Facile Synthesis and Herbicidal Activity of Novel Multisubstituted Pyridine Derivatives

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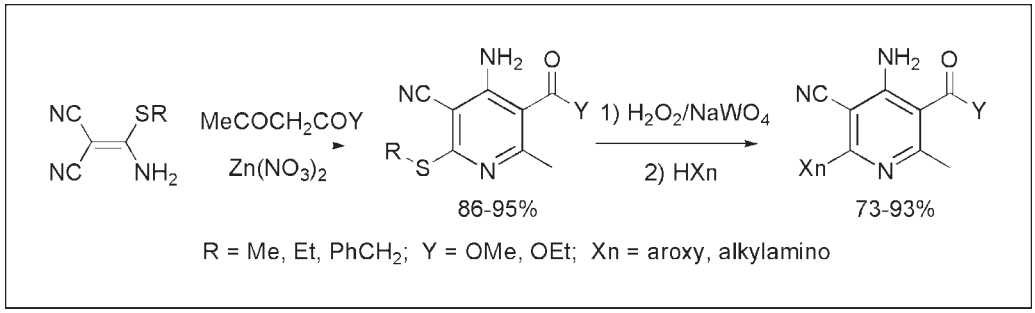

Ketene *N*,*S*-acetals reacted with β-ketoesters in the presence of $Zn(NO_3)_2 \cdot 6H_2O$ as catalyst, in ethanol solvent, giving 6-alkylsulfanylpyridines **4** in good yields without complicated purification procedures. Oxidization of compounds **4** with aqueous hydrogen peroxide in the presence of catalytic sodium wolframate led to the formation of 6-alkylsulfonylpyridine derivatives **5**, which could be further derivatized in the 6-position by nucleophilic reactions with phenols or amines to give multisubstituted pyridine compounds **8**. Bioassays indicated that some of the compounds of the type **8** have good herbicidal activity at a dose of 100 mg/L on the roots of oil rape and barnyard grass.

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INTRODUCTION

Muti-substituted pyridine derivatives occupy a central position in modern heterocyclic chemistry particularly in the pharmaceutical and agrochemical fields [1–4]. Therefore, new and improved synthetic studies about the preparation of this important heterocyclic ring system are of contemporary interest. The Hantzsch reaction has been proved to be a versatile method for the preparation of a large range of pyridines and dihydropyridines with symmetrical substitution patterns [5,6]. But the synthesis of multi-substituted pyridines with unsymmetrical substitution patterns is often difficult and involves multistep sequences, so there is still a great need to develop new approaches to pyridines of this type.

Our interests in the preparation of new heterocyclic compounds prompted us to elaborate novel methods for the synthesis of unsymmetrical multi-substituted pyridines and the evaluation of their biological activities. In this context, we report here an improved and convenient synthesis of the unsymmetrical multisubstituted pyridines **4** from easily accessible staring materials ketene *N*,*S*-acetals **2** and β-ketoesters **3**, as well as the preparation of various functional derivatives **5** and **8** resulting from a oxidization sequence and nucleophilic reactions. A preliminary *in vitro* bioassay indicated that some of the compounds of the type **8** have good herbicidal activity.

RESULTS AND DISCUSSION

The intermediates 1 and **2** can be prepared according to a published method [7]. It was reported that 4-aminopyridine **4** (Scheme 1) was prepared in moderate yield (48%) by using anhydrous stannic chloride as catalyst [8,9]. However, we found that there were some drawbacks with this method which need to be addressed. First, this method requires anhydrous conditions because tin (IV) chloride is readily hydrolyzed in water. Furthermore, the poor solubility of the reactants and the $SnCl_4$ catalyst in toluene, used as the solvent for the reaction, often leads to a low yield and prolonged reaction time. And finally, the complex and cockamamie workup procedure involves a dilution of the reaction mixture with a saturated aqueous solution of sodium carbonate and an extraction of the reactant mixture with ethyl acetate

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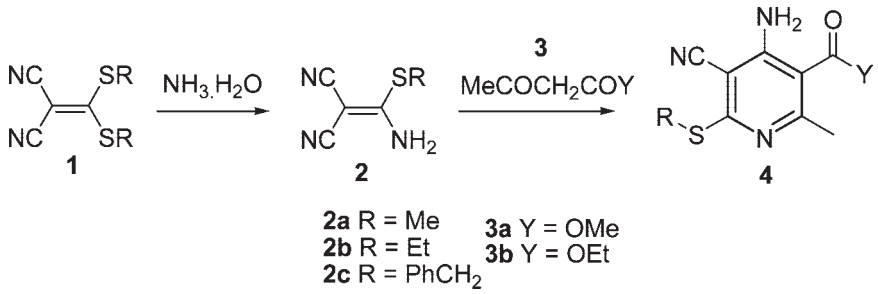
Scheme 1. Synthesis of 6-alkylsulfanyl substituted pyridines **4**.



before the title compound can be isolated and purified by a flash chromatography on silica gel.

In this study, various catalysts, different solvents as well as the reaction times and the molar ratios of reactants were tested to optimize the reaction conditions. The survey of reaction conditions and results are summarized in Table 1. The initial study was performed on the reaction of 2-(amino-methylthio-methylene)-malononitrile with ethyl acetoacetate in the presence of anhydrous $SnCl_4$ (2 equiv.) in refluxing toluene, which gave a yield of 38% of **4b** (entry 1). Corresponding reactions carried out in polar solvents such as ethanol led to none of the required product being observed (entry 2).

It was found that catalysts and solvents have a dramatic influence on the efficiency of the reaction. A variety of catalysts, such as $ZnCl_2$ (entries 3–4), $Zn(OAc)_2 \cdot 2H_2O$ (entry 6), $Zn(NO_3)_2 \cdot 6H_2O$ (entries 7–9), catalyze the reactions more efficiently than $SnCl_4$ (entries 1–2). And when ethanol was used as the solvent, $Zn(NO_3)_2 \cdot 6H_2O$ provided the best catalytic efficiency. We also found that the higher concentration of β-ketoesters (2 equiv.) slightly increased the yield (entry 7 *vs*. entry 8).

When using $Zn(NO_3)_2 \cdot 6H_2O$ as catalyst, we found that there was almost no change on the reaction yields when the reaction time changed from 12 h to 6 h whereas other variables were kept constant (entry 8 *vs*. entry 9). However, when a catalytic amount of triethylbenzylammonium chloride (TEBA) was added to the reaction, a maximum amount of the title compound **4b** was obtained (entry 10).

To investigate the scope of this reaction and to establish its tolerance of different substrates under the optimized conditions, a range of different β-ketoesters **3** and ketene *N,S*-acetals **2** were heated at reflux in ethanol in the presence of stoichiometric amounts of zinc(II) nitrate and a catalytic amount of TEBA. In all the cases investigated (Table 2), the expected pyridine **4** was isolated in good to excellent yield (86–95%), and no regioisomeric products were detected.

