Synthesis of N-Benzoylamino-1,2,3,6-tetrahydropyridine Derivatives as Potential Anti-inflammatory Agents

Bereket Mochona[1] and Kinfe K. Redda[2]

[1]Department of Chemistry, [2]College of Pharmacy and Pharmaceutical Sciences,
Florida A&M University, Tallahassee, FL 32307

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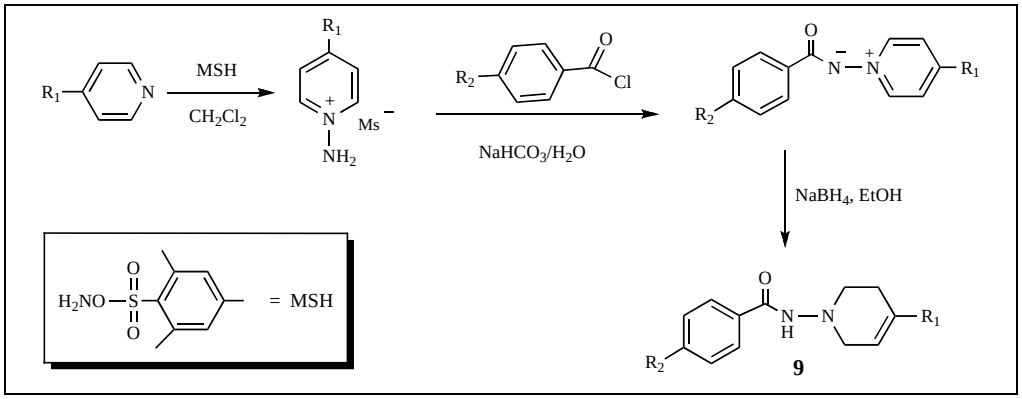

N-Benzoylamino-1,2,3,6-tetrahydropyridines **9a-q** were synthesized from 4-substituted pyridines in four steps. Amination of pyridines was carried out to prepare intermediate N-aminopyridinium mesylates using mesytelenesulfonyl hydroxmate (MSH) as aminating agent. N-aminopyridinium mestylates reacted with appropriately substituted acyl chlorides to form N-ylides as stable crystalline solids. Partial reduction of N-ylides with mild reducing agent afforded N-benzoylamino-1,2,3,6-tetrahydropyridines in fair to good yields.

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INTRODUCTION

Tetrahydropyridine rings have attracted synthetic interests for being essential structures in many agrochemicals as well as medicinal agents (Figure 1). For example, compound **1** is useful as a pesticide [1], compounds **2-4** possess dopaminergic and antipsychotic effects [2-7] and compounds **5** and **6** have anti-inflammatory activities [8,9]. The electrophilic cyclization of iminium ions (Mannich cyclization) to generate unsaturated azacyclic systems [10] and the synthesis of tetrahydropyridine derivatives by partial reduction of N-ylides constitute some of the most important methods for preparing tetrahydropyridines.

The synthesis of tetrahydropyridines *via* partial reduction of N-ylides using mild reducing agents has been extensively investigated by Redda *et al.*, to prepare N-benzoylamino-1,2,3,6-tetrahydropyridine derivatives as anti-inflammatory agents [11-13].

In previous papers, we reported the synthesis and anti-inflammatory activity profiles of a few 1,2,3,6-tetrahydropyridines [14]. The results showed the

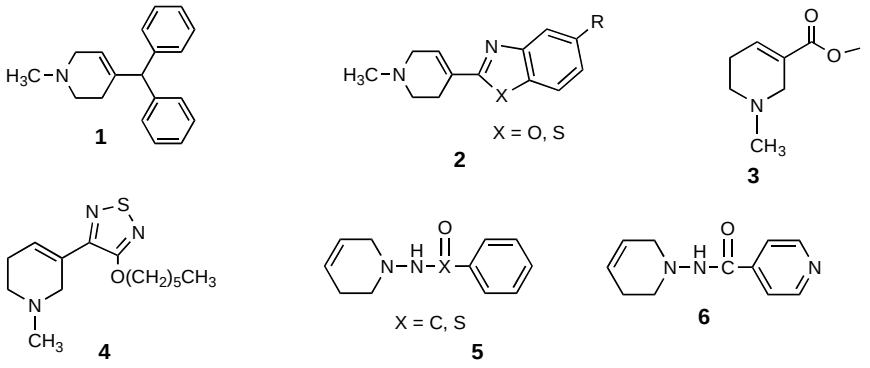
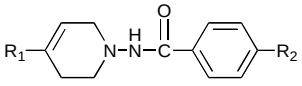


