Synthesis of 1-(Substituted Phenylcarbonyl/sulfonylamino)-1,2,3,6-tetrahydropyridine-5-carboxylic acid diethylamides as Potential Anti-inflammatory Agents

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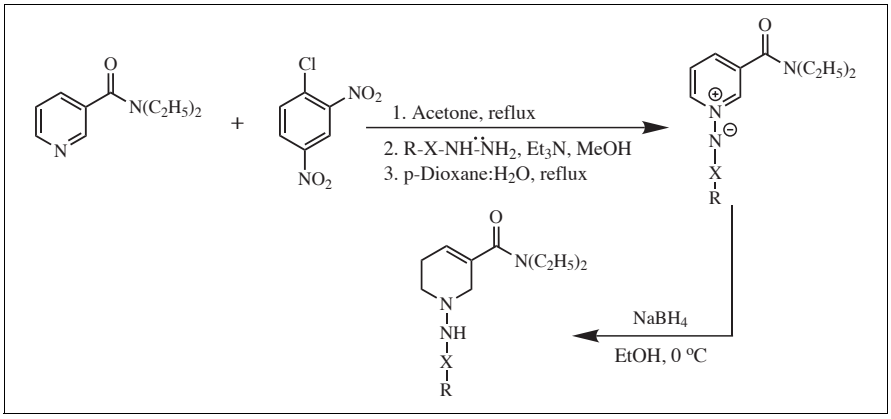

Fifteen novel 1-(substituted phenylcarbonyl/sulfonylamino)-1,2,3,6-tetrahydro- pyridine-5-carboxylic acid diethylamide (**7, 15**) were synthesized in fair to good yields *via* sodium borohydride reduction of the corresponding 1-(substituted phenylcarbonyl/ sulfonylimino)-3-diethylcarbamoyl pyridinium ylides (**6, 14**) in absolute ethanol.

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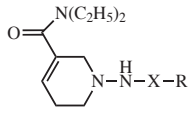
Introduction.

Nonsteroidal anti-inflammatory drugs are a nonhomogeneous family of pharmacologically active compounds used in the treatment of acute and chronic inflammation, pain, and fever. Functionalized tetrahydropyridine (THPs) ring systems are widely found in biologically active natural products and pharmaceuticals [1-7]. 1,2,3,4-Tetrahydroisoquinolines and tetrahydropyridines are found in nature as alkaloids of a large number of plant species. These compounds exhibit a wide rage of physiological activities and they act as precursors for many other groups of alkaloids such as morphinans, aporphines and protoberberines. Synthetically prepared 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is a potent neurotoxic substance which causes chronic Parkinsonism in humans when used intraveneously. Fries *et al.*, indicated that MPTP and its analogs have less or no toxicity when alkyl groups were introduced on the tetrahydropyridine ring [8-11]. Earlier work [12,13] by Knaus and co-workers indicated the synthesis of a series of *N*-(carbonylamino)-1,2,3,6-tetrahydropyridines (THPs) which showed anti-inflammatory, analgesic and hyperglycemic activities with no observed toxicities. Tetrahydropyridines are also important starting materials for the synthesis of benzomorphans, compounds with an analgesic activity similar to that of the morphinans [14,15]. It became evident that the pharmacological activities of the THP derivatives depended greatly on the position and nature of the substitutents on the THP ring structure [12,16,17]. Our research interest has focused on the anti-inflammatory activities of several THP ring containing compounds **1**. In literature survey some of these compounds showed hypotensive, analgesic, antipyretic and anti-inflammatory activities with no observed toxicity even at very high dose levels [6,16,18-24]. All of these compounds contained a carbonyl or sulfonyl group in their structure at position (**X**).



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R = C_6H_5, 4-CH_3-C_6H_5, 4-OCH_3-C_6H_5, 4-F-C_6H_5, 4-Cl-C_6H_5, 3-Br-C_6H_5, 4-NH_2-C_6H_5, 4-pyridyl, 3-pyridyl, 3,4,5-trimethoxy-C_6H_5, 4-*tert*-butyl-C_6H_5, 2-thiophene, 2-furan
X = Carbonyl, Sulfonyl

In a recent approach, the carbonyl group of the THPs was replaced with a sulfonyl group producing new derivatives with significantly enhanced anti-inflammatory activities [25]. Our previous reports indicated that alkyl groups on the THP ring system possessed reasonably higher anti-inflammatory activity

[16,17,19]. In the current report, we have synthesized compounds maintaining the 1,2,3,6-tetrahydropyridine-5-carboxylic acid diethylamide ring and having modifications on the phenyl ring and interchanging the sulfonyl/carbonyl group at position (X). These groups were chosen on the expectation that they would exert appropriate lipophilic, steric and electronic effects on the molecule. The compounds will be subject to biological testing to establish their anti-inflammatory, and analgesic activities.

The synthesis of the target compounds (**7**) is shown in Scheme 1 and the synthesis of the target compounds (**15**) is shown in Scheme 2. In Scheme 1, 1-chloro-2,4-dinitrobenzene (**3**) was reacted with *N,N*-diethyl nicotinamide (**2**) in acetone under reflux for 12 hours. This nucleophilic aromatic substitution reaction gave the salt, 3-diethylcarbamoyl-1-(2,4-dinitrophenyl) pyridinium chloride (**4**). Nucleophilic attack of pyridyl or substituted benzoyl hydrazides or sulfonyl hydrazides on the pyridinium chloride (**4**) in methanol containing triethylamine at room temperature for 12 hours resulted in the formation of 2,4-dinitroanilinoderivatives (**5**). Hydrolysis of the product (**5**) with water: *p*-dioxane (1:4 v/v) mixture under reflux for 12 hours furnished the *N*-(substituted phenyl carbonyl/sulfonylimino)-3-diethyl-carbamoyl pyridinium ylides (**6**). Sodium borohyride reduction of ylides (**6**) in absolute ethanol at 0 °C for 7 hours afforded then ***N***-(substituted phenylcarbonyl/ sufonylamino)-1,2,3,6-tetrahydropyridine-5-carboxylic acid diethylamide (**7**).

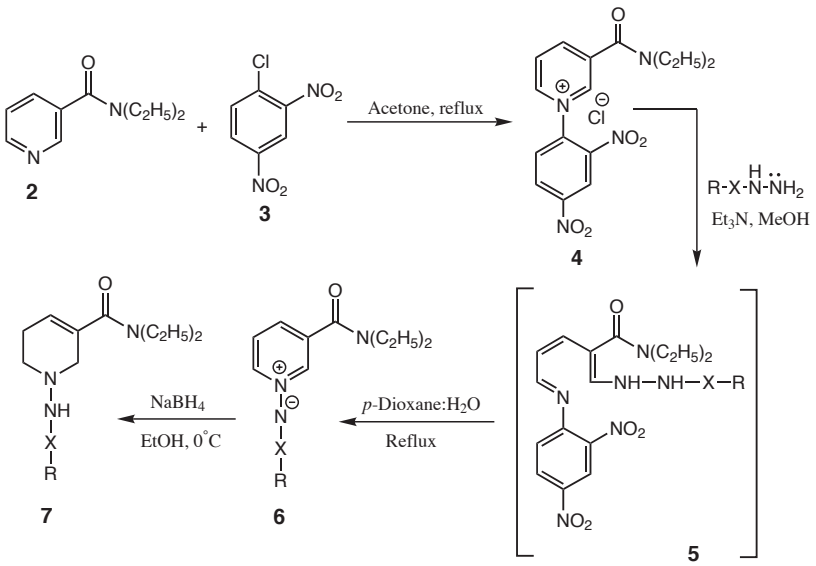
In Scheme 2, *O*-mesitylene sulfonyl hydroxylamine (MSH) (**11**) was used to prepare the *N*-amino salt as an aminating agent [26]. Mesitelene sulfonly chloride (**9**) was added with stirring to a solution of ethylacetohydroxymate (**8**) and triethylamine in dimethylformamide at 0 °C. After 1 hour, the reaction mixture was poured onto ice/water to give ethyl *O*-mesitylene sulfonylacetohydroxamate (**10**) in 88.0 % yield. Stirring the mixture of (**10**) in *p*-dioxane with 70% perchloric acid and allowing them to react for 40 min, gave a white solid of MSH (**11**) in 63.2% yeild. *N,N*-Diethylnicotinamide (**2**) was reacted with MSH (**11**) in dichloromethane to produce 1-amino-(3-diethyl-carbamoyl)pyridine mesitylenesulfonate (**12**). Reaction of (**12**) with substituted acid chlorides (**13**) in anhydrous tetrahydrofuran at 70 °C gave stable ylides (**14a**-**14d**). Sodium borohydride reduction of (**14a-14d**) in absolute ethanol furnished the target compounds 1-(substituted phenylcarbonylamino)-1,2,3,6-tetrahydropyridne-5-carboxlic acid diethylamides (**15a-15d**).