Bearing in mind the fact that the alkylsulfanyl group of compound **4** can be oxidized into alkylsulfonyl group, we became interested in identifying new ways to synthesize pyridines in which the methylsulfonyl group could serve as a leaving group to facilitate C—C bond-forming in the reactions. 6-Alkylsulfanyl pyridine derivatives **4** was treated with aqueous hydrogen peroxide in the presence of sodium wolframate as catalyst to give 6-alkylsulfonyl pyridine derivatives **5**. Acetic acid was a solvent of choice for the reaction stated in the literature [10]. In our case, however, acetic acid was not the best candidate as the reaction proceed in acetic acid at room

Table 1

Optimization of the reaction conditions.

Entry	Catalyst	Ratio **2a**:**3b**:catalyst	Conditions	Time (h)	Yield (%)[a]
1	$SnCl_4$	1:1:2	Toluene/reflux	8	38
2	$SnCl_4$	1:1:2	Ethanol/reflux	8	Failed
3	$ZnCl_2$	1:1:2	Toluene/reflux	12	48
4	$ZnCl_2$	1:1:2	Ethanol/reflux	12	60
5	$ZnSO_4 \cdot 7H_2O$	1:1:2	Ethanol/reflux	12	31
6	$Zn(OAc)_2 \cdot 2H_2O$	1:1:2	Ethanol/reflux	12	70
7	$Zn(NO_3)_2 \cdot 6H_2O$	1:1:2	Ethanol/reflux	12	73
8	$Zn(NO_3)_2 \cdot 6H_2O$	1:2:2	Ethanol/reflux	12	80
9	$Zn(NO_3)_2 \cdot 6H_2O$	1:2:2	Ethanol/reflux	6	78
10	$Zn(NO_3)_2 \cdot 6H_2O$ + TEBA	1:2:2	Ethanol/reflux	6	95

[a] Yield of pure isolated product.

Table 2

Yields of compounds **4–7**.

Compounds	R	Y	Yield (%)[a,b]	Compds	R	Y	Yield (%)[a]
4a	Me	MeO	90	**5a**	Me	MeO	85
4b	Me	EtO	95	**5b**	Me	EtO	91
4c	Et	MeO	86	**5c**	Et	MeO	78
4d	Et	EtO	91	**5d**	Et	EtO	83
4e	$PhCH_2$	MeO	87	**6**	\	EtO	50
4f	$PhCH_2$	EtO	89	**7**	\	EtO	67

[a] Yield of pure isolated product.
[b] Using $Zn(NO_2)_{2.} \cdot 6H_2O$ and TEBA as catalyst.

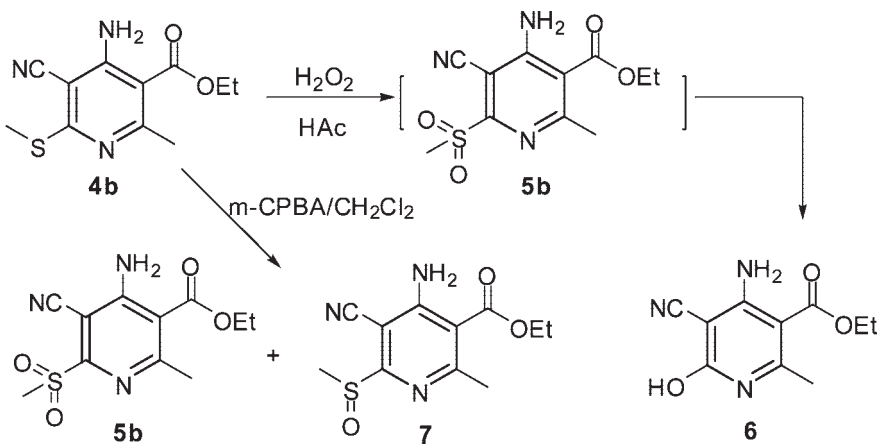
temperature or refluxing temperature gave mainly the byproduct of 4-amino-5-cyano-6-hydroxy-2-methyl-3-ethyloxycarbonyl pyridine **6** (Scheme 2). It may be due in part to the instability of 6-methylsulfonyl pyridine **5b** which could be hydrolyzed under the strong polar conditions.

On the other hand, when the reaction was performed in a less polar solvent of dichloromethane with *m*-chloroperbenzoic acid (*m*-CPBA) as oxidizing reagent, a mixture of 6-methylsulfonyl pyridine **5b** and 6-methylsulfinyl pyridine **7** were obtained (Scheme 2). In addition to these observations, we also attempted to use other solvents such as ethanol, methanol, acetonitrile, or even mixtures of these solvents coupled with different oxidizing reagents. Finally, H_2O_2-DMF was identified as the best oxidizing reagent-solvent combination in terms of both operational simplicity and yield. Under the optimized conditions, compound **4** was easily transformated into compound **5** with a high yield after refluxing for 2 h in DMF with aqueous hydrogen peroxide in the presence of sodium wolframate as catalyst (Scheme 3). The workup and purification of the reaction products were easy and efficient.

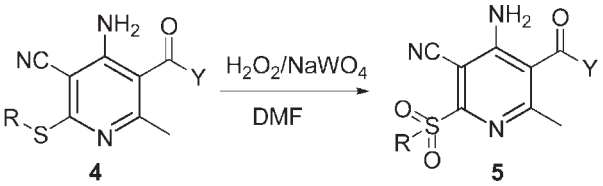
With robust synthesis procedure of 6-methylsulfonyl pyridine **5** in hand, a series of studies on compound **5** were performed to access other 6-substitued pyridine derivatives. The direct reaction of compound **5** with phenols failed to produce 6-aryloxy substituted pyridine **8a–j**. However, when performed in the presence of catalytic potassium carbonate in acetonitrile, the reaction took place and offered **8a–j** in good yield (Scheme 4). Irrespective of the fact whether the substituents on the phenols were electron-withdrawing or electron-releasing groups, the reaction was completed smoothly at refluxing temperature for 1–3 h. On the other hand, when the reaction was performed with NaH as the catalyst, no title product was separated out. This suggested that the compound **5** was unstable and the SO_2R group can be replaced by hydride ion of NaH firstly, which led to the next nucleophilic attack of phenoxides to methylsulfonyl group not occurring.

Conversion of compound **5** into 6-alkylamino substituted pyridine **8k–p** (Scheme 4) was effectively carried out by treatment of acetonitrile solutions of the 6-methylsulfonyl substituted pyridine **5** with 2 equivalent of amines at ambient temperature overnight followed by straight-forward purification of recrystallization. It was noteworthy that the isolated yield of **8k–p** was good despite that the amine is alkylamino or bulkyl heterocycle amino group (Table 3).

Scheme 2. Oxidization of **4b** using HAc and CH_2Cl_2 as solvent.



Scheme 3. Synthesis of 6-alkylsulfonyl pyridines **5**.