Figure 1. Some Biologically Active Tetrahydropyridines.

pharmacological activities of the derivatives of **(6)** depended on the nature of the substitutents on the tetrahydropyridine ring moiety. This investigation is a continuation of the synthesis of 1,2,3,6-tetrahydropyridine designed to modify the tetrahydropyridine ring and phenyl moieties by introducing groups with various electronic properties.

A series of 4-substituted 1,2,3,6-tetrahydropyridines, **9a-q**, were prepared *via* partial reduction of N-ylides with a mild reducing agent, as outlined in Scheme 1. The ylides were prepared by coupling N-aminopyridinium salt (**14**) with appropriate acyl chlorides. N-aminopyridinium salts were prepared by aminating 4-substituted pyridines under a basic condition. Several methods of aminating pyridine derivatives are reported in literature. The use of mesitylenesulfonyl hydroxmate (MSH) was found the most versatile. MSH **(13)** was prepared by the method reported by Tamura and Katritzky [15,16].



(**9**)

Treatment of the N-aminopyridinium derivatives with appropriately substituted acylating agents like acyl chlorides, followed by treatment with a base afforded N-ylides (**15**) as stable crystalline solids. Partial reduction of N-ylides using mild reducing conditions gave the tetrahydropyridines in fair to good yields.

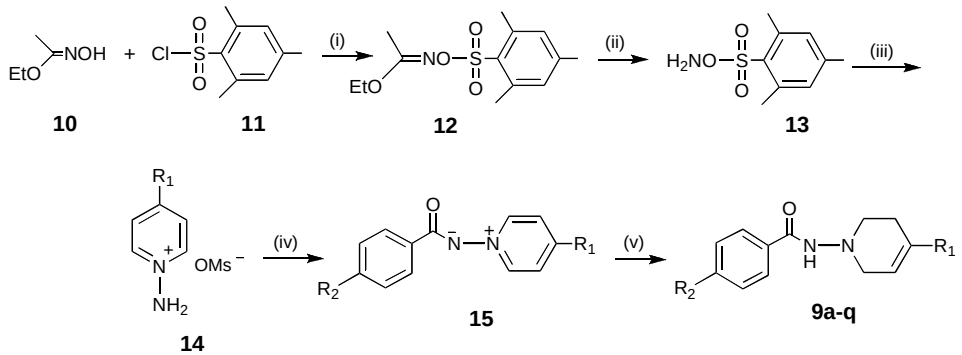
RESULTS AND DISCUSSION

Physical constants of the synthesized tetrahydropyridines are summarized in Table 1. The tetrahydropyridines are thermally stable and soluble in commonly used organic solvents such as chloroform, dichloromethane, ethyl acetate but are insoluble in hexane and petroleum ether. This is in sharp contrast to **(15)** which is soluble in methanol and other polar solvents. Analytical data of compounds **9a-q** is presented in Table 1.

EXPERIMENTAL

Melting points (mp) were determined on Gallenkamp Melting Point apparatus and are uncorrected. The structures of the products described were confirmed by IR, ^{1}H-NMR and elemental analysis data. IR spectra were run with KBr pellets on Perkin-Elmer 1430 FT spectrometer. ^{1}H-NMR spectra were recorded on a Bruker HX-300 spectrometer, using $CDCl_3$ as the solvent unless otherwise specified. Chemical shifts (δ) are reported in parts per million (ppm) downfield from tetramethylsilane (Me_4Si, 0.00ppm) as the internal standard and coupling constants in Hertz (Hz). Elemental analysis was performed in Galbraith Laboratories Inc., Knoxville, TN. Analysis indicated by the symbols of the elements was within ± 0.4% of the theoretical values. Analytical thin layer chromatography was performed on precoated silica-gel using Whatman TLC plates (0.2mm, GF254, E Merck). Spots were located by UV illumination. Solvents were evaporated *in vacuo*. Anhydrous sodium sulfate or phosphorus pentoxide was used as a drying agent. Reaction products were purified, when necessary, by flash chromatography on silica gel 60, (250-400 mesh), with the solvent system indicated. All solvents and chemicals were purchased from Fisher Scientific Company and Sigma-Aldrich Chemical Company and used as received.