Results and Discussion.

The results of the synthesis of the pyridinium ylides (**6** and **14**) and corresponding 1,2,3,6-tetrahydropyridines (**7** and **15**) are presented in Table 1 and Table 2.

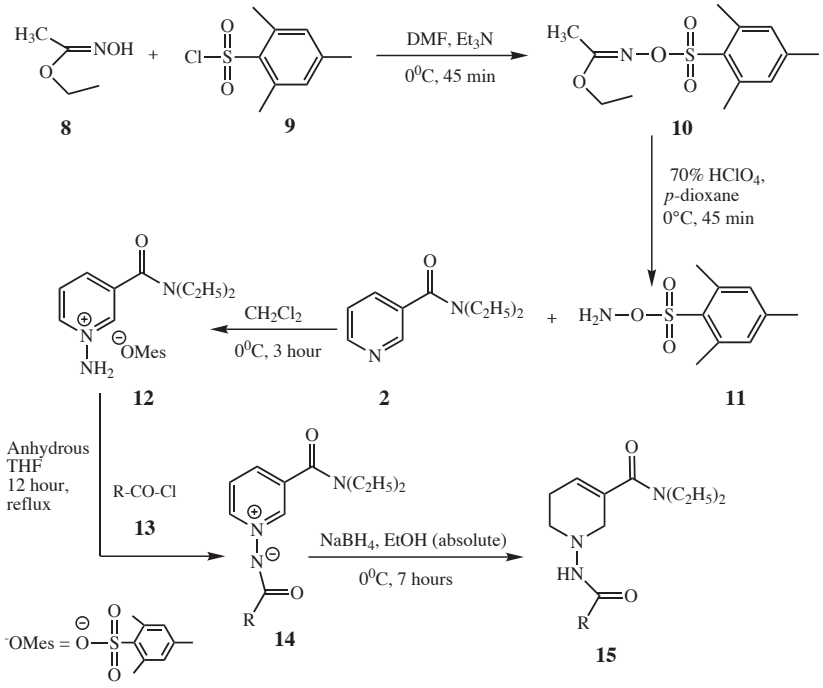
1,2,3,6-Tetrahydropyridines **7** and **15** show typical ^{1}H NMR absorption at approximately δ 3.11 observed as a triplet, which corresponds to C_2-protons coupled to the C_3-protons. Since C_2-protons are directly connected to N-atom of the tetrahydropyridine ring they are deshielded

Scheme 1



R = C_6H_5, 4-CH_3-C_6H_5, 4-OCH_3-C_6H_5, 4-F-C_6H_5, 4-Cl-C_6H_5, 3-Br-C_6H_5, 4-NH_2-C_6H_5, 4-pyridyl, 3-pyridyl,
X = CO, SO_2

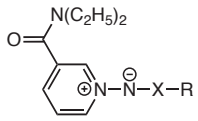
Scheme 2



R = 4-*tert*-butyl-C_6H_5, 3,4,5-tri-methoxy-C_6H_5, 2-thiophene, 2-furan

Table 1

Pyridinium Ylides **6a-6k** and **14a-14d** Synthetic data

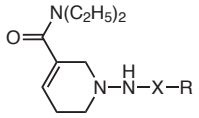


Compound	R	X	M.W.	Mp (°C)	Yield %
6a	3 -pyridyl	CO	298.34	136-138	63.8
6b	4 -pyridyl	CO	298.34	115-117	65.4
6c	phenyl	CO	297.35	99-101	65.6
6d	4-methylbenzyl	CO	311.38	99-100	79.5
6e	4-flurobenzyl	CO	315.34	semi solid	64.3
6f	4-chlorobenzyl	CO	331.8	94-96	66.5
6g	3-bromobenzyl	CO	376.25	97-98	61.7
6h	4-aminobenzyl	CO	312.37	163-165	77.5
6i	phenyl	SO_2	333.41	145-147	60.1
6j	4-methylbenzyl	SO_2	347.43	140-142	77.1
6k	4-methoxybenzyl	SO_2	363.43	125-127	55.9
14a*	3,4,5-trimethoxybenzyl	CO	387.43	51-52	62.1
14b*	4-*tert*-butylbenzyl	CO	353.21	67-68	44.5
14c*	2-thiophenyl	CO	303.38	80-82	83.1
14d*	2-furanyl	CO	287.31	132-133	82.2

* compounds **14a-14d** is prepared in Scheme 2.

Table 2

1,2,3,6-Tetrahydropyridines **7a-7k** and **15a-15d** Synthetic Data



Compound	R	X	M.W.	Mp (°C)	Yield %
7a	3 -pyridyl	CO	302.37	127-129	38.5
7b	4 -pyridyl	CO	302.37	124-126	50.4
7c	phenyl	CO	301.38	48-50	53.1
7d	4-methylbenzyl	CO	315.41	120-122	38.4
7e	4-flurobenzyl	CO	319.37	125-126	43.3
7f	4-chlorobenzyl	CO	335.83	137-139	48.6
7g	3-bromobenzyl	CO	380.28	53-55	55.3
7h	4-aminobenzyl	CO	316.4	178-180	34.4
7i	phenyl	SO_2	337.44	132-134	42.3
7j	4-methylbenzyl	SO_2	351.46	148-150	58.0
7k	4-methoxybenzyl	SO_2	367.46	145-147	49.4
15a*	3,4,5-trimethoxybenzyl	CO	391.46	151-152	40.7
15b*	4-*tert*-butylbenzyl	CO	357.49	96-98	30.8
15c*	2-thiophene	CO	307.41	48-50	38.4
15d*	2-furan	CO	291.35	50-51	48.2

* Compounds **15a-15d** is prepared in Scheme 2.

thus absorbing at a lower field than those of C_3-protons, which are farther away form the N-atom and C_3-protons are expected to absorb at around δ 2.41 when compared to C_2-protons. On the other hand, C_6-protons generally absorb at δ 3.71 and are seen at slightly lower field than the C_2-protoons because they are near the double bond and N-atom environment. The broad singlet at around δ 3.71 was assigned to C_6-protons, which have very weak coupling with C_4-proton. The peak at δ 5.84 is a unique indication of vinyl proton of the terahydropyridines on the C_4-proton. The infrared (ir) spectrum confirmed the presence of structural features in targeted compounds, which typically display absorption approximately at 3200 (NH), 1660 (CO) cm^{-1}. The pharmacological evaluations of the compounds for anti-inflammatory and analgesic activities are underway.

EXPERIMENTAL

^{1}H nmr spectra were determined on a Brucker HX 300 MHz spectrometer using $CDCl_3$ as a solvent and the chemical shifts are reported in parts per million (δ ppm) downfield from tetramethylsilane as an internal standard. Infrared spectra obtained on a Perkin-Elmer FTIR 1430 spectrometer, using KBr pellets unless otherwise stated. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN, USA. Melting points were determined on a Mel-Temp 3.0 melting point apparatus and were uncorrected. Chemicals and solvents were purchased from Sigma-Aldrich Chemical Company Inc., Milwaukee, Wisconsin, Fisher Scientific Company, Suwanee, Georgia. Separations on column chromatography were performed on silica gel (Fisher Brand 200-425 mesh). All reactions and purification procedures were monitored by TLC on Whatmann AL SIL G/UV, 250μm layer flexible plates, with visualization under UV light.

