH_3), 59.8 (CH_2), 100.7 (C_3), 107.6 (C_{4a}), 122.8 ($C_{4'}$), 123.7 ($C_{5'}$), 126.7 ($C_{3'}$), 146.7 (C_2), 147.7 (C_{7a}), 151.7 ($C_{2'}$), 167.5 (CO), 169.5 (CO); EIMS, m/z : (M^+, 334).

Anal. Calcd. for $C_{16}H_{18}N_2O_4S$: C, 57.47; H, 5.43; N, 8.38; S, 9.59. Found: C, 57.23; H, 5.39; N, 8.45; S, 9.50.

Methyl 6-(2-Chloroethyl)-5-oxo-2-methyl-4-(2-thienyl)-1,4,5,7-tetrahydropyrrolo[3,4-*b*]pyridine-3-carboxylate (**7f**).

This compound was obtained in 50% yield after recrystallization from ethanol, mp 298-301°, IR (KBr): 3243 (N-H), 2950 (C-H), 1692 (C=O) cm^{-1}; ^{1}H NMR: δ 2.29 (s, 3H, CH_3), 3.13 (t, 2H, CH_2, J = 5.4 Hz), 3.58 (s, 3H, OCH_3), 3.68 (t, 2H, CH_2, J = 5.4 Hz), 4.08 (d, 1H, CH_2-N, J = 18.0 Hz), 4.18 (d, 1H, CH_2-N, J = 18.0 Hz), 5.02 (s, 1H, H_4), 6.73 (dd, 1H, $H_{3'}$, J = 3.4 and 1.4 Hz), 6,87 (dd, 1H, $H_{4'}$, J = 3.4 and 5.2 Hz), 7,23 (dd, 1H, $H_{5'}$, J = 5.2 and 1.4 Hz), 9.66 (s, 1H, N-H); ^{13}C NMR: δ 19.1 (CH_3), 31.8 (C_4), 41.5 (CH_2), 47.5 (CH_2), 50.7 (OCH_3), 100.9 (C_3), 107.0 (C_{4a}), 122.9 ($C_{4'}$), 123.8 ($C_{5'}$), 126.7 ($C_{3'}$), 146.6 (C_2), 148.1 (C_{7a}), 151.5 ($C_{2'}$), 167.4 (CO), 169.6 (CO); EIMS, m/z : (M^+, 352).

Anal. Calcd. for $C_{16}H_{17}ClN_2O_3S$: C, 54.47; H, 4.86; N, 7.94; S, 9.09. Found: C, 54.40; H, 4.90; N, 7.85; S, 9.07.

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