The compounds obtained were characterized fully by using spectroscopic methods (IR, ^{1}H NMR and EI-MS) and elemental analysis. For example, the IR spectra of **8a** revealed CN and C=O absorption bands at 2225 and 1689 cm^{-1} respectively, the signals attributable to the NH_2 are found at 3450 and 3346 cm^{-1}. The ^{1}H NMR spectrum of **8a** also shows the signals of NH_2 at 6.66 ppm as a broad absorption. The MS spectrum of **8a** shows strong molecular ion peak at *m/z* 331 with 100% abundance. In the case of **8h** [11], the structure was additionally confirmed by single-crystal X-ray diffraction (Fig. 1).

The preliminary herbicidal activity of compounds **8** series was evaluated comparable to a commercial herbicide 2,4-D, against two representative targets, oil rape and barnyard grass, at concentrations of 100 mg/L and 10 mg/L, according to a literature method [12]. The results are listed in Table 3 and show that these compounds have moderate to good herbicidal activity against the roots of these two species at the rate of 100 mg/L, especially against the root of oil rape. Compound with substituted phenoxy moiety in position 6 of the pyridine ring showed much better activity than 6-amino-substituted compounds. Switching the substituent Y from methoxy to ethoxy has no obvious effect on the inhibition rates.

In summary, we have developed an improved and convenient synthetic method for the preparation of multisubstituted pyridine derivatives with unsymmetrical substitution patterns. Some multisubstituted pyridines-containing compounds could be synthesized from simple precursors which are assembled in a modular fashion from readily available and inexpensive starting materials. The biological evaluation showed that some compounds have good herbicidal activities and we feel that this method will further facilitate exploration of this increasingly important pharmacophore.

EXPERIMENTAL

Melting points were measured on an electrothermal melting point apparatus and are uncorrected. Mass spectra were measured on a Finnigan Trace MS 2000 spectrometer. IR spectra were recorded on a PE-983 infrared spectrometer as KBr pellets with absorption in cm^{-1}. ^{1}H NMR spectra were recorded in $CDCl_3$ or DMSO on a Varian Mercury 400 spectrometer and resonances were given in ppm (δ) relative to TMS (δ 0.00 ppm). ^{13}C NMR spectra were recorded using $CDCl_3$ as the solvent on a Varian Mercury 600 spectrometer and resonances are given in ppm (δ) relative to $CDCl_3$ (δ 77.00 ppm). The elementary analysis was performed on a Vario EL III elementary analysis instrument. All of the solvents and materials were reagent grade and purified as required.

General procedure for the preparation of compounds (4a–f). A mixture of 2-(alkylsulfanyl-amino-methylene)-malononitrile **2** (10 mmol) and $Zn(NO_2)_2 \cdot 6H_2O$ (20 mmol) and a catalytic amount of TEBA (0.2 mmol) were added to a stirred solution of β-ketoesters **3** (20 mmol) in ethanol (30 mL). The solution was heated in an oil bath and refluxed for 6–8 h, and then cooled to room temperature. The crude precipitated product was collected by filtration. Further purification was accomplished by recrystallization from ethanol to give pure products **4a–f**.

4-Amino-5-cyano-2-methyl-6-methylsulfanyl-nicotinic acid methyl ester (4a). This compound was obtained as white solid, mp 141.2–143.2°C, yield 90%; IR: 3418, 3315, 3197, 3002, 2214(CN), 1690(C=O), 1610, 1550, 1238, 1096 cm^{-1} ; ^{1}H NMR ($CDCl_3$): δ 2.61 (s, 3H, SCH_3), 2.68 (s, 3H, py-CH_3), 3.92 (s, 3H, OCH_3), 6.70 ppm (s, 2H, NH_2); ^{13}C NMR ($CDCl_3$): δ 12.8, 27.6, 52.0, 89.1, 104.5, 114.5, 156.4, 163.7, 165.1, 168.2 ppm; ms: *m/z* 238 (M^+ +1, 15), 237 (M^+, 100), 236 (M^+ −1, 32), 205 (21), 177 (29); *Anal.* Calcd for $C_{10}H_{11}N_3O_2S$: C, 50.62; H, 4.67; N, 17.71; S, 13.51. Found: C, 50.90; H, 4.92; N, 17.78; S, 13.88.

4-Amino-5-cyano-2-methyl-6-methylsulfanyl-nicotinic acid ethyl ester (4b). This compound was obtained as white solid, mp 136.0–138.0°C, yield 95%; IR: 3406, 3309, 3200, 2983, 2219(CN), 1682(C=O), 1618, 1546, 1241, 1097 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.41 (t, 3H, OCH_2CH_3, J = 7.2 Hz), 2.62 (s, 3H, SCH_3), 2.70 (s, 3H, py-CH_3), 4.39 (q, 2H, OCH_2, J = 7.2 Hz), 6.68 ppm (s, 2H, NH_2); ^{13}C NMR ($CDCl_3$): δ 12.8, 14.1, 27.6, 61.4, 89.1, 104.7, 114.5, 156.4, 163.6, 164.9, 167.8 ppm; ms: *m/z* 252 (M^+ +1, 23), 251 (M^+, 100), 250 (M^+ −1, 41), 223 (47), 205 (31), 177(30); *Anal.* Calcd for $C_{11}H_{13}N_3O_2S$: C, 52.57; H, 5.21; N, 16.72; S, 12.76. Found: C, 52.75; H, 4.80; N, 16.89; S, 12.72.

4-Amino-5-cyano-6-ethylsulfanyl-2-methyl-nicotinic acid methyl ester (4c). This compound was obtained as white solid, mp 137.2–139.2°C, yield 86%; IR: 3406, 3310, 3276, 2951,

Scheme 4. Synthesis of 6-aroxy and 6-alkylamino substituted pyridines **8**.

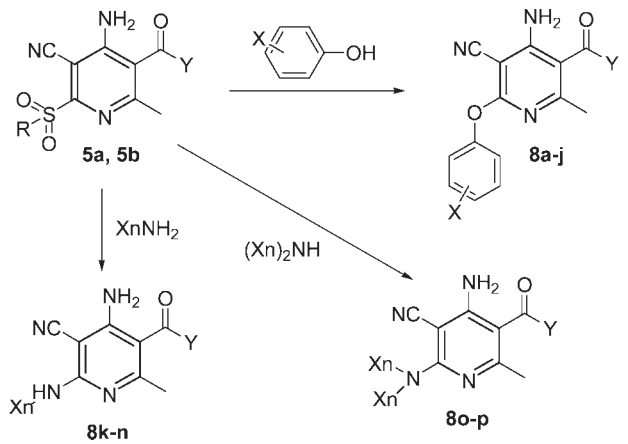
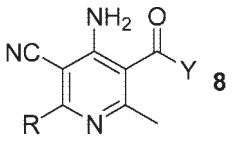


Table 3

Yields and heribicidal activity (% inhibition) of compounds **8**.