General Procedure A.

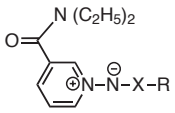
3-[(Diethylamino)carbonyl]-1-[(3-pyridylcarbonyl)imino]pyridinium Ylide (**6a**).

N, N-Diethylnicotinamide (**2**) (10 g, 56.1 mmoles) was added to a stirring solution of 1-chloro-2, 4-dinitrobenzene (**3**) (11.37 g, 56.1 mmoles) in acetone (150 ml) drop wise addition over a period of 15 minutes and the reaction mixture was refluxed for 12 hours. The reaction mixture was cooled to room temperature and filtered. The residue was washed with acetone (3 X 100 ml) and dried *in vacuo* at room temperature. The crude product 3-diethylcarbamoyl-1-(2,4-dinitrophenyl)pyridinium chloride salt (**4**) was *vacuum* filtered and crystallized from ethyl acetate:methanol (4:1 v/v 50 ml) to afford 12.34 g (57.76%) of pale yellow crystals, mp 157-158 °.

Compound (**4**) (3.00 g, 7.89 mmoles) was dissolved in methanol (100 ml) and stirred at 0 °C for 10 minutes followed by addition of (1.08 g, 7.89 mmoles) nicotinic acid hydrazide. To this solution (1.0 ml) triethylamine was added and the mixture stirred at 0° for 1 hour and continued to stir at room temperature for 12 hours. The brown precipitate that formed was filtered and washed with 50 ml of hexane and 300 ml of water. The residue was immediately refluxed in water: *p*-dioxane (80 ml, 1:4 v/v) for 12 hours to afford a clear solution. The reaction medium was evaporated under reduced pressure and obtained the brownish residue. The crude product was chromatographed on a column

Table 3

Elemental Analysis of the Pyridinium ylides (**6a-6k** and **14a-14d**)



Compound	R	Molecular Formula	MW	Analysis % Calcd./Found		
				C	H	N
6a	3-pyridyl	$C_{16}H_{18}N_4O_2$	298.34	64.41	6.08	18.78
				64.50	6.10	18.88
6b	4-pyridyl	$C_{16}H_{18}N_4O_2$	298.34	64.41	6.08	18.78
				64.62	6.15	19.02
6c	phenyl	$C_{17}H_{19}N_3O_2$	297.35	68.76	6.44	14.13
				68.76	6.54	13.95
6d	4-methylbenzyl	$C_{18}H_{21}N_3O_2$	311.38	69.43	6.80	13.49
				69.34	6.87	13.60
6e	4-flurobenzyl	$C_{17}H_{18}FN_3O_2$	315.34	64.75	5.75	13.33
				65.00	5.84	13.45
6f	4-chlorobenzyl	$C_{17}H_{18}ClN_3O_2$	331.18	61.54	5.47	12.66
				61.42	5.54	12.74
6g	3-bromobenzyl	$C_{17}H_{18}BrN_3O_2$	376.25	54.27	4.82	11.17
				54.36	4.90	11.20
6h	4-aminobenzyl	$C_{17}H_{20}N_4O_2$	312.37	65.37	6.45	17.94
				65.45	6.55	18.13
6i	phenyl	$C_{16}H_{19}N_3O_3S$	333.41	57.64	5.74	12.60
				57.72	5.81	12.71
6j	4-methylbenzyl	$C_{17}H_{21}N_3O_3S$	347.43	58.77	6.09	12.09
				58.65	6.09	12.18
6k	4-methoxybenzyl	$C_{17}H_{21}N_3O_4S$	363.43	56.18	5.82	11.56
				58.27	5.94	11.69
14a*	3,4,5-trimethoxybenzyl	$C_{20}H_{25}N_3O_5$	387.43	62.00	6.50	10.85
				62.13	6.58	10.93
14b*	4-*tert*-butylbenzyl	$C_{21}H_{27}N_3O_2$	353.46	71.36	7.70	11.89
				71.45	7.79	12.09
14c*	2-thiophenyl	$C_{15}H_{17}N_3O_2S$	303.38	59.38	5.65	13.85
				59.47	5.76	13.99
14d*	2-furanyl	$C_{15}H_{17}N_3O_3$	287.31	62.71	5.96	14.63
				62.87	6.06	14.88

* Compounds **14a-14d** is prepared in Scheme 2.

(2.5 X 22 cm) of silica gel (200-425 mesh) using ethyl acetate: methanol (3:2 v/v, 500 ml) as the eluent. The product was recrystallized form ethyl acetate to afford 1.3 g (63.8%) of yellow crystals, mp 136-138°. The other derivatives were similarly prepared and purified. IR (potassium bromide): ν 1644, 1591 (C=O) cm^{-1}; ^{1}H nmr ($CDCl_3$): δ 1.23 (t, 6H, J = 7 Hz, CH_2-*CH_3*), 3.41 (d, 2H, J = 6.1 Hz, *CH_2*-CH_3), 3.55 (d, 2H, J = 6.0 Hz, *CH_2*-CH_3), 7.33 (dd, 1H, J = 4.8, 3.0 Hz, C_5-H), 7.73 (dd, 1H, J= 6.6, 0.9 Hz, C_4-H), 7.95 (tt, 1H, J = 1.5, 1.5 Hz, C_5-H), 8.39 (tt, 1H, J = 2.1, 2.1 Hz, C_4-H), 8.64 (d, 1H, J = 3.9 Hz, C_6-H), 8.84 (tt, 1H, J = 1.2, 1.5 Hz, C_6-H), 9.01 (s, 1H, C_2-H), 9.34 (s, 1H, C_2-H).

Anal. Calcd. for $C_{16}H_{18}N_4O_2$: C, 64.41; H, 6.08; N, 18.78. Found: C, 64.50; H, 6.10; N, 18.88.

3-[(Diethylamino)carbonyl]-1-[(4-pyridylcarbonyl)imino]pyridinium Ylide (**6b**).

The compound **6b** was obtained following General Procedure A has yellow color solid, 2.6 g (65.4%), mp115-117°; ir (potassium bromide): ν 1630, 1597 (C=O) cm^{-1}; ^{1}H nmr ($CDCl_3$): δ 1.25 (t, 6H, J = 7 Hz, CH_2-*CH_3*), 3.41 (d, 2H, J = 6.6 Hz, *CH_2*-CH_3), 3.56 (d, 2H, J = 6.0 Hz, *CH_2*-CH_3), 7.75 (dd, 1H, J= 6.3, 0.9 Hz, C_5-H), 7.96 (dd, 2H,J = 0.9, 2.1 Hz, C_2 -H, C_6 -H), 7.98 (t, 1H, J = 1.5 Hz, C_4-H), 8.69 (d, 2H, J = 4.8 Hz, C_3 -H, C_5 -H), 8.82 (tt, 1H, J = 1.2, 1.2 Hz C_6-H), 9.00 (s, 1H, C_2-H).

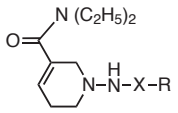
Anal. Calcd. for $C_{16}H_{18}N_4O_2$: C, 64.41; H, 6.08; N, 18.78. Found: C, 64.51; H, 6.15; N 19.02.

1-(Benzoylamino)-3-[(diethylamino)carbonyl]pyridinium Ylide (**6c**).