General Procedure for Sulfonylation. Powdered mesitylenesulfonyl chloride (1 mmol) was added to a solution of ethylacetohydroxymate (1 mmol) and triethyl amine in dimethyl formamide in small portions over a period of about 20 minutes with stirring under ice cooling. (Precipitation of triethyl ammonium mesitylenesulfonate was noted soon after the first addition of the chloride). After addition was complete, triethyl amine (1 ml) was added to keep the reaction mixture basic. Stirring continued for additional 20 min at 5-10 °C and the reaction mixture was poured into ice/water. A white precipitated solid was collected and washed thoroughly with cold water (yield 70-80%). The crude product was used for the next step without further purification.



Scheme -1 Reactions and conditions: (i) DMF, Et_3N, 0^0C (ii) p-dioxane/H_2O, 70% $HClO_4$, 1h, 0^OC (iii) 4-substituted Py, CH_2Cl_2, 0^oC, 1h (iv) 4-substituted acylchloride, THF, 70 - 75^{o}C b) $NaHCO_3/H_2O$ (v) $NaBH_4$, EtOH, 0^oC, 4h.

Table 1

Physical and Analytical Data of 1,2,3,6-THPs

Compound	R_1	R_2	mp(°C)	Yield (%)	Molecular Formula	Analysis % Calcd./Found		
						C	H	N
9a	Ph	H	128-130	56	$C_{18}H_{18}N_2O$	77.67	6.52	10.06
						77.46	6.38	9.88
9b	CH_2Ph	H	156-157	65	$C_{19}H_{20}N_2O$	78.05	6.89	9.58
						77.64	7.07	9.39
9c	$CH(Ph)_2$	H	189-190	46	$C_{25}H_{24}N_2O$	81.49	6.57	7.60
						80.41	6.72	7.34
9d	Ph-propyl	H	141-142	51	$C_{21}H_{24}N_2O$	78.71	7.55	8.74
						78.55	7.76	8.59
9e	Et	H	131-133	56	$C_{14}H_{18}N_2O$	78.05	6.89	9.58
						77.89	6.66	9.46
9f	t-Bu	H	182-183	72	$C_{16}H_{22}N_2O$	74.38	8.58	10.84
						73.56	8.64	10.56
9g	H	Ph	132-133	58	$C_{18}H_{18}N_2O$	77.67	6.52	10.06
						77.50	6.48	9.98
9h	H	t-BU	146-148	62	$C_{16}H_{22}N_2O$	74.38	8.58	10.80
						74.12	8.76	10.70
9i	H	n-Pr	123-125	54	$C_{15}H_{20}N_2O$	73.74	8.25	11.47
						73.62	8.46	11.60
9j	H	n-Bu	132-134	46	$C_{16}H_{22}N_2O$	74.38	8.58	10.84
						74.12	8.76	10.70
9k	H	C_4H_4*	178-179	42	$C_{16}H_{16}N_2O$	76.16	6.39	11.10
						75.27	6.43	10.69
9l	CH_2Ph	F	166-167	72	$C_{19}H_{19}N_2OF$	73.52	6.17	9.02
						73.49	6.36	8.93
9m	CH_2Ph	Cl	141-142	74	$C_{19}H_{19}N_2OCl$	69.82	5.85	8.57
						69.75	6.04	8.56
9n	CH_2Ph	Me	142-143	68	$C_{20}H_{22}N_2O$	78.39	7.24	9.14
						78.22	7.39	9.08
9o	CH_2Ph	Et	131-133	46	$C_{20}H_{24}N_2O$	78.71	7.55	8.74
						78.39	7.38	8.92
9p	CH_2Ph	OMe	160-161	56	$C_{20}H_{22}N_2O_2$	74.50	6.88	8.69
						73.30	6.35	8.97
9q	CH_2Ph	OEt	138-140	61	$C_{21}H_{24}N_2O_2$	74.97	7.19	8.33
						74.70	6.98	8.67