Compounds	R	Y	Yield (%)[a]	Oil rape (root/stalk)		Barnyard grass (root/stalk)	
				100 mg/L	10 mg/L	100 mg/L	10 mg/L
8a	4-Br-C_6H_4O	MeO	77	85/69	38/31	79/52	59/35
8b	4-Cl-2-F-C_6H_3O	MeO	75	60/27	16/12	72/13	48/13
8c	3-MeO-C_6H_4O	MeO	83	52/27	28/8	69/44	62/44
8d	3-NO2-C_6H_4O	MeO	75	74/62	45/19	83/39	59/22
8e	C_6H_5O	MeO	79	90/65	54/27	73/48	52/35
8f	C_6H_5O	EtO	88	79/42	16/19	79/39	52/30
8g	4-Cl-C_6H_4O	EtO	93	68/27	45/0	79/39	59/28
8h	2-NO2-C_6H_4O	EtO	87	90/65	54/27	72/48	52/35
8i	2,3-diMe-C_6H_3O	EtO	90	59/50	35/19	90/44	72/44
8j	4-Me-C_6H_4O	EtO	89	77/52	67/44	84/28	33/14
8k	EtNH	EtO	90	/[b]	/[b]	/[b]	/[b]
8l	*n*-PrNH	EtO	89	/[b]	/[b]	/[b]	/[b]
8m	*n*-BuNH	MeO	87	48/47	40/33	55/33	27/7
8n	$PhCH_2NH$	MeO	73	63/47	48/40	67/48	52/30
8o	Triazol-1-yl	EtO	78	73/40	32/8	75/39	41/28
8p	Piperdin-1-yl	EtO	82	/[b]	/[b]	/[b]	/[b]
	2,4-D			99/94	99/81	99/72	90/70

[a] Yield of pure isolated product.
[b] Not tested.

2213(CN), 1689(C=O), 1612, 1546, 1240, 1093 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.37 (t, 3H, $SCH_2\underline{CH_3}$, J = 7.2 Hz), 2.68 (s, 3H, Py-$\underline{CH_3}$), 3.25(q, 2H, $S\underline{CH_2}CH_3$, J = 7.2 Hz), 3.92(s, 3H, OCH_3), 6.72 ppm (s, 2H, NH_2); ^{13}C NMR ($CDCl_3$): δ 14.6, 24.4, 27.6, 51.9, 89.2, 104.4, 114.5, 156.5, 163.7, 164.9, 168.2 ppm; ms: m/z 251 (M^+, 66), 236 (26), 218 (81), 204 (15), 191

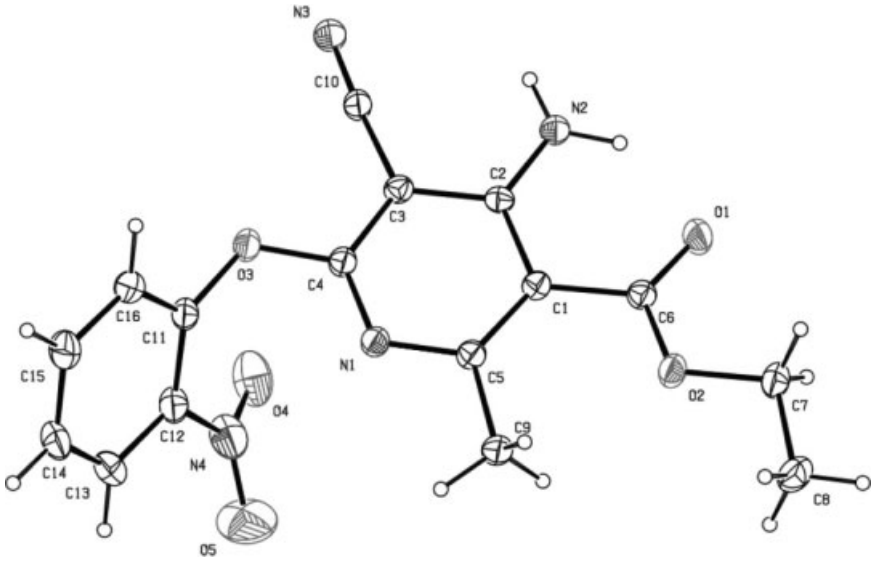


Figure 1. The molecular structure of compound **8h**.

(100), 186 (41), 159 (47), 130 (29); *Anal.* Calcd for $C_{11}H_{13}N_3O_2S$: C, 52.57; H, 5.21; N, 16.72; S, 12.76. Found: C, 52.90; H, 4.97; N, 16.60; S, 12.36.

4-Amino-5-cyano-6-ethylsulfanyl-2-methyl-nicotinic acid ethyl ester (4d). This compound was obtained as white solid, mp 145.0–146.9°C, yield 91%; IR: 3411, 3305, 3268, 2978, 2213(CN), 1680(C=O), 1609, 1544, 1240, 1092 cm^{-1}; ^1H NMR ($CDCl_3$): δ (ppm): 1.37 (t, 3H, CH_3, J = 7.2 Hz), 1.41 (t, 3H, CH_3, J = 7.2 Hz), 2.68 (s, 3H, Py-CH_3), 3.25 (q, 2H, SCH_2CH_3, J = 7.6 Hz), 4.38 (q 2H, OCH_2CH_3, J = 7.2 Hz,), 6.69 ppm (s, 2H, NH_2); ^{13}C NMR ($CDCl_3$): δ 14.6, 24.4, 27.6, 51.9, 61.3, 89.2, 104.4, 114.5, 156.5, 163.7, 164.9, 168.2 ppm; ms: *m/z* 265 (M^+, 36), 250 (7), 232 (30), 204 (62), 191 (99), 186 (57), 159 (100), 131 (50); *Anal.* Calcd for $C_{12}H_{15}N_3O_2S$: C, 54.32; H, 5.70; N, 15.84; S, 12.08. Found: C, 54.53; H, 5.41; N, 16.04; S, 12.35.

4-Amino-6-benzylsulfanyl-5-cyano-2-methyl-nicotinic acid methyl ester (4e). This compound was obtained as yellow solid, mp 139.4–141.7°C, yield 87%; IR: 3426, 3307, 3004, 2211(CN), 1677(C=O), 1603, 1547, 1250 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.71 (s, 3H, Py-CH_3), 3.92 (s, 3H, OCH_3), 4.51 (s, 2H, PhCH_2), 6.69 (s, 2H, NH_2), 7.24–7.41 ppm (m, 5H, Ph-H); ^{13}C NMR ($CDCl_3$): δ 27.6, 33.9, 52.1, 89.1, 104.8, 114.4, 127.3, 128.4, 129.1, 137.4, 156.6, 163.7, 164.2, 168.2 ppm; ms: *m/z* 314 (M^+ +1, 17), 313 (M^+, 100), 312 (M^+ −1, 27), 280 (18), 255 (4); *Anal.* Calcd for $C_{16}H_{15}N_3O_2S$: C, 61.32; H, 4.82; N, 13.41; S, 10.23. Found: C, 61.41; H, 4.39; N, 13.33; S, 10.53.