The compound **6c** was obtained following General Procedure to furnish pail yellow color compound in (2.56 g) 65.6% yield, mp 99-101°; ir (potassium bromide): ν 1636, 1625 (C=O) cm^{-1}; ^{1}H nmr ($CDCl_3$): δ 1.24 (t, 6H, J = 6 Hz, CH_2-*CH_3*), 3.41 (d, 2H, J = 6.3 Hz, *CH_2*-CH_3), 3.56 (d, 2H, J = 6.5 Hz, *CH_2*-CH_3), 7.40-7.45 (m, 3H, C_3 , C_4 and C_5 -H), 7.70 (dd, 2H, J = 6.3, 6.9 Hz, C_2, C_6 -H), 7.91 (tt, 1H, J = 1.2, 1.5 Hz, C_5-H) 8.14 (t, 1H, J = 1.8

Table 4

Elemental Analysis of the Tetrahydropyridines (**7a-7k** and **15a-15d**)



Compound	R	Molecular Formula	MW	Analysis % Calcd./Found		
				C	H	N
7a	3-pyridyl	$C_{16}H_{22}N_4O_2$	302.37	63.55	7.33	18.53
				63.80	7.42	18.79
7b	4-pyridyl	$C_{16}H_{22}N_4O_2$	302.37	63.55	7.33	18.53
				63.20	7.38	18.34
7c	phenyl	$C_{17}H_{23}N_3O_2$	301.38	67.75	7.69	13.94
				67.90	7.85	14.03
7d	4-methylbenzyl	$C_{18}H_{25}N_3O_2$	315.41	68.54	7.99	13.32
				68.55	8.07	13.27
7e	4-flurobenzyl	$C_{17}H_{22}FN_3O_2$	319.37	63.93	6.94	13.16
				64.07	7.03	13.44
7f	4-chlorobenzyl	$C_{17}H_{22}ClN_3O_2$	335.83	60.80	6.60	12.51
				60.78	6.58	12.42
7g	3-bromobenzyl	$C_{17}H_{22}BrN_3O_2$	380.28	53.69	5.83	11.05
				53.78	5.94	11.20
7h	4-aminobenzyl	$C_{17}H_{24}N_4O_2$	316.40	64.53	7.65	17.71
				64.62	7.79	17.38
7i	phenyl	$C_{16}H_{23}N_3O_3S$	337.44	56.95	6.87	12.45
				57.10	6.96	12.56
7j	4-methylbenzyl	$C_{17}H_{25}N_3O_3S$	351.46	58.09	7.17	11.96
				58.27	7.24	12.08
7k	4-methoxybenzyl	$C_{17}H_{25}N_3O_4S$	367.46	55.57	6.86	11.44
				55.36	6.98	11.53
15a*	3,4,5-trimethoxybenzyl	$C_{20}H_{29}N_3O_5$	391.46	61.36	7.47	10.73
				61.00	7.60	10.60
15b*	4-*tert*-butylbenzyl	$C_{21}H_{31}N_3O_2$	357.49	70.55	8.74	11.75
				70.74	8.83	11.99
15c*	2-thiophenyl	$C_{15}H_{21}N_3O_2S.$ $0.115H_2O$	311.56	57.83	6.87	13.49
				57.92	7.11	13.13
15d*	2-furanyl	$C_{15}H_{21}N_3O_3$	291.35	61.84	7.27	14.42
				61.72	7.48	14.10

* Compounds **15a-15d** is prepared in Scheme 2.

Hz, C_4-H), 8.82 (tt, 1H, J= 1.2, 1.5 Hz, C_6-H), 9.01 (s, 1H, C_2-H).

Anal. Calcd. for $C_{17}H_{19}N_3O_2$: C, 68.67; H, 6.44; N, 14.13. Found: C, 68.76; H, 6.54; N, 13.95.

3-[(Diethylamino)carbonyl]-1-[(4-methylbenzoyl)imino]pyridinium Ylide (**6d**).

The compound **6d** was obtained following General Procedure A to furnish (**6d**) has yellow crystals in 79.5 % (2.6 g) yield, mp 99-100°; ir (potassium bromide): ν 1625, 1615 (C=O) cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.21 (t, 6H, J = 6.9 Hz, CH_2-CH_3), 2.37 (s, 3H, CH_3 group of phenyl), 3.37 (d, 2H, J = 5.9 Hz, CH_2-CH_3), 3.54 (d, 2H, J = 5.7 Hz, CH_2-CH_3), 7.19 (d, 2H, J = 8.1 Hz, C_3 -H, C_5 -H), 7.62 (dd, 1H, J = 6.6, 6.3 Hz, C_5-H), 7.89 (tt, 1H, J = 1.2, 1.2 Hz, C_4-H) 8.00 (d, 2H, J = 8.1 Hz, C_2 ,C_6 -H), 8.77 (tt, 1H, J = 1.2, 1.2 Hz, C_6-H), 8.95 (s, 1H, C_2-H).

Anal. Calcd. for $C_{18}H_{21}N_3O_2$: C, 69.43; H, 6.80; N, 13.49. Found: C, 69.34; H, 6.87; N, 13.60.

3-Diethylaminocarbonyl-1-(4-fluorobenzoylimino)pyridinium Ylide (**6e**).

The compound **6e** was obtained following General Procedure A has a brownish semi-solid (1.6 g, 64.3 %), ir (potassium bromide): ν 1628, 1618 (C=O) cm^{-1}**;** ^1H nmr ($CDCl_3$): δ 1.24 (t, 6H, J = 6.7 Hz, CH_2-CH_3), 3.35 (d, 2H, J = 6 Hz, CH_2-CH_3), 3.55 (d, 2H, J = 5.8 Hz, CH_2-CH_3), 7.47 (d, 2H, J = 8.4 Hz, C_3 -H C_5 -H), 7.97 (dd, 2H, J = 7.1, 7.8 Hz, C_2 -H, C_6 -H), 8.23 (d, 1H, J = 8.5 Hz, C_5-H), 8.34 (d, 1H, J = 6.7 Hz, C_4-H), 8.99 (s, 1H, C_2-H), 9.23 (d, 1H, J = 5.9 Hz, C_6-H).

Anal. Calcd. For $C_{17}H_{18}FN_3O_2$: C, 64.75; H, 5.75; N, 13.33. Found: C, 65.00; H, 5.84; N, 13.45.

1-[(4-Chlorobenzoyl)imino]-3-[(diethylamino)carbonyl]pyridinium Ylide (**6f**).

The compound **6f** was obtained following General Procedure A has a yellow color solid in 66.5% (2.9 g) yield, mp 94-96 °; ir (potassium bromide): ν 1635, 1628 (C=O) cm^{-1}; ^1H nmr

($CDCl_3$): δ 1.23 (t, 6H, J = 6.9 Hz, CH_2-*CH_3*), 3.43 (d, 2H, J = 5.9 Hz, *CH_2*-CH_3), 3.55 (d, 2H, J = 5.7 Hz, *CH_2*-CH_3), 7.47 (d, 2H, J = 8.4 Hz, C_3 -H C_5 -H), 7.97 (dd, 2H, J = 7.2, 8.7 Hz, C_2 -H, C_6 -H), 8.23 (d, 1H, J = 8.4 Hz, C_5-H), 8.33 (tt, 1H, J = 1.2, 1.2 Hz, C_4-H) 8.99 (tt, , 1H, J = 1.2, 1.2 Hz, C_6-H), 9.04 (s, 1H, C_2-H).

Anal. Calcd. for $C_{17}H_{18}ClN_3O_2$: C, 61.54; H, 5.47; N, 12.66. Found: C, 61.42; H, 5.54; N, 12.74.

1-[(3-Bromobenzoyl)imino]-3-[(diethylamino)carbonyl]pyridinium Ylide (**6g**).

The compound **6g** was obtained following General Procedure A has shiny yellow color solid in 61.7% (3.0 g) yield, mp 97-98°, ir (potassium bromide): ν 1628, 1616 (C=O) cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.25 (t, 6H, J = 6.7 Hz, CH_2-*CH_3*), 3.34 (d, 2H, J = 6 Hz, *CH_2*-CH_3), 3.54 (d, 2H, J = 5.8 Hz, *CH_2*-CH_3), 7.27 (d, 1H, J = 7.7 Hz, C_5 -H), 7.54 (d, 1H, J = 7.8 Hz, C_4 -H), 7.71 (t, 1H, J = 6.6 Hz, C_6 -H) 7.94 (d, 1H, J = 7.8 Hz, C_2 -H), 8.05 (d, 1H, J= 7.7 Hz, C_5-H), 8.28 (t, 1H, J = 1.7 Hz, C_4-H) 8.78 (d, 1H, J = 6.3 Hz, C_6-H), 8.96 (s, 1H, C_2-H).

