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NIOBIUM PENTACHLORIDE PROMOTED SYNTHESIS OF TETRAHYDROPIRIDINES BY MULTICOMPONENT REACTION

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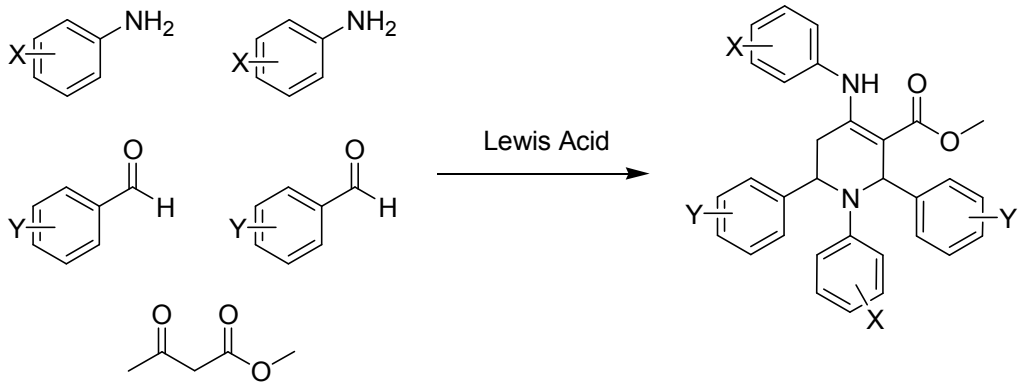
ABSTRACT
One-pot multicomponent synthesis of tetrahydropyridine derivatives between aniline derivatives, benzaldehyde and two different β-keto ester (methyl and ethyl acetoacetate) using niobium pentachloride as catalyst under mild conditions, providing good yields.

KEYWORDS: tetrahydropiridines derivatives, Niobium Pentachloride, Multicomponent reaction, Natural Products.

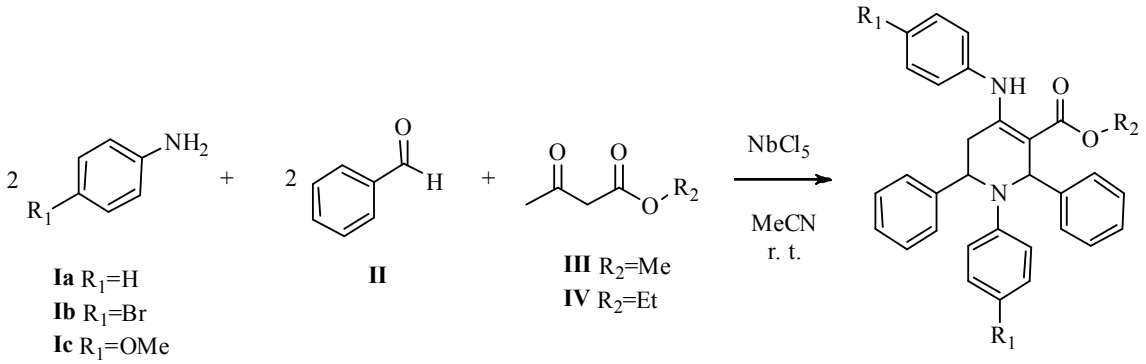
INTRODUCTION
Tetrahydropyridines are known for having great pharmacological potential due to the piperidine ring, present in various natural products structures.The piperidine subunit is known as a good farmacophore, being present in various natural and synthetic products[i-vi].
Tetrahydropyridines are used in the treatment of Parkinson and Alzheimer diseases[vii-xii], and are also used in neurodegeneration studies[xiii]. They present muscarinic[i,xiv,xv], nicotinic[xvi], analgesic[xvii], hyperglycemic[xvii] and antipsychotic[xviii] activity, among others. Some tetrahydropyridine derivatives are also responsible for calcium ions flux regulation[xvi,xix,xx], and for GABA (gamma-Aminobutyric acid) inhibition[xviii,xxi]. Recently, Misra and co-authors described some good results of antimalarial activity for tetrahydropyridine derivatives against the *Plasmodium falciparum*[xxii].
Due to those reasons, in the last years, a great effort has been made to develop new methods in an attempt to synthesize the tetrahydropyridine derivatives, seeking more efficiency and lesser environmental impact. There are several ways to produce the tetrahydropyridine derivatives, such as the cyclocondensation of Carbonyl compounds and amines[xxiii], cyclocondensation of δ-haloimines[xxiv], pyridine salts hydrogenation[xxv], Hantzsch cyclization[xix,xxvi,xxvii,xxviii], Diels-Alder reactions[xxix,xxx] and Makayama Michaels[xxxi-xxxiii]. Many of these methods involve long synthetic routes, with low yields and products mixture.
In contrast to those routes, a different method – involving a multicomponent reaction, in which five components react in the same reaction pot in the presence of a Lewis Acid – was recently described in the literature (scheme I). In this method, 2.0 mmols of aniline derivative, 2.0 mmols

of benzaldehyde derivative and 1.0 mmol of methyl acetoacetate were used, presenting low yield and high reaction time[xxxiv-xlvi].