4-Amino-6-benzylsulfanyl-5-cyano-2-methyl-nicotinic acid ethyl ester (4f). This compound was obtained as yellow solid, mp 109.7–112.0°C, yield 89%; IR: 3419, 3312, 2986, 2211(CN), 1673(C=O), 1606, 1546, 1237 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.41 (t, 3H, OCH_2CH_3, J = 7.2 Hz), 2.72 (s, 3H, Py-CH_3), 4.38 (q, 2H, OCH_2CH_3, J = 7.2 Hz), 4.51 (s, 2H, PhCH_2), 6.70 (s, 2 H, NH_2), 7.24–7.41 ppm (m, 5 H, Ph-H); ^{13}C NMR ($CDCl_3$): δ 14.1, 27.5, 33.9, 61.2, 88.9, 104.9, 114.3, 127.2, 128.4, 129.1, 137.4, 156.6, 163.5, 163.9, 167.7 ppm; ms: *m/z* 328 (M^+ +1, 18), 327 (M^+, 100), 326 (M^+ −1, 74), 299 (11), 255 (28), 212 (38); *Anal.* Calcd for $C_{17}H_{17}N_3O_2S$: C, 62.36; H, 5.23; N, 12.83; S, 9.79. Found: C, 62.14; H, 4.97; N, 12.76; S, 9.63.

General procedure for the preparation of compounds (5a–d, 6,7). A mixture of 4-amino-5-cyano-2-methyl-6-alkylsulfanyl-nicotinic acid alkyl esters **4a–d** (10 mmol) and the catalysis sodium wolframate (0.1 mmol) were added to DMF (30 mL) and heated to 40°C. A solution of aqueous hydrogen peroxide (12 mmol) in ethanol (5 mL) was added at a rate of 1d/s to keep the internal temperature below 50°C. The mixture stirred at 60°C for 3 h and then cooled. The reaction mixture poured into 300 mL of water and the solution was stirred for 4–6 h at room temperature and the precipitate was collected by filtration. The products were air dried and recrystallized from ethanol to give pure product 4-amino-5-cyano-6-alkylsulfonyl- 2-methyl-nicotinic acid alkyl esters **5a–d.**

When this reaction was performed in a solvent of acetic acid, the product **6** was obtained in 50% yield. And when the same reaction was carried out in presence of m-chloroperbenzoic acid (m-CPBA), as oxidizing reagent in CH_2Cl_2, a mixture of 6-methylsulfonyl pyridine **5b** and 6-methylsulfinyl pyridine **7** were obtained. The purification procedure was carried out by flash silica gel chromatography using petroleum ether/ethyl acetate (3:1, v/v) as eluent to give product **7** in 67% yield and **5b** in 25% yield.

4-Amino-5-cyano-6-methylsulfonyl-2-methyl-nicotinic acid methyl ester (5a). This compound was obtained as white solid, mp 172.0–174.0°C, yield 85%; IR: 3409, 3298, 2928, 2223(CN), 1697(C=O), 1613, 1554, 1307, 1255, 1138 cm^{-1}; ^1H NMR ($CDCl_3$): δ2.76 (s, 3H, Py-CH_3), 3.32 (s, 3H, SO_2CH_3), 3.99 (s, 3H, OCH_3), 7.05 ppm (s, 2H, NH_2); ms: *m/z* 269 (M^+, 7), 237 (5), 218 (9), 205 (51), 190 (14), 175 (52), 158 (21), 129 (28); *Anal.* Calcd for $C_{10}H_{11}N_3O_4S$: C, 44.60; H, 4.12; N, 15.60; S, 11.91. Found: C, 44.73; H, 4.00; N, 15.42; S, 12.27.

4-Amino-5-cyano-6-methylsulfonyl-2-methyl-nicotinic acid ethyl ester (5b). This compound was obtained as white solid, mp 154.3–156.0°C, yield 91%; IR: 3415, 3287, 2924, 2224(CN), 1690(C=O), 1606, 1550, 1274, 1139 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.45 (t, 3H, OCH_2CH_3, J = 7.2 Hz), 2.76 (s, 3H, Py-CH_3), 3.32 (s, 3H, SO_2CH_3), 4.46 (q, 2H, OCH_2CH_3, J = 7.2 Hz), 7.05 ppm (s, 2H, NH_2); ^{13}C NMR ($CDCl_3$): δ 14.0, 27.0, 39.3, 62.4, 89.3, 110.3, 111.8, 157.5, 159.6, 163.8, 166.5 ppm; ms: *m/z* 284 (M^+ +1, 4), 283 (M^+, 25), 237 (14), 219 (100), 191 (19), 175 (63), 131 (36); *Anal.* Calcd for $C_{11}H_{13}N_3O_4S$: C, 46.63; H, 4.63; N, 14.83; S, 11.32. Found: C, 46.87; H, 4.54; N, 15.04; S, 11.25.

4-Amino-5-cyano-6-ethylsulfonyl-2-methyl-nicotinic acid methyl ester (5c). This compound was obtained as white solid, mp 128.0–129.3°C, yield 78%; IR: 3427, 3342, 2926, 2226(CN), 1731(C=O), 1640, 1529, 1570, 1324, 1252, 1137 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.41(t, 3H, $SO_2CH_2CH_3$, J = 7.2 Hz), 2.76 (s, 3H, Py-CH_3), 3.53(q, 2H, $SO_2CH_2CH_3$, J = 7.2 Hz), 3.99(s, 3H, OCH_3), 7.10 ppm (s, 2H,NH_2); ms: *m/z* 283 (M^+, 2), 252 (8), 218 (36), 205 (52), 192 (100), 191 (87), 176 (24), 160 (25), 131 (49); *Anal.* Calcd for $C_{11}H_{13}N_3O_4S$: $C_{11}H_{13}N_3O_4S$: C, 46.63; H, 4.63; N, 14.83; S, 11.32. Found: C, 46.73; H, 4.34; N, 14.83; S, 11.51.

4-Amino-5-cyano-6-ethylsulfonyl-2-methyl-nicotinic acid ethyl ester (5d). This compound was obtained as white solid, mp 102.5–103.7°C, yield 83%, IR: 3421, 3327, 2921, 2226(CN), 1694(C=O), 1611, 1526, 1553, 1316, 1140 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.39–1.59 (m, 6H, 2* CH_3), 2.76 (s, 3H, Py-CH_3), 3.52(q, 2H, $SO_2CH_2CH_3$, J = 7.2 Hz), 4.47(q, 2H, OCH_2CH_3, J = 6.8 Hz), 7.12 ppm (s, 2H, NH_2); ms: *m/z* 298 (M^+ +1, 2), 297 (M^+, 3), 233 (9), 205 (25), 187 (5), 161 (12), 132 (20); *Anal.* Calcd for $C_{11}H_{13}N_3O_4S$: $C_{12}H_{15}N_3O_4S$: C, 48.47; H, 5.08; N, 14.13; S, 10.78. Found: C, 48.73; H, 4.78; N, 14.12; S, 11.06.