Anal. Calcd. for $C_{17}H_{18}BrN_3O_2$: C, 54.27; H, 4.82; N, 11.17. Found: C, 54.36; H, 4.90; N, 11.20.

1-(4-Aminobenzoylimino)-3-diethylcarbamoyl-pyridinium Ylide (**6h**).

The compound **6h** was obtained following General Procedure A to furnish **6h** has a yellow crystals in 77.5% (1.9 g) yield, mp 163-165°, ir (potassium bromide): ν 1630, 1617 (C=O), 3236 (NH_2) cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.12 (t, 6H, J = 7.0 Hz, CH_2-*CH_3*), 2.50 (brs, 2H, -NH_2), 3.40 (q, 4H, J = 6.5, 6.6 Hz, *CH_2*-CH_3), 6.67 (dd, 2H, J = 6.5, 6.6 Hz, C_3 -H C_5 -H), 7.66 (dd, 2H, J = 6.3, 7.2 Hz, C_2 -H, C_6 -H), 7.88 (d, 1H, J= 8.5 Hz, C_5-H), 7.97 (t, 1H, J = 6.9 Hz, C_4-H), 8.81 (dd, 1H, J= 0.9, 1.2 Hz, C_6-H) , 8.98 (s, 1H, C_2-H).

Anal. Calcd. For $C_{17}H_{20}N_4O_2$: C, 65.37; H, 6.45; N, 17.94. Found: C, 65.45; H, 6.55; N, 18.13.

3-[(Diethylamino)carbonyl]-1-[(phenylsulfonyl)imino]pyridinium Ylide (**6i**).

The compound **6i** was obtained following General Procedure A to furnish **6i** has yellow crystals in 60.1% (3.1 g) yield, mp 145-147°, ir (potassium bromide): ν 1644 (C=O), 1284 and 1138 (SO_2) cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.08 (t, 3H, J = 7.0 Hz, -CH_2-*CH_3*), 1.21 (t, 3H, J = 7.5 Hz, -CH_2-*CH_3*), 3.15 (d, 2H, J = 6.0 Hz, -*CH_2*-CH_3), 3.49 (d, 2H, J = 6.0 Hz, -*CH_2*-CH_3), 7.33-7.40 (m, 3 H, C_3 , C_4 and C_5 -H), 7.60 (dd, 1H, J = 1.5, 1.5 Hz, C_5-H), 7.71 (tt, 2H, J = 1.5, 1.8 Hz, C_2 , C_6 -H), 7.97 (tt, 1H, J = 1.2, 1.2 Hz, C_4-H), 8.44 (d, 1H, J = 6.3 Hz, C_6-H), 8.47 (s, 1H, C_2-H).

Anal. Calcd. for $C_{16}H_{19}N_3O_3S$: C, 57.64; H, 5.74; N, 12.60. Found: C, 57.72; H, 5.81; N, 12.71.

3-[(Diethylamino)carbonyl]-1-[(4-methylphenylsulfonyl)imino]-pyridinium Ylide (**6j**).

The compound **6j** was obtained following General Procedure A to furnish **6j** has yellow color solid in 77.1% (3.5 g) yield, mp 140-142 °, ir (potassium bromide): ν 1636 (C=O) and 1285, 1137 (SO_2) cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.08 (t, 3H, J = 7.0 Hz, -CH_2-*CH_3*), 1.21 (t, 3H, J = 6.9 Hz, -CH_2-*CH_3*), 2.33 (s, 3H, -CH_3 of phenyl ring), 3.16 (d, 2H, J = 5.8 Hz, -*CH_2*-CH_3), 3.50 (d, 2H, J = 5.7 Hz, -*CH_2*-CH_3), 7.15 (d, 2H, J = 7.8 Hz, C_3 , C_5 -H), 7.56 (d, 2H, J = 7.8 Hz, C_2 , C_6 -H), 7.60 (dd, 1H, J = 1.5, 1.5 Hz, C_5-H), 7.95 (tt, 1H, J = 1.5, 1.2 Hz, C_4-H), 8.44 (tt, 1H, J = 1.2, 1.2 Hz, C_6-H), 8.48 (s, 1H, C_2-H).

Anal. Calcd. for $C_{17}H_{21}N_3O_3S$: C, 58.77; H, 6.09; N, 12.09. Found: C, 58.65: H, 6.09: N, 12.18.

3-[(Diethylamino)carbonyl]-1-[(4-methoxyphenylsulfonyl)imino]-pyridinium Ylide (**6k**).

The compound **6k** was obtained following General Procedure A to furnish off-white color solid in 55.9% (2.6 g) yield, mp 125-127°, ir (potassium bromide): ν 1634 (C=O) and 1287, 1145 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.10 (t, 3H, J = 7.0 Hz, -CH_2-*CH_3*), 1.20 (t, 3H, J = 7.5 Hz, -CH_2-*CH_3*), 3.17 (d, 2H, J = 6.0 Hz, -*CH_2*-CH_3), 3.51 (d, 2H, J = 6.0 Hz, -*CH_2*-CH_3), 3.79 (s, 3H, -OCH_3 of phenyl ring), 6.84 (dd, 2H, J = 3.0, 3.0 Hz, C_3 , C_5 -H), 7.57 (dd, 1H, J = 6.3, 6.3 Hz, C_5-H), 7.66 (tt, 2H, J = 2.7, 2.1 Hz, C_2 , C_6 -H), 7.94 (tt, 1H, J = 1.2, 1.2 Hz, C_4-H), 8.44 (tt, 1H, J =1.2, 1.5 Hz, C_6-H), 8.50 (s, 1H, C_2-H).

Anal. Calcd. for $C_{17}H_{21}N_3O_4S$: C, 56.18; H, 5.82; N, 11.56. Found: C, 58.27; H, 5.94; N, 11.69.

General Procedure B.

3-Diethylcarbamoyl-1-(3,4,5-trimethoxybenzoylimino)pyridinium Ylide (**14a**).

1-Amino-3-diethylcarbamoyl pyridinium mesitylene-sulfonates (**12**) were synthesized by the method described earlier by Tamura *et al* [26]. To an ice-cold solution of (**12**) (5.0 g, 12.71 mmoles) in anhydrous tetrahydrofuran (80 ml) was added 3,4,5-trimethoxy benzenesulfonyl chloride (**13a**) (5.86 g, 25.42 mmoles) drop wise. The reaction was allowed to reflux for 12 hours at 70°. After cooling to room temperature, the reaction was quenched by adding 40 ml of a saturated aqueous sodium bicarbonate solution. The mixture was shaken repeatedly in a separatory funnel and allowed to stand for a few minutes. The solution was extracted with chloroform (3 x 100 ml), drying over anhydrous sodium sulfate, filtration and solvent was removed *in vacuo* gave the crude product, which was purified by column chromatography (2.5 x 22 cm) on silica gel (200-425 mesh) using ethyl acetate:methanol (9:1v/v) as eluent. The resultant product (**14a**) was white crystalline solid obtained in 62.1% (3.1 g) yield, mp 51-52°; ir (potassium bromide): ν 1630, 1610 (C=O) cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.04 (t, 3H, J = 6.3 Hz, -CH_2-*CH_3*), 1.18 (t, 3H, J = 6.3 Hz, -CH_2-*CH_3*), 2.24 (s, 3H, *p*-OCH_3), 2.64 (s, 6H, *m*-OCH_3), 3.21 (d, 2H, J = 6.6 Hz, -*CH_2*-CH_3), 3.47 (d, 2H, J = 6.6 Hz, -*CH_2*-CH_3), 6.84 (s, 2H, -C_2 , C_6 -H), 7.69 (dd, 1H, J = 6.3, 6.3 Hz, C_5-H), 7.87 (t, 1H, J = 6.9 Hz, C_4-H), 9.0 (s, 1H, C_6-H), 9.17 (d, 1H, J = 6.6 Hz, C_2-H).