Scheme I. Synthesis of tetrahydropyridine derivatives in the presence of a Lewis acid.

Some of the Lewis acids are not easily available or are expensive. In addition, they require longer reaction times and result in products with poor yields. Therefore, developing simple and efficient synthetic methods for preparing this type of compound is increasingly important.
In this work, we have reported our studies on the use of Niobium Pentachloride ($NbCl_5$) as a catalyst in these multicomponent reactions. Niobium pentachloride is highly electrophilic and, therefore, can act as a Lewis acid, catalyzing several organic reactions[xlvii-liv]. As part of our research work on synthetic methodologies using niobium pentachloride in a variety of reactions[lv-lxiv], in this work, we described our studies in the pentacomponent one-pot reaction for the synthesis of tetrahydropyridine derivatives using niobium pentachloride as catalyst, in reaction between aniline derivatives (**I a-h**), benzaldehyde (**II**) and β-keto ester {methyl acetoacetate (**III**) or ethyl acetoacetate (**IV**)}, in the presence of 50 mol% of $NbCl_5$, producing the tetrahydropyridine derivatives **Va-h** and **VIa-h**, with good yields and good reaction times. (scheme II).



Ia R_1=H
Ib R_1=Br
Ic R_1=OMe
Id R_1=F
Ie R_1=Cl
If R_1=I
Ig R_1=Me
Ih R_1=NO_2

II

III R_2=Me
IV R_2=Et

V (a-h) R_2=Me
VI (a-h) R_2=Et

Scheme II. Multicomponent reaction catalyzed by niobium pentachloride.

RESULTS AND DISCUSSION

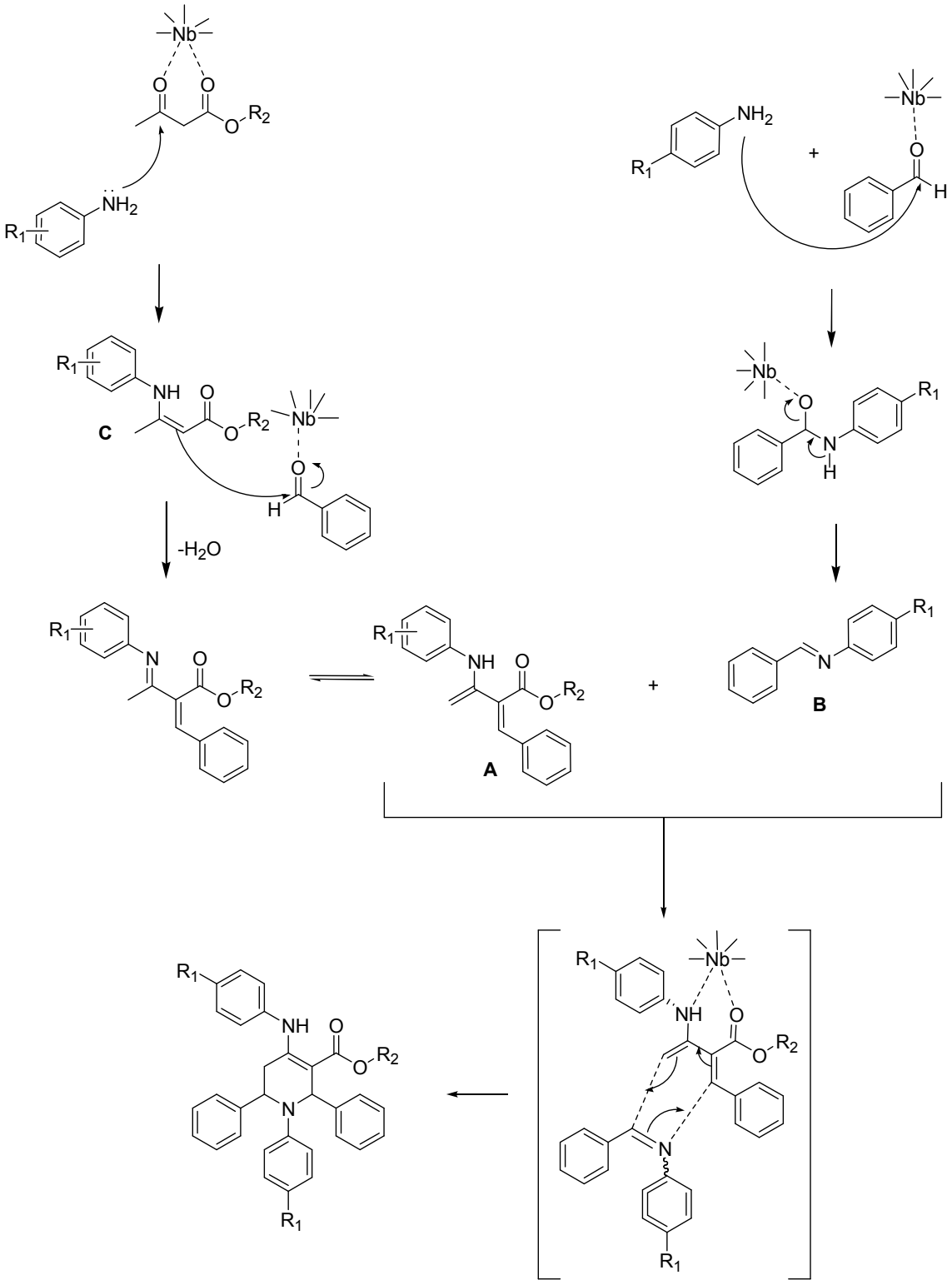
The multicomponent reactions between benzaldehyde (**II**) (2,0 eq.), aniline derivatives (**I a-h**) (2.0 eq.) and β-keto ester (**III** or **IV**) (1.0 eq.) were conducted under an atmosphere of N_2, at room temperature, under constant stirring and using anhydrous acetonitrile (CH_3CN) as solvent. Niobium Pentachloride was used as a catalyst in the proportion of 50% for each mol of aniline derivative. The products **V (a-h)** and **VI(a-h)** were purified by recrystallization in ethanol and characterized by spectroscopic and spectrometric methods. Table I shows the results obtained for these multicomponent reactions catalyzed by $NbCl_5$.