4-Amino-5-cyano-6-hydroxy-2-methyl-nicotinic acid ethyl ester (6). This compound was obtained as white solid, mp >270°C, yield 50%; ^1H NMR (DMSO): δ 1.28 (t, 3H, OCH_2CH_3, J = 7.2 Hz), 2.42 (s, 3H, Py-CH_3), 4.26 (q, 2H, OCH_2CH_3, J = 7.2 Hz), 7.58 (s, 2H, NH_2), 11.68 ppm (s, 1H, OH); *Anal.* Calcd for $C_{10}H_{11}N_3O_3$: C, 54.29; H, 5.01; N, 19.00. Found: C, 54.43; H, 4.97; N, 18.83.

4-Amino-5-cyano-6- methylsulfinyl-2-methyl-nicotinic acid ethyl ester (7). This compound was obtained as white solid, mp 132.2–134.4°C, yield 67%; ^1H NMR ($CDCl_3$): δ 1.44 (t 3H, OCH_2CH_3, J = 7.2 Hz,), 2.76 (s, 3H, Py-CH_3), 2.94 (s, 3H, $SOCH_3$), 4.46 (q, 2H, OCH_2CH_3, J = 7.2 Hz), 7.04 ppm (s, 2H, NH_2); ms: *m/z* 267 (M^+, 12), 250 (10), 219 (72), 175 (100), 131 (11); *Anal.* Calcd. for $C_{11}H_{13}N_3O_3S$: C, 49.43; H, 4.90; N, 15.72; S, 12.00. Found: C, 49.51; H, 4.44; N, 15.62; S, 12.26.

General procedure for the preparation of compounds (8a–j). A mixture of 4-amino-5-cyano-6-methylsulfonyl-2-methyl-nicotinic acid alkyl ester **5a** or **5b** (5mmol) and

catalytic amount of K_2CO_3 (0.1 mmol) were added to a solution of substituted phenol (5 mmol) in anhydrous acetonitrile (20 mL). The solution was heated to 80°C in an oil bath to bring the mixture to reflux for 1–2 h and then cooled to room temperature. The precipitated crude product was collected by filtration. The filtrate was recrystallized from dichloromethane/petroleum ether to give pure 4-amino-5-cyano-2-methyl-6-substitutedphenoxy- nicotinic acid alkyl ester **8a–j.**

4-Amino-5-cyano-6-(4-bromophenoxy)-2-methyl-nicotinic acid methyl ester (8a). This compound was obtained as white solid, mp 161.0–163.0°C, yield 77%; IR: 3400, 3308, 2955, 2225(CN), 1689(C=O), 1616, 1546, 1567, 1270, 1160 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.07 (s, 3H, Ar-CH_3), 2.32 (s, 3H, Ar-CH_3), 2.48 (s, 3H, Py-CH_3), 3.90 (s, 3H, OCH_3), 6.80 (s, 2H, NH_2), 6.92–7.11 ppm (m, 3H, Ar-H); ms: *m/z* 311 (M^+, 29), 310 (10), 296 (49), 264 (28), 236 (19), 103 (41), 91 (44), 77 (100), 66(19); *Anal*. Calcd. for $C_{17}H_{17}N_3O_3$: C, 65.58; H, 5.50; N, 13.50. Found: C, 65.35; H, 5.11; N, 13.41.

4-Amino-5-cyano-6-(4-chloro-2-fluorophenoxy)-2-methyl-nicotinic acid methyl ester (8b). This compound was obtained as white solid, mp 184.0–184.7°C, yield 75%; IR: 3409, 3318, 2959, 2223(CN), 1692(C=O), 1627, 1551, 1497, 1574, 1269, 1094 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.49 (s, 3H, Py-CH_3), 3.90 (s, 3H, OCH_3), 6.90 (s, 2H, NH_2), 7.15–7.18 ppm (m, 3H, Ar-H). ms: *m/z* 335 (M^+, 49), 303 (29), 275 (82), 236 (24) 213 (22), 170 (100), 169 (83), 129 (43), 77 (31), 66 (75); *Anal*. Calcd. for $C_{15}H_{11}ClFN_3O_3$: C, 53.66; H, 3.30; N, 12.52. Found: C, 53.99; H, 3.30; N, 12.41.

4-Amino-5-cyano-6-(3-methoxyphenoxy)-2-methyl-nicotinic acid methyl ester (8c). This compound was obtained as white solid, mp 188.0–190.0°C, yield 83%; IR: 3412, 3313, 2964, 2221(CN), 1688(C=O), 1613, 1568, 1501, 1263, 1090 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.46 (s, 3H, CH_3), 3.75 (s, 3H, Ar-OCH_3), 3.89 (s, 3H, OCH_3), 6.80 (s, 2H, NH_2), 6.96–7.22 ppm (m, 4H, Ar-H). ^{13}C NMR ($CDCl_3$): δ 27.4, 51.9, 55.9, 78.3, 104.4, 112.8, 114.1, 120.7, 122.9, 126.4, 141.5, 151.6, 159.1, 164.0, 165.3, 168.1 ppm; ms: *m/z* 313 (M^+, 11), 298 (26), 250 (62), 222 (34), 210 (18), 194 (15), 173 (19), 147 (24), 91 (46), 77 (100); *Anal*. Calcd for $C_{16}H_{15}N_3O_3$: C, 61.34; H, 4.83; N, 13.41. Found: C, 61.56; H, 4.51; N, 13.23.

4-Amino-5-cyano-6-(3-nitrophenoxy)-2-methyl-nicotinic acid methyl ester (8d). This compound was obtained as yellow solid, mp 141.0–143.0°C, yield 75%; IR: 3387, 3281, 2954, 2232(CN), 1695(C=O), 1630, 1598, 1531, 1575, 1269, 1097 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.42 (s, 3H, Py-CH_3), 3.90 (s, 3H, OCH_3), 6.90 (s, 2H, NH_2), 7.34–8.12 ppm (m, 4H, Ar-H); ms: *m/z* 296 ($M^+ - O_2$, 11), 283 ($M^+ - NO_2$, 44), 282 (100), 250 (43), 222 (9), 206 (10), 91 (7), 77 (6); *Anal*. Calcd. for $C_{15}H_{12}N_4O_5$: C, 54.88; H, 3.68; N, 17.07. Found: C, 55.16; H, 3.64; N, 16.89.

4-Amino-5-cyano-2-methyl-6-phenoxy-nicotinic acid methyl ester (8e). This compound was obtained as white solid, mp 171.0–173.0°C, yield 79%; IR: 3393, 3286, 2957, 2229(CN), 1692(C=O), 1630, 1594, 1492, 1267, 1096 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.41 (s, 3H. Py-CH_3), 3.90 (s, 3H, OCH_3), 6.90 (s, 2H, NH_2) 7.34–8.12 ppm (m, 5H, Ar-H); ^{13}C NMR ($CDCl_3$): δ 27.4, 52.0, 78.8, 104.6, 113.9, 121.6, 125.3, 129.2, 152.3, 159.1, 163.8, 165.4, 167.9 ppm; ms: *m/z* 284 (M^+ +1, 7), 283 (M^+, 55), 282 (M^+ −1, 23), 251(17), 225 (63), 222 (44), 194 (28), 130 (22), 118 (75), 77 (100); *Anal*. Calcd for $C_{15}H_{13}N_3O_3$: C, 63.60; H, 4.63; N, 14.83. Found: C, 63.89; H, 4.57; N, 14.70.