Anal. Cacld. for $C_{20}H_{25}N_3O_5$: C, 62.00; H, 6.50: N, 10.85. Found: C, 62.13; H, 6.58; N, 10.93.

1-(4-*tert*-Butylbenzoylimino)-3-diethylcarbamoylpyridinium Ylide (**14b**).

The compound **14b** was obtained following General Procedure B to furnish **14b** has white solid obtained in 44.5% (1.0 g) yield, mp 67-68°; ir (potassium bromide): ν 1635, 1620 (C=O) cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.18 (t, 6H, J = 6.3 Hz, -CH_2-*CH_3*), 1.21 (s, 9H, -*t*-butyl group), 3.21 (d, 2H, J = 6.6 Hz, -*CH_2*-CH_3), 3.47 (d, 2H, J = 6.6 Hz, -*CH_2*-CH_3), 7.37 (d, 2H, J = 9.0 Hz, C_3 , C_5 - H), 7.64 (dd, 2H, J = 7.2, 7.5 Hz, C_2 , C_6 -H), 7.87 (d, 1H, J = 7.5 Hz, C_5-H), 8.01(d, 1H, J = 8.7 Hz, C_4-H), 8.77 (d, 1H, J = 6.6 Hz, C_6-H), 8.93 (s, 1H, C_2-H).

Anal. Calcd. for $C_{21}H_{27}N_3O_2$: C, 71.36; H, 7.70; N, 11.89. Found: C, 71.45; H, 7.79; N, 12.09.

3-Diethylcarbamoyl-1-[(thiophene-2-carbonyl)imino]pyridinium Ylide (**14c**).

The compound **14c** was obtained following General Procedure B to furnish **14c** has yellow needles obtained in 83.1% (2.5 g) yield, mp 80-82°; ir (potassium bromide): ν 1631, 1615 (C=O) cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.22 (t, 6H, J = 6.4 Hz, -CH_2-CH_3), 3.24 (d, 2H, J = 6.6 Hz, -CH_2-CH_3), 3.47 (d, 2H, J = 6.6 Hz, -CH_2-CH_3), 6.41 (dd, 1H, J = 1.9, 1.8 Hz, -C_3 -H), 7.10 (dd, 1H, J = 1.2, 2.4 Hz, -C_4 -H), 7.50 (dd, 1H, J = 0.9, 1.2 Hz, -C_5 -H), 7.72 (dd, 1H, J= 1.5, 1.5 Hz, C_5-H), 7.94 (tt, 1H, J= 1.5, 1.2 Hz, C_4-H), 8.75 (tt, 1H, J = 1.2, 1.2 Hz, C_6-H), 9.02 (s, 1H, C_2-H).

Anal. Calcd. for $C_{15}H_{17}N_3O_2S$: C, 59.38; H, 5.65; N, 13.85. Found: C, 59.47; H, 5.76; N, 13.99.

3-Diethylcarbamoyl-1-[(furan-2-carbonyl)-imino]pyridinium Ylide (**14d**).

The compound **14d** was prepared as outlined in General Procedure B has a white solid 82.2% (3.1 g) yield, mp 132-133°; ir (potassium bromide): ν 1628, 1618 (C=O) cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.21 (t, 6H, J = 6.3 Hz, -CH_2-CH_3), 3.21 (d, 2H, J = 6.6 Hz, -CH_2-CH_3), 3.47 (d, 2H, J = 6.6 Hz, -CH_2-CH_3), 6.46 (dd, 1H, J = 1.8, 1.8 Hz, -C_3 -H), 7.07 (dd, 1H, J = 0.9, 2.4 Hz, -C_4 -H), 7.49 (dd, 1H, J = 0.6, 0.9 Hz, -C_5 -H), 7.70 (dd, 1H, J = 1.5, 1.5 Hz, C_5-H), 7.93 (tt, 1H, J = 1.5, 1.2 Hz, C_4-H), 8.79 (tt, 1H, J = 1.2, 1.2 Hz, C_6-H), 9.01 (s, 1H, C_2-H).

Anal. Calcd. for $C_{15}H_{17}N_3O_3$: C, 62.71; H, 5.96; N, 14.63. Found: C, 62.87; H, 6.06; N, 14.88.

General procedure C.

1-(3-Pyridylcarbonylamino)-1,2,3,6-tetrahydropyridine-5-carboxylic acid diethylamide (**7a**).

3-[(Diethylamino)carbonyl]-1-[(3-pyridylcarbonyl)imino]pyridinium ylide (**6a**) (1.0 g, 3.35 mmoles) was stirred in 80 mL of absolute ethanol at 0° for 30 minutes. Sodium borohydride (0.51 g, 13.40 mmoles) was added and the reduction was carried out at 0°. The stirring proceeded for 7 hours and the reaction was monitored by TLC. The reaction mixture was treated with 15 g of ice and allowed to warm up to room temperature. The product was extracted with methylene chloride (4 X 100 ml) and water (2 X 100 ml) and washed with 60 ml of brine. The combined methylene chloride extracts were dried over anhydrous sodium sulfate, filtered and evaporated *in vacuo*. The residue was chromatographed on a column of silica gel (200-425 mesh) using ethyl acetate: methanol (3:2 v/v 500 ml) as an eluent and afford (**7a**) as white solid which was recrystallized with ethyl acetate:hexane (2:3 v/v, 50 ml) to produce a white crystalline solid, 50.4% (0.51 g) yield, mp 127-128°; ir (potassium bromide): ν 3235(NH), 1662 and 1604 (C=O) cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.12 (t, 6H, J = 6.7 Hz, -CH_2-CH_3), 2.41-2.44 (m, 2H, C_3-H), 3.13 (t, 2H, J = 6.7 Hz, C_2H), 3.43 (q, 4H, J = 6.9, 7.0 Hz, -CH_2-CH_3), 3.73 (d, 2H, J = 1.8 Hz, C_6-H), 5.76-5.80 (m, 1H, C_4-H, olefinic), 7.52 (d, 2H, J = 5.9 Hz, C_5 -H), 8.40 (d, 1H, J = 6.1 Hz, C_6 -H), 8.70 (d, 2H, J = 5.9 Hz, C_6 -H), 8.75 (s, 1H, -NH, D_2O exchangeable).

Anal. Calcd. for $C_{16}H_{22}N_4O_2$: C, 63.55; H, 7.33; N, 18.53. Found: C, 63.20; H, 7.38; N, 18.34.

1-(4-Pyridylcarbonylamino)-1,2,3,6-tetrahydropyridine-5-carboxylic acid diethylamide (**7b**).

The compound **7b** was obtained following General Procedure C has white solid 50.4% (0.51 g) yield, mp 124-126°; ir (potassium bromide): ν 3233 (NH), 1660 and 1608 (C=O) cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.11 (t, 6H, J = 6.7 Hz, -CH_2-CH_3), 2.40-2.43 (m, 2H, C_3-H), 3.12 (t, 2H, J = 6.7 Hz, C_2H), 3.44 (q, 4H, J = 6.9, 7.0 Hz, -CH_2-CH_3), 3.71 (d, 2H, J = 1.8 Hz, C_6-H), 5.76-5.81 (m, 1H, C_4-H, olefinic), 7.65 (d, 2H, J = 5.9 Hz, C_3 , C_5 -H), 8.23 (s, 1H, -NH, D_2O exchangeable), 8.69 (d, 2H, J = 5.8 Hz, C_2 , C_6 -H).

Anal. Calcd. for $C_{16}H_{22}N_4O_2$: C, 63.55; H, 7.33; N, 18.53. Found: C, 63.20; H, 7.38; N, 18.34.

1-Benzoylamino-1,2,3,6-tetrahydropyridine-5-carboxylic acid diethylamide (**7c**).