***9k** is *N*-Naphtholylamino-1,2,3,6-tetrahydropyridine.

General Procedure for Hydrolysis. The crude product from step 1 was dissolved in dioxane:water (4:1) and 70% perchloric acid was added at 0 °C over 10 min. The reaction mixture became pasty due to the precipitation of *O*-mesitylenesulfonyl hydroxylamine perchlorate. After stirring was continued for further 10 min, the reaction mixture was poured onto ice/water to give a white solid, which was collected, and washed with cold petroleum ether to give mesitylenesulfonyl hydroxmate (MSH) (**13**) as an aminating agent (yield 62-70%).

General procedure for Amination. To an ice-cooled solution of pyridine derivatives (1 mmol) in dichloromethane was added drop-wise a solution of *O*-mesitylenesulfonyl-hydroxyylamine (**13**) (1 mmol) in dichloromethane. The reaction mixture was allowed to stand at room temperature for 10 min. after addition of ether, the precipitated crystals were collected and recrystalized from methanol/ethyl acetate to give *N*-amino-pyridinum mesitylenesulfonate (**14**).

General Procedure for Acylation. To an ice-cold solution of **(14)** (8 mmol) in 25 ml of anhydrous tetrahydrofuran was added an acid chloride (12 mmol) with stirring. The reaction was allowed to proceed for 12 h at 70 °C. After cooling to room temperature the reaction was quenched by adding 25 ml of a saturated aqueous sodium bicarbonate solution. The mixture was shaken repeatedly in separatory funnel and allowed to stand for few minutes. Extraction with chloroform (4 x 30 ml), drying over sodium sulfate and removal of the solvent *in vacuo* gave the crude product, which was purified by elution with ethyl acetate - methanol (4:1) in a short column. The initial 100 ml eluate was discarded and further elution with 300 ml afforded **(15)** in fair to good yields.

General Procedure for Reduction. A solution of **(15)** (5 mmol) in 20 ml of absolute ethanol was added drop-wise to a solution of sodium borohydride (50 mmol) in 25 ml of absolute ethanol pre-cooled to 0 °C. The reaction was allowed to proceed for 5 h at 0 °C with stirring. Water (35 ml) was added, and allowed to warm up to room temperature. Extraction with chloroform (3x50 ml), drying over sodium sulfate, and removal of the solvent *in vacuo* gave crude product of **(9)** which was purified by column chromatography using ethyl acetate:hexane (2:3) as eluent to afford a purified compound **(9)** in fair to good yields.

***N*-Benzoylamino-4-phenyl-1,2,3,6-tetrahydropyridine (9a).** This compound was obtained as white powder, yield 56%, mp 128-130°C. ^{1}H NMR ($CDCl_3$) δ 2.38 (t, 2H, C_3-H), 3.29 (t, 2H, C_2-H), 3.78 (d, 2H, C_6-H), 5.70 (s, 1H, C_5-H), 7.09-7.83 (m, 10H, phenyl protons), 7.18 (br, s, NH, deuterium oxide

exchanged). IR(potassium bromide): 3300 (NH), 1667 (CO) cm^{-1}. *Anal.* Calcd. For $C_{18}H_{18}N_2O$: C, 77.67; H, 6.52; N, 10.06. Found: C, 77.46, H, 6.38, N, 9.88.