Table I. Reaction time and yields of the synthesis of tetrahydropyridine derivatives.

Aniline	β-keto ester	Reaction time (h)	Yield (%)
I a	**III**	24	49 (**V a**)
	IV	24	60 (**VI a**)
I b	**III**	24	69 (**V b**)
	IV	24	66 (**VI b**)
I c	**III**	24	61 (**V c**)
	IV	24	70 (**VI c**)
I d	**III**	24	72 (**V d**)
	IV	24	71 (**VI d**)
I e	**III**	24	66 (**V e**)
	IV	24	65 (**VI e**)
I f	**III**	24	68 (**V f**)
	IV	24	63 (**VI f**)
I g	**III**	24	55 (**V g**)
	IV	24	67 (**VI g**)
I h	**III**	48	78 (**V h**)
	IV	48	89 (**VI h**)

Analyzing Table I, it is possible to observe that the products were generated with good yields and a good reaction time, demonstrating that niobium pentachloride is a good catalyst in the reaction between aniline derivatives, benzaldehyde and β-keto esters to synthesize tetrahydropyridine derivatives. We can verify that there is little variation in the results, with similar results that do not depend on the substrate used.

Mechanistically, according to our results and to the literature[xxxii-xliv], the multicomponent reaction for the formation of tetrahydropyridines occurs in three steps, two of them are necessary to the "*in situ*" formation of the intermediates (**A** and **B**) and the third consists of the cycloaddition reaction between these intermediates to obtain the tetrahydropyridine derivatives (scheme III).



Scheme III. Proposed mechanism for the synthesis of tetrahydropyridine derivatives catalyzed by $NbCl_5$.

The intermediate **A** is obtained by the initial reaction between the aniline derivative and the β-keto ester, forming the corresponding enamine **C**. This enamine reacts with one equivalent of the benzaldehyde through Knoevenagel condensation, followed by water elimination and the isomerization of the double bond to obtain **A**. The other intermediate obtained is the Schiff base **B**, resulting from the condensation reaction between the aniline derivative and the benzaldehyde derivative. In the final step, the intermediates **A** and **C** react with each other, in an aza-Diels-Alder reaction, to produce the tetrahydropyridine derivative.
In conclusion, it has been shown that the Niobium pentachloride is an efficient catalyst for multicomponent reactions between benzaldehyde, aniline derivatives and β-keto esters to synthesize the tetrahydropyridine derivatives, with good reaction times (24-48h) and product yields (49-89%), under mild reaction conditions and with operational simplicity.

EXPERIMENTAL

All reactions were performed under N_2 atmosphere using Acetonitrile anhydrous. All of the chemicals were purchased from Sigma-Aldrich Chemical Co. (St. Louis, MO, USA) and used without further purification. Thin-layer chromatography was performed on Aldrich silica gel aluminum sheets, which were visualized with a vanillin/methanol/water/sulfuric acid mixture. Aldrich silica gel 60 was employed for column chromatography. Bruker DRX 400 and DRX 500 spectrometers were used for the NMR spectra ($CDCl_3$ solutions) using tetramethylsilane as internal reference for ^1H and $CDCl_3$ as an internal reference for ^{13}C. A Bruker FTIR model VERTEX 70 was used to record IR spectra (neat or film). HRMS analyses were recorded on micrOTOF (Bruker), with ESI-TOF detector operating on positive mode.