The compound **7c** was obtained following General Procedure C has white solid 53.1% (0.85 g) yield, mp 48-50°; ir (potassium bromide): ν 3238 (NH), 1670, 1604 (C=O) cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.14 (t, 6H, J = 7.2 Hz, -CH_2-CH_3), 2.39-2.43 (m, 2H, C_3-H), 3.15 (t, 2H, J = 6.0 Hz, C_2-H), 3.41 (q, 4H, J = 6.9, 7.5 Hz, -CH_2-CH_3), 3.71 (d, 2H, J = 1.8 Hz, C_6-H), 5.81-5.87 (m, 1H, C_4-H, olefinic), 7.34 (s, 1H, -NH, D_2O exchangeable), 7.41-7.45 (m, 3H, C_3 , C_4 and C_5 -H), 7.75 (d, 2H, J = 6.9 Hz, C_2, C_6 -H).

Anal. Calcd. for $C_{17}H_{23}N_3O_2$: C, 67.75; H, 7.69; N, 13.94. Found: C, 67.90; H, 7.85; N, 14.03.

1-(4-Methyl-benzoylamino)-1,2,3,6-tetrahydropyridine-5-carboxylic acid diethylamide (**7d**).

The compound **7d** was obtained following General Procedure C has white crystals in 38.4% (0.78 g) yield, mp 120-122°; ir (potassium bromide): ν 3240 (NH), 1657, 1608 (C=O) cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.12 (t, 6H, J = 7.0 Hz, -CH_2-CH_3), 2.36 (s, 3H, -CH_3 of phenyl), 2.37-2.42 (m, 2H, C_3-H), 3.11 (t, 2H, J = 5.6 Hz, C_2-H), 3.44 (q, 4H, J = 6.9, 7.0 Hz, -CH_2-CH_3), 3.67 (br s, 2H, C_6-H), 5.79-5.84 (m, 1H, C_4-H, olefinic), 7.19 (d, 2H, J = 7.9 Hz, C_3 , C_5 -H), 7.26 (s, 1H, -NH, D_2O exchangeable), 7.63 (d, 2H, J = 7.9 Hz C_2 , C_6 -H).

Anal. Calcd. for $C_{18}H_{25}N_3O_2$: C, 68.54; H, 7.99; N, 13.32. Found: C, 68.55; H, 8.07; N, 13.27.

1-(4-Fluoro-benzoylamino)-1,2,3,6-tetrahydropyridine-5-carboxylic acid diethylamide (**7e**).

The compound **7e** was obtained following General Procedure C has white solid 43.3% (0.35 g) yield, mp 123-125 °; ir (potassium bromide): ν 3224 (NH), 1660, 1608 (C=O) cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.13 (t, 6H, J = 6.9 Hz, -CH_2-CH_3), 2.38-2.42 (m, 2H, C_3-H), 3.14 (t, 2H, J = 5.4 Hz, C_2-H), 3.40 (q, 4H, J = 7.0 & 7.2 Hz, -CH_2-CH_3), 3.71 (br s, 2H, C_6-H), 5.79-5.83 (m, 1H, C_4-H, olefinic), 7.08 (d, 2H, J = 9.0 Hz, C_3 , C_5 -H), 7.82 (d, 2H, J = 5.4 Hz C_2 , C_6 -H), 7.84 (s, 1H, -NH, D_2O exchangeable).

Anal. Calcd. for $C_{17}H_{22}FN_3O_2$: C, 63.93; H, 6.94; N, 13.16. Found: C, 64.07; H, 7.03; N, 13.44.

1-(4-Chloro-benzoylamino)-1,2,3,6-tetrahydropyridine-5-carboxylic acid diethylamide (**7f**).

The compound **7f** was obtained following General Procedure C has white crystals in 48.6% (0.49 g) yield, mp 137-139 °; ir

(potassium bromide): ν 3226 (NH), 1660, 1608 (C=O) cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.14 (t, 6H, J = 6.9 Hz, -CH_2-*CH_3*), 2.40-2.43 (m, 2H, C_3-H), 3.13 (t, 2H, J = 5.4 Hz, C_2-H), 3.40 (q, 4H, J = 6.3, 7.2 Hz, -*CH_2*-CH_3), 3.70 (br s, 2H, C_6-H), 5.81-5.84 (m, 1H, C_4-H, olefinic), 7.39 (d, 2H, J= 8.4 Hz, C_3 , C_5 -H), 7.53 (s, 1H, -NH, D_2O exchangeable), 7.72 (d, 2H, J = 8.4 Hz C_2 , C_6 -H).

Anal. Calcd. for $C_{17}H_{22}ClN_3O_2$: C, 60.80; H, 6.60; N, 12.51. Found: C, 60.78; H, 6.58; N, 12.42.

1-(3-Bromo-benzoylamino)-1,2,3,6-tetrahydropyridine-5-carboxylic acid diethylamide (**7g**).

The compound **7g** was obtained following General Procedure C has white solid 55.3% (0.57 g) yield, mp 53-55°; ir (potassium bromide): ν 3238 (NH), 1665, 1604 (C=O) cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.12 (t, 6H, J = 6.7 Hz, -CH_2-*CH_3*), 2.39-2.41 (m, 2H, C_3-H), 3.12 (t, 2H, J = 5.2 Hz, C_2-H), 3.41 (q, 4H, J = 6.9, 7.2 Hz, -*CH_2*-CH_3), 3.68 (br s, 2H, C_6-H), 5.81-5.85 (m, 1H, C_4-H, olefinic), 7.29 (d, 1H, J = 7.5 Hz, C_5 -H), 7.45 (s, 1H, -NH, D_2O exchangeable), 7.60 (d, 1H, J = 8.1 Hz, C_4 -H), 7.66 (d, 1H, C_6 -H), 7.89 (s, 1H, C_2 -H).

Anal. Calcd. for $C_{17}H_{22}BrN_3O_2$: C, 53.69; H, 5.83; N, 11.05. Found: C, 53.78; H, 5.94; N, 11.20.

1-(4-Amino-benzoylamino)-1,2,3,6-tetrahydropyridine-5-carboxylic acid diethylamide (**7h**).

The compound **7h** was obtained following General Procedure C has white solid 34.4% (0.28 g) yield, mp 178-180°; ir (potassium bromide): ν 3239 (NH_2), 3225 (NH), 1660, 1608 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.13 (t, 6H, J = 6.9 Hz, -CH_2-*CH_3*), 2.39-2.42 (m, 2H, C_3-H), 2.52 (br s, -NH_2 of phenyl ring), 3.14 (t, 2H, J = 5.4 Hz, C_2-H), 3.40 (q, 4H, J = 6.9, 7.2 Hz, -*CH_2*-CH_3), 3.70 (br s, 2H, C_6-H), 5.82-5.86 (m, 1H, C_4-H, olefinic), 6.66 (d, 2H, J = 8.1 Hz, C_3 , C_5 -H), 7.39 (s, 1H, -NH, D_2O exchangeable), 7.60 (d, 2H, J = 7.8 Hz C_2 , C_6 -H).

Anal. Calcd. for $C_{17}H_{24}N_4O_2$: C, 64.53; H, 7.65; N, 17.71. Found: C, 64.62; H, 7.79N, 17.38.

1-Benzenesulfonylamino-1,2,3,6-tetrahydropyridine-5-carboxylic acid diethylamide (**7i**).

The compound **7i** was obtained following General Procedure C has white granules 42.3% (0.43 g) yield, mp 132-134°; ir (potassium bromide): ν 3197 (NH), 1607 (C=O), and 1340, 1167 (SO_2) cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.08 (t, 6H, J = 6.9 Hz, -CH_2-*CH_3*), 2.19-2.24 (m, 2H, C_3-H), 2.84 (t, 2H, J = 6.0 Hz, C_2-H), 3.25 (d, 2H, J = 2.1 Hz, C_6-H), 3.30 (q, 4H, J = 7.5, 6.9 Hz, -*CH_2*-CH_3), 5.72 (s, 1H, -NH, D_2O exchangeable), 5.75-5.79 (m, 1H, C_4-H, olefinic), 7.48-7.60 (complex multiplet, 3H, C_3 , C_4 and C_5 -H), 7.97 (dd, 2H, J = 1.5, 2.1 Hz C_2 , C_6 -H).