***N*-Benzoylamino-4-benzyl-1,2,3,6-tetrahydropyridine (9b).** This compound was obtained as white solid product, yield 65%, mp 156-157°C. ^{1}H NMR ($CDCl_3$) δ 2.38 (t, 2H, C_3-H), 3.29 (t, 2H, C_2-H), 3.43 (s, 2H, -H_2C-C_6H_5), 3.78 (d, 2H, C_6-H), 5.70 (s, 1H, C_5-H), 7.08-7.15 (m, 5H, -C_6H_5), 7.44-7.48 (d, 1H, $C_{4'}$-H), 7.48-7.50 (d, 2H, C_3'-H and C_5'-H), 7.79-7.82 (d, 2H, $C_{2'}$-H and $C_{6'}$-H), 6.96 (br, s, NH, deuterium oxide exchanged). IR (potassium bromide): 3300 (NH),1667 (CO) cm^{-1}. *Anal.* Calcd. For $C_{19}H_{20}N_2O$: C, 78.05; H, 6.89; N, 9.58. Found: C, 77.64; H, 7.07; N, 9.39.

***N*-Benzoylamino-4-(diphenyl-4-pyridylmethane)-1,2,3,6-tetrahydropyridine (9c).** This compound was obtained as yellow brown powder, yield 46%, mp 189-190°C. ^{1}H NMR ($CDCl_3$) δ 2.38 (t, 2H, C_3-H), 3.29 (t, 2H, C_2-H), 4.60 (s, 1H, -*H*C-(C_6H_5)$_2$, 3.78 (d, 2H, C_6-H), 5.08 (s, 1H, C_5-H), 6.83-7.09 (m, 10H, -HC-(C_6H_5)$_2$), 7.42-7.83 (m, 5H, -C_6H_5), 7.08 (br, s, NH, deuterium oxide exchanged). IR (potassium bromide): 3300 (NH),1667 (CO) cm^{-1}. *Anal.* Calcd. For $C_{25}H_{24}N_2O$: C, 81.49; H, 6.57; N, 7.60. Found: C, 80.41; H, 6.72; N, 7.34.

***N*-Benzoylamino-4-(3-phenylpropyl)-1,2,3,6-tetrahydropyridine (9d).** This compound was obtained as yellow powder, yield 51%, mp 141-142°C. ^{1}H NMR ($CDCl_3$) δ 0.93 (t, 3H, -$CH_2CH_2CH_3$), 1.63 (m, 2H, -$CH_2CH_2CH_3$), 2.38 (t, 2H, C_3-H), 2.55 (t, 2H, -$CH_2CH_2CH_3$), 3.29 (t, 2H, C_2-H), 3.78 (d, 2H, C_6-H), 5.35 (s, 1H, C_5-H), 7.14-7.83 (m, 9H, -phenyl protons), 7.0 (br, s, NH, deuterium oxide exchanged). IR (potassium bromide): 3300 (NH),1667 (CO) cm^{-1}. *Anal.* Calcd. For $C_{21}H_{24}N_2O$: C, 78.71; H, 7.55; N, 8.74. Found: C, 78.55; H, 7.76; N, 8.59.

***N*-Benzoylamino-4-ethyl-1,2,3,6-tetrahydropyridine (9e).** This compound was obtained as yellow brown powder, yield 56%, mp 131-133°C. ^{1}H NMR ($CDCl_3$) δ 2.38 (t, 2H, C_3-H), 3.29 (t, 2H, C_2-H), 3.78 (d, 2H, C_6-H), 5.70 (s, 1H, C_5-H), 7.08-7.15 (m, 5H, -C6H5), 7.44-7.48 (d, 1H, C_4-H), 7.48-7.50 (d, 2H, C_3'-H and C_5'-H), 7.79-7.82 (d, 2H, $C_{2'}$-H and $C_{6'}$-H), 7.22 (br, s, NH, deuterium oxide exchanged). IR (potassium bromide): 3300 (NH), 1667 (CO) cm^{-1}. *Anal.* Calcd. For $C_{19}H_{20}N_2O$: C, 78.05; H, 6.89; N, 9.58. Found: C, 77.89; H, 6.66; N, 9.46.