General Procedure for the Multicomponent Reaction between benzaldehyde, aniline derivatives and β-keto ester with $NbCl_5$:
To a solution of niobium pentachloride (50 mol%) in 1.0 mL of anhydrous Acetonitrile, maintained at room temperature under a nitrogen atmosphere, we added a solution of the benzaldehyde (**II**) (2.0 mmol), methyl acetoacetate (**III**) or ethyl acetoacetate (**IV**) (1.0 mmol) and respectively aniline (**I a-g**) (2.0 mmol) in 5.0 mL of anhydrous Acetonitrile. After completion of the addition, stirring was continued at room temperature. The reaction mixture was quenched with water (3.0 mL). The mixture was extracted with ethyl acetate (10.0 mL). The organic layer was separated and washed with saturated sodium bicarbonate solution (3 x 10.0 mL), saturated brine (2 x 10.0 mL), and then dried over anhydrous magnesium sulfate. The solvent was removed under vacuum and the resulting mixture was dissolved in EtOAc (1.0 mL), followed by the addition of EtOH, which resulted in a yellow solid. This solid was recrystallized in EtOH to obtain a white solid.

1,2,6-Triphenyl-4-phenylamino-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid methyl ester (Va): RMN-^1H (400 MHz, $CDCl_3$): δ(ppm) 10.25 (sl, 1H), 7.33-7.04 (m, 15H), 6.60 (t, J=7.2Hz, 1H), 6.52 (m, 2H), 6.45 (s, 1H), 6.27 (m, 2H), 5.15 (sl, 1H), 3.93 (s, 3H), 2.87 (dd, J_1=15.2 e J_2=5.8 Hz, 1H), 2.76 (dd, J_1=15.2 e J_2=2.5 Hz, 1H). RMN-^{13}C (100 MHz, $CDCl_3$): δ(ppm) 168.6 (C=O), 156.3 (C), 146.9 (C), 143.9 (C), 142.7 (C), 137.8 (C), 128.9 (2 CH), 128.8 (2 CH), 128.6 (2 CH), 128.2 (2 CH), 127.1 (CH), 126.6 (2 CH), 126.4 (2 CH), 126.3 (CH), 125.9 (2 CH), 125.8 (CH), 116.1 (CH), 112.9 (2CH), 97.9 (C), 58.2 (CH), 55.1 (CH), 51.0 (CH_3), 33.6 (CH_2). IR (ν_{max}/cm^{-1}): 1661, 1585, 1502, 1252, 1078, 748, 700. ESI-HRMS: *m/z* calcd for $C_{31}H_{29}N_2O_2$ $[M + H]^+$: 461.22235; found 461.2213.

1-(4-Bromo-phenyl)-4-(4-bromo-phenylamino)-2,6-diphenyl-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid methyl ester (Vb): RMN-^{1}H (400 MHz, $CDCl_3$): δ(ppm) 10.18 (sl, 1H), 7.30-7.11 (m, 16H), 6.38 (d, 3H), 6.10 (d, 2H), 5.11 (sl, 1H), 3.94 (s, 3H), 2.87 (dd, J_1=15.2 e J_2=5.8 Hz, 1H), 2.70 (dd, J_1=15.2 e J_2=2.3 Hz, 1H). RMN-^{13}C (100 MHz, $CDCl_3$): δ(ppm) 168.5 (C=O), 155.5 (C), 145.9 (C), 143.0 (C), 142.1 (C), 136.8 (C), 132.0 (2CH), 131.6 (2CH), 128.9 (2CH), 128.4 (2CH), 127.5 (CH), 127.4 (2CH), 126.6 (CH), 126.5 (2CH), 126.3 (2CH), 119.3 (C), 114.5 (2CH), 108.4 (C), 98.5 (C), 58.3 (CH), 55.2 (CH), 51.2 (CH_3), 33.4 (CH_2). IR (ν_{max}/cm^{-1}): 3259, 1651, 1599, 1500, 1489, 1317, 1254, 1078, 798, 721, 698. ESI-HRMS: *m/z* calcd for $C_{31}H_{27}Br_2N_2O_2$ $[M + H]^+$: 617.04338; found 617.0244.

1-(4-Methoxy-phenyl)-4-(4-methoxy-phenylamino)-2,6-diphenyl-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid methyl ester (Vc): RMN-^{1}H (400 MHz, $CDCl_3$): δ(ppm) 10.09 (sl, 1H), 7.31-7.16 (m, 13H), 6.63 (dd, 4H), 6.43 (d, 2H), 6.33 (s, 1H), 6.19 (d, 2H), 5.05 (sl, 1H), 3.91 (s, 3H), 3.74 (s, 3H), 3.66 (s, 3H), 2.79 (dd, J_1=15.2 e J_2=5.8 Hz, 1H), 2.63 (dd, J_1=15.2 e J_2=2.5 Hz, 1H). RMN-^{13}C (100 MHz, $CDCl_3$): δ(ppm) 168.7 (C=O), 157.8 (C), 157.0 (C), 150.8 (C), 144.2 (C), 143.2 (C), 141.5 (C), 130.6 (C), 128.6 (2CH), 128.2 (2CH), 127.9 (2CH), 127.1 (CH), 126.8 (2CH), 126.5 (2CH), 126.2 (CH), 114.5 (2CH), 113.9 (4CH), 97.0 (C), 58.3 (CH), 55.7 (CH_3), 55.6 (CH), 55.4 (CH_3), 50.9 (CH_3), 33.6 (CH_2). IR (ν_{max}/cm^{-1}): 3257, 1650, 1510, 1236, 1074, 1033, 810, 700. ESI-HRMS: *m/z* calcd for $C_{33}H_{33}N_2O_4$ $[M + H]^+$: 521.24348; found 521.2416.