4-Amino-5-cyano-2-methyl-6-phenoxy-nicotinic acid ethyl ester (8f). This compound was obtained as white solid, mp 126.9–128.5°C, yield 88%; IR: 3402, 3308, 2984, 2230(CN), 1680(C=O), 1625, 1491, 1566, 1265, 1096 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.40 (t, 3H, OCH_2CH_3, J = 7.2 Hz), 2.52 (s, 3H, Py-CH_3),4.38(q 2H, OCH_2CH_3, J = 7.2 Hz,), 6.88 (s, 2H, NH_2), 7.15–7.41 ppm (m, 5 H, Ar-H); ms: *m/z* 298 (M^+ +1, 15), 297 (M^+, 47), 250 (35), 226 (41), 225 (54), 224 (100), 194 (27), 176 (24), 183 (55), 118 (61), 77 (46); *Anal*. Calcd. for $C_{16}H_{15}N_3O_3$: C, 64.64; H, 5.09; N, 14.13. Found: C, 64.54; H, 4.79; N, 14.11.

4-Amino-6-(4-chloro-phenoxy)-5-cyano-2-methyl-nicotinic acid ethyl ester (8g). This compound was obtained as white solid, mp 184.0–184.7°C, yield 93%; IR: 3450, 3346, 2982, 2222(CN), 1708(C=O), 1570, 1490, 1230 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.40 (t, 3H, OCH_2CH_3, J = 7.2 Hz), 2.51 (s, 3H, Py-CH_3), 4.38 (q, 2H, OCH_2CH_3, J = 7.2 Hz), 6.66 (s, 2H, NH_2), 7.10–7.36 ppm (m, 4H, Ar-H); ^{13}C NMR ($CDCl_3$): δ 14.1, 27.4, 61.5, 78.8, 105.0, 113.7, 123.1, 129.2, 130.5, 150.8, 159.2, 163.3, 165.1, 167.4; ms: *m/z* 332 (M^+ +1, 9), 331 (M^+, 100), 302 (15), 284 (33), 258 (91), 222 (19), 194 (21), 152 (64); *Anal*. Calcd for $C_{16}H_{14}ClN_3O_3$: C, 57.93; H, 4.25; N, 12.67. Found: C, 57.88; H, 4.03; N, 12.62.

4-Amino-5-cyano-2-methyl-6-(2-nitrophenoxy)-nicotinic acid ethyl ester (8h). This compound was obtained as yellow solid, mp 141.0–143.0°C, yield 87%; IR: 3386, 3298, 2979, 2229(CN), 1684(C=O), 1618, 1569, 1272 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.38 (t, 3H, OCH_2CH_3, J = 7.2 Hz), 2.42 (s, 3H, Py-CH_3), 4.37 (q, 2H, OCH_2CH_3, J = 7.2 Hz), 6.90 (s, 2H, NH_2), 7.34–8.12 ppm (m, 4H, Ar-H); ^{13}C NMR ($CDCl_3$): δ 14.1, 27.4, 61.5, 78.7, 105.4, 113.4, 125.2, 125.5, 126.2, 134.6, 142.2, 145.2, 159.2, 162.3, 164.9, 167.3 ppm; ms: *m/z* 342 (M^+, 10), 331 (21), 296 (50), 268 (100), 250 (22), 224 (26), 194 (12), 176 (15), 152 (16); *Anal*. Calcd for $C_{16}H_{14}N_4O_5$: C, 56.14; H, 4.12; N, 16.37. Found: C, 56.29; H, 3.81; N, 16.51.

4-Amino-5-cyano-2-methyl-6-(2,3-dimethylphenoxy)-nicotinic acid ethyl ester (8i). This compound was obtained as yellow solid, mp 159.8–161.8°C, yield 90%; IR: 3391, 3297, 2980, 2229(CN), 1679(C=O), 1617, 1543, 1565, 1271, 1100 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.39 (t, 3H, OCH_2CH_3, J = 7.2 Hz), 2.07 (s, 3H, Ar-CH_3), 2.32 (s, 3H, Ar-CH_3); 2.48(s, 3H, Py-CH_3), 4.37 (q, 2H, OCH_2CH_3, J = 7.2 Hz), 6.90 (s, 2H, NH_2), 6.92–7.10 ppm (m, 3H, Ar-H); ms: *m/z* 325 (M^+, 100), 310 (92), 296 (23), 282 (45), 264 (69), 253 (36), 236 (48), 218 (12), 208 (15), 146 (15), 102 (53), 91 (44); *Anal*. Calcd. for $C_{18}H_{19}N_3O_3$: C, 66.45; H, 5.89; N, 12.91. Found: C, 66.47; H, 5.52; N, 13.06.

4-Amino-5-cyano-2-methyl-6-(4-methylphenoxy)-nicotinic acid ethyl ester (8j). This compound was obtained as white solid, mp 106.9–108.3°C, yield 89%; IR: 3397, 3279, 2942, 2224(CN), 1689(C=O), 1626, 1505, 1566, 1266, 1097 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.39 (t, 3H, OCH_2CH_3, J = 7.2 Hz), 2.37 (s, 3H, Ar-CH_3), 2.52(s, 3H, Py-CH_3), 4.37 (q, 2H, OCH_2CH_3, J = 7.2 Hz), 6.92 (s, 2H, NH_2), 7.03–7.19 ppm (m, 3H, Ar-H); ms: *m/z* 311 (M^+, 100), 296 (6), 282 (14), 265 (52), 239 (82), 237 (46), 222 (7), 132 (30), 91 (16), 77 (8); *Anal*. Calcd. for $C_{17}H_{17}N_3O_3$: C, 65.58; H, 5.50; N, 13.50. Found: C, 65.86; H, 5.97; N, 13.57.