***N*-Benzoylamino-4-*tert*-butyl-1,2,3,6-tetrahydropyridine (9f).** This compound was obtained as brown powder, yield 72%, mp 182-183°C. ^{1}H NMR ($CDCl_3$) δ 1.06 (s, 9H, -C(*CH_3*), 2.38 (t, 2H, C_3-H), 3.29 (t, 2H, C_2-H), 3.78 (d, 2H, C_6-H), 5.70 (s, 1H, C_5-H), 7.08-7.15 (m, 5H, -C_6H_5), 7.22 (br, s, NH, deuterium oxide exchanged). IR (potassium bromide): 3300 (NH), 1667 (CO) cm^{-1} *Anal.* Calcd. For $C_{16}H_{22}N_2O$: C, 74.38; H, 8.58; N, 10.84. Found: C, 73.56; H, 8.64; N, 10.56.

***N*-(4'-Biphenylcarbonylamino)-1,2,3,6-tetrahydropyridine (9g).** This compound was obtained as white powder, yield 58%, mp 132-133°C. ^{1}H NMR ($CDCl_3$) δ 2.38 (t, 2H, C_3-H), 3.29 (t, 2H, C_2-H), 3.78 (d, 2H, C_6-H), 5.68 (s, 1H, C_4-H), 5.70 (s, 1H, C_5-H), 7.36-7.87 (m, 9H, -C_6H_4-C_6H_5), 7.18 (br, s, NH, deuterium oxide exchanged). IR 3300 (NH), 1667 (CO) cm^{-1}. *Anal.* Calcd. For $C_{18}H_{18}N_2O$: C, 77.67; H, 6.52; N, 10.06. Found: C, 77.50; H, 6.48; N, 9.98.

***N*-(4'-*tert*-Butylbenzoylamino)-1,2,3,6-tetrahydropyridine (9h).** This compound was obtained as white powder, yield 62%, mp 146-148°C^{1}H NMR ($CDCl_3$) δ 1.06 (s, 9H, -C(*CH_3*), 2.38 (t, 2H, C_3-H), 3.29 (t, 2H, C_2-H), 3.78 (d, 2H, C_6-H), 5.70 (s, 1H, C_5-H), 7.08-7.15 (m, 5H, -C_6H_5), 7.22 (br, s, NH, deuterium oxide exchanged). IR (potassium bromide): 3300 (NH), 1667 (CO) cm^{-1} *Anal.* Calcd. For $C_{16}H_{22}N_2O$: C, 74.38; H, 8.58; N, 10.84. Found: C, 74.12; H, 8.76; N, 10.70.

***N*-(4'-*n*-Propylbenzoylamino)-1,2,3,6-tetrahydropyridine (9i).** This compound was obtained as yellow powder, yield 54%, mp 123-125°C. ^{1}H NMR ($CDCl_3$) δ 0.94 (t, 3H, -$CH_2CH_2CH_3$), 1.64 (m, 2H, -$CH_2CH_2CH_3$), 2.36 (t, 2H, C_3-H), 2.54 (t, 2H, -$CH_2CH_2CH_3$), 3.29 (t, 2H, C_2-H), 3.58 (d, 2H, C_6-H), 5.68 (s, 1H, C_4-H), 6.20 (s, 1H, C_5-H), 7.33 (d, 2H, C_3'-H and C_5'-H), 7.75 (d, 2H, $C_{2'}$-H and $C_{6'}$-H), 7.02 (br, s, NH, deuterium oxide exchanged). IR (potassium bromide): 3300 (NH), 1667 (CO) cm^{-1}. *Anal.*Calcd. For $C_{15}H_{20}N_2O$: C, 73.74; H, 8.25; N, 11.47. Found: C, 73.62; H, 8.46; N, 11.60.

***N*-(4'-*n*-Butylbenzoylamino)-1,2,3,6-tetrahydropyridine (9j).** This compound was obtained as white powder, yield 46%, mp 132-134°C. ^{1}H NMR ($CDCl_3$) δ 0.92 (t, 3H, -$CH_2CH_2CH_2$-CH_3), 1.46 (m, 2H, -$CH_2CH_2CH_2CH_3$), 1.57 (m, 2H, -CH_2CH_2-CH_2CH_3) 2.38 (t, 2H, C_3-H), 2.71 (t, 2H, -$CH_2CH_2CH_2CH_3$) 3.12 (t, 2H, C_2-H), 3.78 (d, 2H, C_6-H), 5.88 (s, 1H, C_4-H), 5.92 (s, 1H, C_5-H), 6.99 (d, 2H, C_3'-H and C_5'-H), 7.82 (d, 2H, $C_{2'}$-H and $C_{6'}$-H), 7.08 (br, s, NH, deuterium oxide exchanged). IR (potassium bromide): 3300 (NH), 1667 (CO) cm^{-1}. *Anal.* Calcd. For $C_{16}H_{22}N_2O$: C, 74.38; H, 8.58; N, 10.84. Found: C, 74.12; H, 8.76; N, 10.70.