1-(4-Fluoro-phenyl)-4-(4-fluoro-phenylamino)-2,6-diphenyl-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid methyl ester (Vd): RMN-^{1}H (400 MHz, $CDCl_3$): δ(ppm) 10.14 (sl, 1H), 7.33-7.15 (m, 12H), 6.80-6.73 (m, 4H), 6.43-6.39 (m, 2H), 6.35 (s, 1H), 6.21-6.18 (m, 2H), 5.08 (sl, 1H), 3.93 (s, 3H), 2,84 (dd, J_1=15.2 e J_2=5.8 Hz, 1H), 2.62 (dd, J_1=15.2 e J_2=2.5 Hz, 1H). RMN-^{13}C (100 MHz, $CDCl_3$): δ(ppm) 168.6 (C=O), 160.8 (J_{CF}=245.9 Hz), 156.3 (C), 155.0 (J_{CF}=234.9 Hz), 143.5 (C), 143.4 (C), 142.7 (C), 133.7 (C), 128.8 (2CH), 128.3 (2CH), 128.2 (2CH), 128.1 (CH), 127.4 (CH), 126.6 (2CH), 126.5 (CH), 126.4 (2CH), 115.8 (CH), 115.6 (CH), 115.4 (CH), 115.2 (CH), 113.5 (CH), 97.8 (C), 58.4 (CH), 55.5 (CH), 51.1 (CH_3), 33.6 (CH_2). IR (ν_{max}/cm^{-1}): 1659, 1595, 1506, 1254, 1229, 1182, 1067, 810, 770, 698. ESI-HRMS: *m/z* calcd for $C_{31}H_{27}F_2N_2O_2$ $[M + H]^+$: 497.20351; found 497.2026.

1-(4-Chloro-phenyl)-4-(4-chloro-phenylamino)-2,6-diphenyl-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid methyl ester (Ve): RMN-^{1}H (400 MHz, $CDCl_3$): δ(ppm)10.19 (sl, 1H), 7.33-7.20 (m, 10H), 7.15 (dd, 2H), 7.05 (d, 2H), 7.02 (d, 2H), 6.42 (d, 2H), 6.38 (s, 1H), 6.14 (d, 2H), 5.10 (sl, 1H), 3.94 (s, 3H), 2.85 (dd, J_1=15.2 e J_2=5.8 Hz, 1H), 2.69 (dd, J_1=15.2 e J_2=2.5 Hz, 1H). RMN-^{13}C (100 MHz, $CDCl_3$): δ(ppm) 168.5 (C=O), 155.6 (C), 145.5 (C), 143.1 (C), 142.2 (C), 136.3 (C), 131.5 (C), 129.0 (2CH), 128.8 (2CH), 128.7 (2CH), 128.4 (2CH), 127.5 (CH), 127.1 (2CH), 126.6 (CH), 126.5 (2CH), 126.3 (2CH), 121.2 (C), 113.9 (2CH), 98.4 (C), 58.3 (CH), 55.2 (CH), 51.2 (CH_3), 33.5 (CH_2). IR (ν_{max}/cm^{-1}): 3259, 1651, 1601, 1491, 1317, 1254, 1078, 800, 729, 698. ESI-HRMS: *m/z*calcd for $C_{31}H_{27}Cl_2N_2O_2$ $[M + H]^+$: 529.14441; found 529.1419.

1-(4-Iodo-phenyl)-4-(4-iodo-phenylamino)-2,6-diphenyl-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid methyl ester (Vf): RMN-^{1}H (400 MHz, $CDCl_3$): δ(ppm) 10.19 (sl, 1H), 7.39 (d, 2H), 7.32-7.13 (m, 12H), 6.36 (s, 1H), 6.30 (d, 2H), 5.98 (d, 2H), 5.10 (sl, 1H), 3.94 (s, 3H), 2.85 (dd, J_1=15.2 e J_2=5.8 Hz, 1H), 2.72 (dd, J_1=15.2 e J_2=2.3 Hz, 1H). RMN-^{13}C (100 MHz, $CDCl_3$): δ(ppm) 168.4 (C=O), 155.3 (C), 146.4 (C), 143.0 (C), 142.0 (C), 138.0 (2CH), 137.5 (C), 137.4 (2CH), 128.9 (2CH), 128.4 (2CH), 127.5 (2CH), 126.6 (CH), 126.5 (2CH), 126.3 (2CH), 117.8 (CH), 115.3 (2CH), 98.6 (C), 90.2 (C), 77.6 (C), 58.2 (CH), 55.1 (CH), 51.3 (CH_3), 33.4 (CH_2).

IR(ν_{max}/cm^{-1}): 3259, 1655, 1591, 1516, 1317, 1254, 1076, 795, 768, 698. ESI-HRMS: *m/z* calcd for $C_{31}H_{27}I_2N_2O_2$ $[M + H]^+$: 713.01565; found 713.0160.