Anal. Calcd. for $C_{16}H_{23}N_3O_3S$: C, 56.95; H, 6.87; N, 12.45. Found: C, 57.10; H, 6.96; N, 12.56.

1-(4-Methyl-benzenesulfonylamino)-1,2,3,6-tetrahydropyridine-5-carboxylic acid diethylamide (**7j**).

The compound **7j** was obtained following General Procedure C has white crystals 58.0% (0.25 g) yield, mp 148-150°; ir (potassium bromide): ν 3116 (NH), 1602 (C=O), and 1289, 1167 (SO_2) cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.07 (t, 6H, J = 7.0 Hz, -CH_2-*CH_3*), 2.18-2.22 (m, 2H, C_3-H), 2.40 (s, 3H, -CH_3 of phenyl ring), 2.83 (t, 2H, J = 5.8 Hz, C_2-H), 3.23 (d, 2H, J = 2.0 Hz, C_6-H), 3.30 (q, 4H, J = 7.5, 6.9 Hz, -*CH_2*-CH_3), 5.74 (s, 1H, -NH, D_2O exchangeable), 5.74-5.78 (m, 1H, C_4-H, olefinic), 7.28 (d, 2H, J = 8.0 Hz, C_3 , C_5 -H), 7.82 (d, 2H, J = 8.2 Hz C_2 , C_6 -H).

Anal. Calcd. for $C_{17}H_{25}N_3O_3S$: C, 58.09; H, 7.17; N, 11.96. Found: C, 58.27; H, 7.24; N, 12.08.

1-(4-Methoxy-benzensulfonylamino)-1,2,3,6-tetrahydropyridine-5-carboxylic acid diethylamide (**7k**).

The compound **7k** was obtained following General Procedure C has white granules 49.4% (0.43 g) yield, mp 145-147°; ir (potassium bromide): ν 3118 (NH), 1600 (C=O), and 1333, 1163 (SO_2) cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.07 (t, 6H, J = 7.2 Hz, -CH_2-*CH_3*), 2.18-2.22 (m, 2H, C_3-H), 2.82 (t, 2H, J = 5.8 Hz, C_2-H), 3.25 (d, 2H, J = 2.0 Hz, C_6-H), 3.31 (q, 4H, J = 6.5, 6.9 Hz, -*CH_2*-CH_3), 3.85 (s, 3H, -OCH_3 of phenyl ring) 5.54 (s, 1H, -NH, D_2O exchangeable), 5.75-5.78 (m, 1H, C_4-H, olefinic), 6.95 (dd, 2H, J = 2.1, 2.0 Hz, C_3 , C_5 -H), 7.87 (dd, 2H, J = 2.2, 2.0 Hz, C_2 , C_6 -H).

Anal. Calcd. for $C_{17}H_{25}N_3O_4S$: C 55.57, H 6.86, N 11.44; found: C 55.36, H 6.98, N 11.53.

1-(3,4,5-Trimethoxy-benzoylamino)-1,2,3,6-tetrahydropyridine-5-carboxylic acid diethylamide (**15a**).

The compound **15a** was obtained following General Procedure C has white solid 40.7% (0.41 g) yield, mp 151-152°; ir (potassium bromide): ν 3239 (NH), 1654, 1602 (C=O) cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.13 (t, 6H, J = 6.9 Hz, -CH_2-*CH_3*), 2.38-2.42 (m, 2H, C_3-H), 3.14 (t, 2H, J = 5.4 Hz, C_2-H), 3.40 (q, 4H, J = 6.6, 6.9 Hz, -*CH_2*-CH_3), 3.71 (brs, 1H, C_6-H), 3.86 (s, 3H, -*m*-OCH_3 of phenyl ring), 3.89 (s, 6H, *p*-OCH_3 of phenyl ring), 5.82-5.86 (m, 1H, C_4-H, olefinic), 6.98 (s, 2H, C_2 , C_6 -H), 7.41 (s, 1H, -NH, D_2O exchangeable).

Anal. Calcd. for $C_{20}H_{29}N_3O_5$: C, 61.36; H, 7.47; N, 10.73. Found: C, 61.00; H, 7.60; N 10.60.

1-(4-*tert*-Butyl-benzoylamino)1,2,3,6-tetrahydropyridine-5-carboxylic acid diethyl- amide (**15b**).

The compound **15b** was obtained following General Procedure C has white solid 30.8% (0.25 g) yield, mp 96-98°; ir (potassium bromide): ν 3240 (NH), 1656, 1606 (C=O) cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.12 (t, 6H, J = 6.9 Hz, -CH_2-*CH_3*), 1.30 (s, 9H, -*t*-butyl group), 2.39-2.42 (m, 2H, C_3-H), 3.11 (t, 2H, J = 5.6 Hz, C_2-H), 3.39 (q, 4H, J = 6.6, 6.9 Hz, -*CH_2*-CH_3), 3.67 (br s, 2H, C_6-H), 5.82-5.85 (m, 1H, C_4-H, olefinic), 7.26 (s, 1H, -NH, D_2O exchangeable),7.41 (d, 2H, J = 8.4 Hz, C_3 , C_5 -H), 7.67 (d, 2H, J = 8.3 Hz, C_2 , C_6 -H).

Anal. Calcd. for $C_{21}H_{31}N_3O_2$: C, 70.55; H, 8.74; N, 11.75. Found: C, 70.74; H, 8.83; N, 11.99.

1-[(Thiophene-2-carbonyl)-amino]-1,2,3,6-tetrahydropyridine-5-carboxylic acid diethylamide (**15c**).

The compound **15c** was obtained following General Procedure C has white solid 38.4% (0.41 g) yield, mp 48-50°; ir (potassium bromide): ν 3226 (NH), 1660, 1608 (C=O) cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.13 (t, 6H, J = 6.9 Hz, -CH_2-*CH_3*), 2.39-2.42 (m, 2H, C_3-H), 3.13 (t, 2H, J = 6.1 Hz, C_2-H), 3.42 (q, 4H, J = 6.9, 7.2 Hz, -*CH_2*-CH_3), 3.67 (br s, 2H, C_6-H), 5.81-5.85 (m, 1H, C_4-H, olefinic), 6.45-6.49 (m, 1H, C_3 -H), 7.19 (d, 2H, J = 2.7 Hz, C_4 -H), 7.46 (d, 1H, J = 7.5 Hz, C_5 -H), 7.49 (s, 1H, -NH, D_2O exchangeable).

Anal. Calcd. for $C_{15}H_{21}N_3O_2S.0.115H_2O$(311.56): C, 57.83; H, 6.87; N, 13.49. Found: C, 57.92; H, 7.11; N, 13.13.

1-[(Furan-2-carbonyl)-amino]-1,2,3,6-tetrahydropyridine-5-carboxylic acid diethyl- amide (**15d**).

The compound **15d** was obtained following General Procedure C has white solid 48.2% (0.49 g) yield, mp 50-51 °; ir (potassium bromide): ν 3238 (NH), 1665, 1604 (C=O) cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.14 (t, 6H, J = 6.9 Hz, -CH_2-CH_3), 2.39-2.43 (m, 2H, C_3-H), 3.12 (t, 2H, J = 5.4 Hz, C_2-H), 3.40 (q, 4H, J = 6.9, 7.2 Hz, -CH_2-CH_3), 3.66 (br s, 2H, C_6-H), 5.85-5.88 (m, 1H, C_4-H, olefinic), 6.45-6.49 (m, 1H, C_3 -H), 7.16 (d, 2H, J = 2.7 Hz, C_4 -H), 7.44 (d, 1H, J = 7.5 Hz, C_5 -H), 7.47 (s, 1H, -NH, D_2O exchangeable).

Anal. Calcd. for $C_{15}H_{21}N_3O_3$: C, 61.84; H, 7.27; N, 14.42. Found: C, 61.72; H, 7.48; N, 14.10.

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