***N*-Naphtholylamino-1,2,3,6-tetrahydropyridine (9k).** This compound was obtained as yellow brown, yield 42%, mp 178-179°C. ^{1}H NMR ($CDCl_3$) δ 2.38 (t, 2H, C_3-H), 3.29 (t, 2H, C_2-H), 3.78 (d, 2H, C_6-H), 5.62 (s, 1H, C_4-H), 5.68 (s, 1H, C_4-H), 7.52-8.35 (m, 7H, -$C_{10}H_7$), 6.98 (br, s, NH, deuterium oxide exchanged). IR (potassium bromide): 3300 (NH), 1667 (CO) cm^{-1}. *Anal.* Calcd. For $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10. Found: C, 74.27; H, 6.43; N, 10.69.

***N*-(4'-Fluorobenzoylamino)-4-benzyl-1,2,3,6-tetrahydropyridine (9l).** This compound was obtained as white crystalline solid, yield 72%, mp 166-167°C. ^{1}H NMR ($CDCl_3$) δ2.30 (t, 2H, C_3-H), 3.29 (t, 2H, C_2-H), 3.43 (s, 2H, -H_2C-C_6H_5), 3.78 (d, 2H, C_6-H), 5.96 (s, 1H, C_5-H), 7.08-7.17 (m, 5H, -C_6H_5), 7.25-7.31 (d, 2H, $C_{3'}$-H and $C_{5'}$-H), 7.70-7.73 (d, 2H, $C_{2'}$-H and $C_{6'}$-H) 8.22 (br, s, NH, deuterium oxide exchanged). IR (potassium bromide): 3300 (NH),1665 (CO) cm^{-1} *Anal.* Calcd. For $C_{19}H_{19}N_2OF$: C, 73.52; H, 6.17; N, 9.02. Found: C, 73.49; H, 6.36; N, 8.93

***N*-(4'-Chlorobenzoylamino)-4-benzyl-1,2,3,6-tetrahydropyridine (9m).** This compound was obtained as light yellow solid product, yield 74%, mp 141-142°C. ^{1}H NMR ($CDCl_3$) δ2.32 (t, 2H, C_3-H), 3.31 (t, 2H, C_2-H), 3.43 (s, 2H, -H_2C-C_6H_5), 3.77 (d, 2H, C_6-H), 5.96 (s, 1H, C_5-H), 7.08-7.17 (m, 5H, -C_6H_5), 7.40-7.43 (d, 2H, $C_{3'}$-H and $C_{5'}$-H), 7.72-7.75 (d, 2H, $C_{2'}$-H and $C_{6'}$-H) 8.22 (br, s, NH, deuterium oxide exchanged). IR (potassium bromide): 3300 (NH),1665 (CO) cm^1 *Anal.* Calcd. For $C_{19}H_{19}N_2OCl$: C, 69.82; H, 5.85; N, 8.57. Found: C, 69.75; H, 6.04; N, 8.56.

***N*-(4'-Methylbenzoylamino)-4-benzyl-1,2,3,6-tetrahydropyridine (9n).** This compound was obtained as white solid powder, yield 68%, mp 142-143°C. ^{1}H NMR ($CDCl_3$) δ2.23 (s, 3H, -CH_3), 2.32 (t, 2H, C_3-H), 3.31 (t, 2H, C_2-H), 3.43 (s, 2H, -H_2C-C_6H_5), 3.77 (d, 2H, C_6-H), 5.96 (s, 1H, C_5-H), 7.10-7.17 (m, 7H, -C_6H_5, $C_{3'}$-H and $C_{5'}$-H), 7.72-7.75 (d, 2H, $C_{2'}$-H and $C_{6'}$-H) 8.22 (br, s, NH, deuterium oxide exchanged). IR (potassium bromide): 3300 (NH), 1667 (CO) cm^{-1}. *Anal.* Calcd. For $C_{20}H_{22}N_2O$: C, 78.39; H, 7.24; N, 9.14. Found: C, 78.22; H, 7.39; N, 9.08.