2,6-Diphenyl-1-p-tolyl-4-p-tolylamino-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid methyl ester (Vg): RMN-^{1}H (400 MHz, $CDCl_3$): δ(ppm) 10.16 (sl, 1H), 7.32-7.17 (m, 10H), 6.88 (t, 4H), 6.43-6.39 (m, 3H), 6.14 (d, 2H), 5.10 (sl, 1H), 3.92 (s, 3H), 2.83 (dd, J_1=15.2 e J_2=5.8 Hz, 1H), 2.72 (dd, J_1=14.9 e J_2=2.5 Hz, 1H), 2.25 (s, 3H), 2.15 (s, 3H). RMN-^{13}C (100 MHz, $CDCl_3$): δ(ppm) 168.6 (C=O), 156.7 (C), 144.8 (C), 144.2 (C), 143.0 (C), 135.7 (C), 135.1 (C), 129.4 (4CH), 128.6 (2CH), 128.2 (2CH), 127.1 (CH), 126.7 (2CH), 126.4 (2CH), 126.2 (CH), 126.0 (2CH, 125.0 (C), 112.8 (2CH), 97.4 (C), 58.2 (CH), 55.2 (CH), 50.9 (CH_3), 33.5 (CH_2), 20.9 (CH_3), 20.1 (CH_3). IR(ν_{max}/cm^{-1}): 3259, 1655, 1591, 1516, 1317, 1254, 1076, 795, 768, 698. ESI-HRMS: *m/z* calcd for $C_{33}H_{33}N_2O_2$ $[M + H]^+$: 489.25365; found 489.2544.

1-(4-Nitro-phenyl)-4-(4-nitro-phenylamino)-2,6-diphenyl-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid methyl ester (Vh): RMN-^{1}H (400 MHz, $CDCl_3$): δ(ppm) 10.55 (sl, 1H), 7.98 (m, 4H), 7.36-7.25 (m, 10H), 7.16-7.14 (m, 2H), 6.56-6.53 (m, 3H), 6.41 (d, 2H), 5.32 (sl, 1H), 4.01 (s, 3H), 3.07 (dd, J_1=15.4 e J_2=5.6 Hz, 1H), 2.95 (dd, J_1=15.2 e J_2=1.8 Hz, 1H). RMN-^{13}C (100 MHz, $CDCl_3$): δ(ppm) 168.1 (C=O), 153.2 (C), 151.6 (C), 144.2 (C), 143.8 (C), 141.1 (C), 140.4 (C), 137.9 (C), 129.3 (2CH), 128.9 (2CH), 128.2 (CH), 127.4 (CH), 126.1 (2CH), 126.0 (2CH), 125.8 (2CH), 125.0 (2CH), 123.2 (2CH), 112.2 (2CH), 101.6 (C), 58.7 (CH), 55.8 (CH), 51.9 (CH_3), 33.6 (CH_2). IR (ν_{max}/cm^{-1}): 1657, 1581, 1516, 1487, 1335, 1257, 1121, 1068, 752, 704. ESI-HRMS: *m/z* calcd for $C_{31}H_{27}N_4O_6$ $[M + H]^+$: 551.19251; found 551.1914.

1-(4-Bromo-phenyl)-4-(4-bromo-phenylamino)-2,6-diphenyl-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid ethyl ester (VIb): RMN-^{1}H (400 MHz, $CDCl_3$): δ(ppm) 10.23 (sl, 1H), 7.30-7.11 (m, 16H), 6.39 (d, 3H), 6.10 (d, 2H), 5.10 (sl, 1H), 4.52-4.43 (m, 1H), 4.36-4.29 (m, 1H), 2.86 (dd, J_1=15.2 e J_2=5.8 Hz, 1H), 2.70 (dd, J_1=15.2 e J_2=2.0 Hz, 1H), 1.47 (t, 3H). RMN-^{13}C (100 MHz, $CDCl_3$): δ(ppm) 168.1 (C=O), 155.3 (C), 145.9 (C), 143.1 (C), 142.1 (C), 136.9 (C), 131.9 (2CH), 131.6 (2CH), 128.9 (2CH), 128.4 (2CH), 127.5 (CH), 127.3 (2CH), 126.6 (CH), 126.5 (2CH), 126.3 (2CH), 119.1 (C), 114.6 (2CH), 108.4 (C), 98.8 (C), 59.9 (CH_2), 58.3 (CH), 55.2 (CH), 33.4 (CH_2), 14.8 (CH_3). IR (ν_{max}/cm^{-1}): 3232, 1643, 1601, 1489, 1315, 1248, 1068, 798, 719, 698. ESI-HRMS: *m/z* calcd for $C_{32}H_{29}Br_2N_2O_2$ $[M + H]^+$: 631.05903; found 631.0296.