General procedure for the preparation of compounds (8k–p). A mixture of 4-amino-5-cyano-6-methylsulfonyl-2-methyl-nicotinic acid alkyl ester **5a** or **5b** (5 mmol),

alkylamines or heterocycleamines (10 mmol), and 20 mL of acetonitrile was stirred for 4–5 h at room temperature. The color of the reaction mixture was changed into yellow. The reaction mixture was poured into 100 mL of water and this solution was stirred for 2 h. The crude product that precipitated was collected by filtration. The filtrate was recrystallized from dichloromethane/petroleum ether to give pure 4-amino-5-cyano-2-methyl-6-alkylamino-nicotinic acid alkyl esters **8 k–p.**

4-Amino-5-cyano-2-methyl-6-ethylamino-nicotinic acid ethyl ester (8k). This compound was obtained as white solid, mp 151.0–154.0°C, yield 90%; ^{1}H NMR ($CDCl_3$): δ 1.24(t, 3H, $NHCH_2\underline{CH_3}$, J = 7.2 Hz), 1.38(t, 3H, $OCH_2\underline{CH_3}$, J = 7.2 Hz), 2.60 (s, 3H, Py-CH_3), 3.55–3.61(m, 2H, $\underline{NHCH_2}CH_3$), 4.33(q, 2H, $O\underline{CH_2}CH_3$, J = 6.8 Hz), 5.08(s, 1H, $\underline{NH}$), 6.68 ppm (s, 2H, $\underline{NH_2}$); ms: m/z 248 (M^+, 100), 233(88.0), 219 (84.8), 205(64.9), 187 (46.8), 174 (98.7), 159 (38.0), 117 (6.0), 44 (7.9); *Anal*. Calcd. for $C_{12}H_{16}N_4O_2$: C, 58.05; H, 6.50; N, 22.57. Found: C, 57.75; H, 6.02; N, 22.77.

4-Amino-5-cyano-2-methyl-6-propylamino-nicotinic acid ethyl ester (8l). This compound was obtained as white solid, mp 141.0–142.0°C, yield 89%; ^{1}H NMR ($CDCl_3$): δ 0.97(t, J = 7.2 Hz, 3H, $NHCH_2\underline{CH_3}$), 1.38(t, J = 7.2 Hz, 3H, $OCH_2\underline{CH_3}$), 1.63(m, 2H, $CH_2\underline{CH_2}CH_3$), 2.60 (s, 3H, Py-CH_3), 3.50(q, J = 6.8 Hz, 2H, $NH\underline{CH_2}CH_2$), 4.33(q, J = 7.2 Hz, 2H, $O\underline{CH_2}CH_3$), 5.12(s, 1H, $\underline{NH}$), 6.68 ppm (s, 2H, NH_2); ^{13}C NMR ($CDCl_3$): δ 11.3, 14.3, 22.9, 28.3, 42.8, 60.6, 72.5, 99.5, 116.3, 158.4, 158.5, 166.3, 168.2 ppm; *Anal*. Calcd. for $C_{13}H_{18}N_4O_2$: C, 59.53; H, 6.92; N, 21.36. Found: C, 59.46; H, 6.74; N, 21.50.

4-Amino-5-cyano-2-methyl-6-butylamino-nicotinic acid methyl ester (8m). This compound was obtained as white solid, m.p. 139.9–141.3°C, yield 87%; IR: 3424, 3349, 2959, 2201(CN), 1669(C=O), 1611, 1507, 1565, 1274, 1092 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.95(t, J = 7.2 Hz, 3H, $CH_2\underline{CH_3}$), 1.37–1.42(m, 2H, $CH_2\underline{CH_2}CH_3$), 1.55–1.62 (m, 2H, $\underline{CH_2}CH_2CH_3$), 2.60 (s, 3H, Py-$\underline{CH_3}$), 3.54(q, J = 6.4 Hz, 2H, $\underline{NHCH_2}CH_2$), 3.87(s, 3H, $O\underline{CH_3}$), 5.12(s, 1H, NH), 6.68 ppm (s, $\underline{2H}$, $\underline{NH_2}$); ms: m/z 262 ($\underline{M^+}$, 38), 247 (7), 233 (55), 219 (100), 206 (46), 187 (78), 174 (49), 159 (19); *Anal*. Calcd. for $C_{13}H_{18}N_4O_2$: C, 59.53; H, 6.92; N, 21.36. Found: C, 59.30; H, 7.12; N, 21.05.

4-Amino-5-cyano-2-methyl-6-benzylamino-nicotinic acid methyl ester (8n). This compound was obtained as white solid, m.p. 138.8–140.8°C, yield 73%; IR: 3423, 3345, 2949, 2202(CN), 1673(C=O), 1602, 1503, 1562, 1284, 1091 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.62 (s, 3H, Py-CH_3), 3.88(s, 3H, OCH_3), 4.75(d, J = 5.6 Hz, 2H, $NH\underline{CH_2}$), 5.44(s, 1H, NH), 6.74 (s, 2H, NH_2), 7.28–7.37 ppm (m, $\underline{5H}$, Ph-H); ^{13}C NMR ($CDCl_3$): δ 28.2, 44.8, 51.5, 72.8, 99.8, 116.0, 127.5, 127.8, 128.6, 138.5, 158.1, 158.4, 166.4, 168.5 ppm; ms: m/z 296 (M^+, 100), 263 (11), 236 (6), 218 (8), 191 (16), 159 (10), 106 (66), 91 (27); *Anal*. Calcd. for $C_{16}H_{16}N_4O_2$: C, 64.85; H, 5.44; N, 18.91. Found: C, 65.28; H, 5.39; N, 18.74.

4-Amino-5-cyano-2-methyl-6-triazolyl-nicotinic acid ethyl ester (8o). This compound was obtained as yellow solid, m.p. 196.0–198.0°C, yield 78%; ^{1}H NMR ($CDCl_3$): δ 1.45(t, J = 7.2 Hz, 3H, $OCH_2\underline{CH_3}$), 2.75 (s, 3H, Py-CH_3), 4.45(q, J = 7.2 Hz, 2H, $O\underline{CH_2}CH_3$), 7.08 (s, 2H, NH_2), 8.19(s, 1H, triazole-H), 9.18 ppm (s, 1H, triazole-H); ms: m/z 272 (M^+, 44.9), 227 (91.4), 225(100), 199 (26), 173 (10), 144 (6); *Anal*. Calcd. for $C_{12}H_{12}N_6O_2$: C, 52.94; H, 4.44; N, 30.87. Found: C, 53.22; H, 4.64; N, 31.12.

4-Amino-5-cyano-2-methyl-6-piperdinyl-nicotinic acid ethyl ester (8p). This compound was obtained as yellow solid, m.p. 108.0–110.0°C, yield 82%; ^{1}H NMR ($CDCl_3$): δ 1.38(t, J = 7.2 Hz, 3H, $OCH_2\underline{CH_3}$), 1.67(d, J = 7.2 Hz, 6H, 3*CH_2), 2.56 (s, 3H, Py-CH_3), 3.82(d, J = 7.2 Hz, 4H, 2*CH_2), 4.32(q, J = 7.2 Hz, 2H, $O\underline{CH_2}CH_3$), 6.88 ppm (s, 2H, NH_2); ^{13}C NMR ($CDCl_3$): δ 14.2, 24.6, 26.0, 28.1, 48.3, 60.5, 73.3, 98.9, 117.7, 158.9, 160.3, 164.4, 168.2 ppm; ms: m/z 288 (M^+, 100), 259 (46), 245 (33), 231 (26), 205(64), 187 (37), 173 (52), 158 (35), 84 (75); *Anal*. Calcd. for $C_{15}H_{20}N_4O_2$: C, 62.48; H, 6.99; N, 19.43. Found: C, 62.18; H, 7.26; N, 19.21.

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