***N*-(4'-Ethylbenzoylamino)-4-benzyl-1,2,3,6-tetrahydropyridine (9o).** This compound was obtained as white solid product (46%), mp 131-133°C. ^{1}H NMR ($CDCl_3$) δ1.24-1.27 (t, 3H, -CH_2CH_3), 2.23 (s, 3H, –CH_3), 2.32 (t, 2H, C_3-H), 2.82-2.84 (m, 2H, -CH_2CH_3), 3.31 (t, 2H, C_2-H), 3.43 (s, 2H, -H_2C-C_6H_5), 3.77 (d, 2H, C_6-H), 5.96 (s, 1H, C_5-H), 7.10-7.17 (m, 7H, -C_6H_5 $C_{3'}$-H and $C_{5'}$-H), 7.72-7.75 (d, 2H, $C_{2'}$-H and $C_{6'}$-H) 8.22 (br, s, NH, deuterium oxide exchanged). IR (potassium bromide): 3300 (NH), 1667 (CO) cm^{-1}. *Anal*. Calcd. For $C_{21}H_{24}N_2O$: C, 78.71; H, 7.55; N, 8.74. Found: C, 78.39; H, 7.38; N, 8.92.

***N*-(4'-Methoxybenzoylamino)-4-benzyl-1,2,3,6-tetrahydropyridine (9p).** This compound was obtained as white crystalline solid, yield 56%, mp 160-161°C. ^{1}H NMR ($CDCl_3$), 2.38 (t, 2H, C_3-H), 2.41 (t, 2H, C_2-H), 3.43 (s, 2H, -H_2C-C_6H_5), 3.62 (d, 2H, C_6-H), 3.98 (s, 3H, -OCH_3), 5.96 (s, 1H, C_5-H), 7.08-7.17 (m, 5H, -C_6H_5), 6.97-7.00 (d, 2H, $C_{3'}$-H and $C_{5'}$-H), 7.98-8.01(d, 2H, $C_{2'}$-H and $C_{5'}$-H) 8.22 (br, s, NH, deuterium oxide exchanged). IR (potassium bromide): 3300 (NH),1663 (CO) cm^{-1}. *Anal*. Calcd. For $C_{20}H_{22}N_2O_2$: C, 74.50; H, 6.88; N, 8.69. Found: C, 73.30; H, 6.35; N, 8.97.

***N*-(4'-Ethoxybenzoylamino)-4-benzyl-1,2,3,6-tetrahydropyridine (9q)** This compound was obtained as yellow powder, yield 61%, mp 138-140°C. ^{1}H NMR ($CDCl_3$) δ1.35-1.38 (t, 3H, -OCH_2CH_3), 2.38 (t, 2H, C_3-H), 2.41 (t, 2H, C_2-H), 3.43 (s, 2H, -H_2C-C_6H_5), 3.62 (d, 2H, C_6-H), 3.98-4.02 (m, 2H, -OCH_2CH_3), 5.96 (s, 1H, C_5-H), 7.08-7.17 (m, 5H, -C_6H_5), 6.97-7.00 (d, 2H, $C_{3'}$-H and $C_{5'}$-H), 7.98-8.01(d, 2H, $C_{2'}$-H and $C_{5'}$-H) 8.22 (br, s, NH, deuterium oxide exchanged). IR (potassium bromide): 3300 (NH), 1663 (CO) cm^{-1}. *Anal*. Calcd. For $C_{21}H_{24}N_2O_2$: C, 74.97; H, 7.19; N, 8.33. Found: C, 74.70; H, 6.98; N, 8.67.

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