1-(4-Methoxy-phenyl)-4-(4-methoxy-phenylamino)-2,6-diphenyl-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid ethyl ester (VIc): RMN-^{1}H (400 MHz, $CDCl_3$): δ(ppm) 10.13 (sl, 1H), 7.33-7.16 (m, 10H), 6.66 (d, 2H), 6.60 (d, 2H), 6.45 (d, 2h), 6.34 (s, 1H), 6.19 (d, 2H), 5.05 (sl, 1H), 4.47-4.40 (m, 1H), 4.35-4.26 (m, 1H), 3.74 (s, 3H), 3.66 (s, 3H), 2.79 (dd, J_1=15.2 e J_2=5.8 Hz, 1H), 2.64 (dd, J_1=15.2 e J_2=2.8 Hz, 1H), 1.44 (t, 3H). RMN-^{13}C (100 MHz, $CDCl_3$): δ(ppm) 168.3 (C=O), 157.7 (C), 156.9 (C), 150.8 (C), 144.4 (C), 143.3 (C), 141.2 (C), 130.7 (C), 128.6 (2CH), 128.1 (2CH), 127.9 (2CH), 127.1 (CH), 126.8 (2CH), 126.5 (2CH), 126.2 (CH), 114.5 (2CH), 114.0 (2CH), 113.9 (2CH), 97.2 (C), 59.5 (CH_2), 58.3 (CH), 55.6 ($2CH_3$), 55.4 (CH), 33.6 (CH_2), 14.8 (CH_3). IR(ν_{max}/cm^{-1}): 3242, 1647, 1593, 1508, 1236, 1072, 1038, 806, 700. ESI-HRMS: *m/z* calcd for $C_{34}H_{35}N_2O_4$ $[M + H]^+$: 535.25913; found 535.2570.

1-(4-Fluoro-phenyl)-4-(4-fluoro-phenylamino)-2,6-diphenyl-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid ethyl ester (VId): RMN-^{1}H (400 MHz, $CDCl_3$): δ(ppm) 10.18 (sl, 1H), 7.33-7.15 (m, 10H), 6.79-6.74 (m, 4H), 6.44-6.39 (m, 2H), 6.36 (s, 1H), 6.22-6.18 (m, 2H), 5.08 (sl, 1H), 4.50-4.43 (m, 1H), 4.36-4.28 (m, 1H), 2.83 (dd, J_1=15.2 e J_2=5.8 Hz, 1H), 2.62 (dd, J_1=15.2 e J_2=2.5 Hz, 1H), 1.47 (t, 3H). RMN-^{13}C (100 MHz, $CDCl_3$): δ(ppm) 168.2 (C=O), 160.8 (JCF=245.9 Hz), 156.1 (C), 155.0 (JCF=234.9 Hz), 143.6 (C), 143.4 (C), 142.8 (C), 133.8 (C), 128.8 (2CH), 128.3 (2CH), 128.1 (CH), 128.0 (CH), 127.4 (CH), 126.6 (2CH), 126.4 (CH),

126.4 (2CH), 115.8 (CH), 115.5 (CH), 115.4 (CH), 115.2 (CH), 113.7 (CH), 113.6 (CH), 59.8 (CH_2), 58.4 (CH), 55.5 (CH), 33.6 (CH_2), 14.8 (CH_3). IR (ν_{max}/cm^{-1}): 3240, 1645, 1593, 1508, 1317, 1249, 1225, 1209, 1070, 812, 768, 698. ESI-HRMS: *m/z* calcd for $C_{32}H_{29}F_2N_2O_2$ $[M + H]^+$: 511.21916; found 511.2193.

1-(4-Chloro-phenyl)-4-(4-chloro-phenylamino)-2,6-diphenyl-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid ethyl ester (VIe): RMN-^{1}H (400 MHz, $CDCl_3$): δ(ppm) 10.24 (sl, 1H), 7.33-7.22 (m, 8H), 7.16-7.14 (m, 2H), 7.05 (d, 2H), 7.00 (d, 2H), 6.43 (d, 2H), 6.41 (s, 1H), 6.17 (d, 2H), 5.10 (sl, 1H), 4.51-4.43 (m, 1H), 4.37-4.29 (m, 1H), 2.85 (dd, J_1=15.2 e J_2=5.8 Hz, 1H), 2.70 (dd, J_1=15.2 e J_2=2.3 Hz, 1H), 1.47 (t, 3H). RMN-^{13}C (100 MHz, $CDCl_3$): δ(ppm) 168.2 (C=O), 155.4 (C), 145.5 (C), 143.3 (C), 142.3 (C), 136.4 (C), 131.4 (C), 129.0 (2CH), 128.8 (2CH), 128.7 (2CH), 128.4 (2CH), 127.5 (CH), 127.0 (2CH), 126.6 (CH), 126.5 (2CH), 126.3 (2CH), 121.2 (C), 114.0 (2CH), 98.7 (C), 59.9 (CH_2), 58.3 (CH), 55.2 (CH), 33.5 (CH_2), 14.8 (CH_3). IR (ν_{max}/cm^{-1}): 1645, 1603, 1495, 1319, 1250, 1070, 802, 727, 698. ESI-HRMS: *m/z* calcd for $C_{32}H_{29}Cl_2N_2O_2$ $[M + H]^+$: 543.16006; found 543.1578.

1-(4-Iodo-phenyl)-4-(4-iodo-phenylamino)-2,6-diphenyl-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid ethyl ester (VIf): RMN-^{1}H (400 MHz, $CDCl_3$): δ(ppm) 10.24 (sl, 1H), 7.38 (d, 2H), 7.31-7.21 (m, 10H), 7.15-7.13 (m, 2H), 6.38 (s, 1H), 6.30 (d, 2H), 5.98 (d, 2H), 5.10 (sl, 1H), 4.50-4.42 (m, 1H), 4.37-4.29 (m, 1H), 2.85 (dd, J_1=15.2 e J_2=5.8 Hz, 1H), 2.72 (dd, J_1=15.2 e J_2=2.3 Hz, 1H), 1.47 (t, 3H). RMN-^{13}C (100 MHz, $CDCl_3$): δ(ppm) 168.1 (C=O), 155.1 (C), 146.5 (C), 143.1 (C), 142.1 (C), 138.0 (2CH), 137.6 (C), 137.5 (2CH), 128.9 (2CH), 128.4 (2CH), 127.5 (CH), 127.4 (2CH), 126.6 (CH), 126.5 (2CH), 126.3 (2CH), 115.3 (2CH), 98.9 (C), 90.1 (C), 77.6 (C), 60.0 (CH_2), 58.2 (CH), 55.1 (CH), 33.4 (CH_2), 14.8 (CH_3). IR (ν_{max}/cm^{-1}): 1647, 1601, 1497, 1317, 1250, 1072, 1007, 797, 716, 698. ESI-HRMS: *m/z* calcd for $C_{32}H_{29}I_2N_2O_2$ $[M + H]^+$: 727.03130; found 727.0293.

2,6-Diphenyl-1-p-tolyl-4-p-tolylamino-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid ethyl ester (VIg): RMN-^{1}H (400 MHz, $CDCl_3$): δ(ppm) 10.20 (s, 1H), 7.34-7.16 (m, 10H), 6.88-6.86 (m, 4H), 6.42 (d, 3H), 6.14 (d, 2H), 5.10 (sl, 1H), 4.48-4.40 (m, 1H), 4.36-4.28 (m, 1H), 2.83 (dd, J_1=15.2 e J_2=5.8 Hz, 1H), 2.73 (dd, J_1=15.2 e J_2=2.5 Hz, 1H), 2.25 (s, 3H), 2.15 (s, 3H), 1.45 (t, 3H). RMN-^{13}C (100 MHz, $CDCl_3$): δ(ppm) 168.3 (C=O), 156.5 (C), 144.8 (C), 144.4 (C), 143.0 (C), 135.5 (C), 135.2 (C), 129.5 (2CH), 129.4 (2CH), 128.6 (2CH), 128.2 (2CH), 127.0 (CH), 126.7 (2CH), 126.4 (2CH), 126.2 CH), 125.9 (2CH), 125.0 (C), 112.9 (2CH), 97.7 (C), 59.6 (CH_2), 58.2 (CH), 55.2 (CH), 33.6 (CH_2), 20.9 (CH_3), 20.1 (CH_3), 14.8 (CH_3). IR (ν_{max}/cm^{-1}): 3240, 1647, 1593, 1516, 1315, 1248, 1074, 795, 700. ESI-HRMS: *m/z* calcd for $C_{34}H_{35}N_2O_2$ $[M + H]^+$: 503.26930; found 503.2679.

1-(4-Nitro-phenyl)-4-(4-nitro-phenylamino)-2,6-diphenyl-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid ethyl ester (VIh): RMN-^{1}H (400 MHz, $CDCl_3$): δ(ppm) 10.61 s, 1H), 8.01-7.97 (m, 4H), 7.38-7.24 (m, 10H), 7.17-7.13 (m, 2H), 6.57-6.52 (m, 3H), 6.41 (d, 2H), 5.31 (sl, 1H), 4.58-4.50 (m, 1H), 4.44-4.35 (m, 1H), 3.09-3.03 (m, 1H), 2.98-2.92 (m, 1H), 1.52 (t, 3H). RMN-^{13}C (100 MHz, $CDCl_3$): δ(ppm) 168.4 (C=O), 153.1 (C), 151.6 (C), 144.1 (C), 143.9 (C), 141.1 (C), 140.4 (C), 137.9 (C), 129.2 (2CH), 128.8 (2CH), 128.2 (CH), 127.3 (CH), 126.1 (2CH), 126.0 (2CH), 125.8 (2CH), 125.0 (2CH), 123.2 (CH), 123.0 (CH), 112.2 (2CH), 101.9 (C), 60.8 (CH_2), 58.7 (CH), 55.8 (CH), 33.6 (CH_2), 14.7 (CH_3); IR (ν_{max}/cm^{-1}): 1657, 1581, 1516, 1487, 1335, 1257, 1121, 1068, 752, 704.ESI-HRMS: *m/z* calcd for $C_{32}H_{29}N_4O_6$ $[M + H]^+$: 565.20816; found 565.2068.

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