New Pyrazolyl-Nicotinic Acids, Methyl Esters, and 1,3,4-Oxadiazolyl-pyrazolyl-pyridine Tricyclic Scaffold Derivatives from 6-Hydrazinylnicotinic Acid Hydrazide Hydrate

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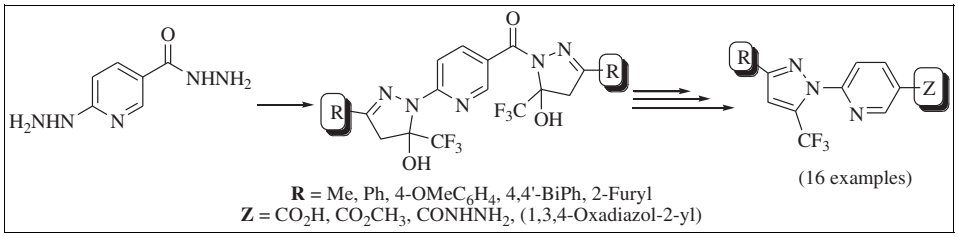

This paper describes an efficient approach for the synthesis of a new series of 6-[3-alkyl(aryl/heteroaryl)-5-trifluoromethyl-1*H*-pyrazol-1-yl]nicotinic acids (where alkyl = CH_3; aryl = Ph, 4-OCH_3Ph, 4,4′-BiPh; and heteroaryl = 2-Furyl) from the hydrolysis reaction of alkyl(aryl/heteroaryl)substituted 2-(5-trifluoromethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazol-1-yl)-5-(5-trifluoromethyl-5-hydroxy-4,5-dihydro-1*H*-1-carbonylpyrazol-1-yl)pyridines, under basic conditions and at 70–95% yields. In a subsequent step, the esterification reaction of pyrazolyl-nicotinic acids done in thionyl chloride and methanol led to the isolation of a series of methyl 6-[alkyl(aryl/heteroaryl)-5-trifluoromethyl-1*H*-pyrazol-1-yl] nicotinates as stable hydrochloride salts at 64–84% yields, which could be easily converted to hydrazides to give new oxadiazolyl-pyrazolyl-pyridine tricyclic scaffolds at good yields from a [4 + 1] cyclocondensation reaction with 1,1,1-triethoxyethane and 1-(triethoxymethyl)benzene as the reagent/solvent.

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INTRODUCTION

Nicotinic acid (niacin, pyridine-3-carboxilic acid, and vitamin B3) is most commonly associated with its nutritional role as a vitamin, and its absence leads to pellagra. In addition, it is the precursor to the various forms of the nicotinamide adenine dinucleotide coenzyme [1,2] and is one of the oldest drugs used to treat dyslipidemia. Long term studies have demonstrated that nicotinic acid therapy reduces mortality from coronary heart disease [3,4]. Nicotinic acid is also the foundation for a plethora of commercial compounds, from antibacterial and anticancer drugs in the pharmaceutical industry, to charge control agents in photocopier toner [5].

Pyrazoles [6a] are important compounds that have many derivatives with anti-hyperglycemic, analgesic, anti-inflammatory, anti-pyretic, antibacterial, hypoglycemic and sedative-hypnotic properties [6b–e]. The synthesis of pyrazole derivatives has been extensively explored by our research group through the cyclocondensation reaction of 4-alkoxy-1,1,1-trihalo-3-alken-2-ones and different hydrazines, and thus contemplating their biological activities as analgesic and anti-inflammatory [7], antimycobacterial [8], antimicrobial [9], antinociceptive [10], and antioxidant agents [11].

Among five-membered aromatic heterocycles, 1,3,4-oxadiazoles are another important class of aromatic heterocycles displaying a broad spectrum of biological activities (Fig. 1), such as 5-HT-receptor antagonists [12], benzodiazepine[13] and muscarinic receptor agonists [14], and tyrosinase inhibitors [15]. Many substituted 1,3,4-oxadiazoles have also shown antibacterial [16–18], antimicobacterial [19], antifungal [20,21], anti-inflammatory [22,23], analgesic [24], anticonvulsivant [25,26], antihypoglycemic [27], and insecticidal properties [28]. Compounds containing oxadiazole moieties have been described as possessing anticancer [29] or muscle relaxant activity [30] and have been used as fluorescent whiteners [31]. To the best of our knowledge, the synthesis of non-symmetrical 2,5-disubstituted 1,3,4-oxadiazoles has mainly been done by dehydration of diacylhydrazines or oxidative cyclization of aldehyde *N*-acylhydrazones, but many other reagents and reaction conditions have been reported to achieve their obtainment [32].

On the other hand, halogenated heterocyclic have an important role, not only as synthetic and chemical intermediates but also as pharmacological agents [33], especially when this halogen is the fluorine atom [34a]. The replacement of hydrogen atoms with fluorine substituents in organic substrates is of great interest in synthetic chemistry because of the strong electronegativity of fluorine and small steric footprint of fluorine atoms [34b]. More specifically,

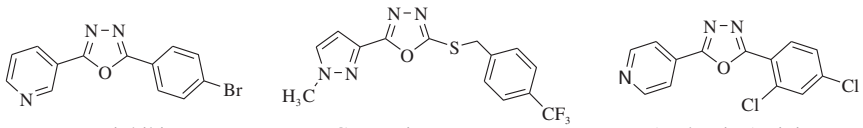


Figure 1. Heterocycles containing pyrazole, 1,3,4-oxadiazole, and pyridine moieties.

the influence of the trifluoromethyl substituent on physiological activity is due mainly to the increased lipophilicity of the molecules, causing greater cell permeability [35].

Although there have been many reports on the synthesis and pharmacological attributes of nicotinic acid [4,36–42], a review of the literature revealed that only one patent reported the synthesis of nicotinic acid derivatives that present structural similarities to 6-pyrazolyl-nicotinic acids, that is, a pyrazolyl ring attached to the 6-position of the pyridine ring. However, it is important to mention that trifluoromethyl-substituted pyrazoles or pyridines were not included in this Japanese patent [43].

According to the literature data reviewed previously, it seems important to us to expand the reaction scope of the compounds of **3** in order to develop easier and more efficient methods for obtaining molecules with further biological and commercial interest, for example, new pyrazolyl-substituted nicotinic acid derivatives, esters, and triheterocyclic systems such as 1,3,4-oxadiazolyl-pyrazolyl-pyridines.

Herein, we would like to report a simple method for the synthesis of a new series of 6-[3-alkyl(aryl/heteroaryl)-5-trifluoromethyl-1*H*-pyrazol-1-yl]nicotinic acids (**8**) [44] derived from the hydrolysis reaction of 2-(5-trifluoromethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazol-1-yl)-5-(5-trifluorometh yl-5-hydroxy-4,5-dihydro-1*H*-pyrazol-1-yl-1-carbonyl) pyridines (**3**) (Scheme 1) [45]. Subsequently, the esterification reaction of pyrazolyl-nicotinic acids (**8**), which allows the isolation of a series of methyl 6-[alkyl(aryl/heteroaryl)-5-tri fluoromethyl-1*H*-pyrazol-1-yl]nicotinate hydrochloride derivatives (**9**), is also presented (Scheme 2). Finally, we demonstrate that the compounds of **9** can easily be converted to hydrazides (**10**) by treatment with hydrazine hydrate to give (at good yields) a new oxadiazole-pyrazole-pyridine tricyclic scaffold (**11**) from the [4 + 1] cyclocondensation reaction of the respective hydrazides with 1,1,1-triethoxyethane (**4a**) and 1-(triethoxymethyl)benzene (**4b**) as the solvent/reagent.

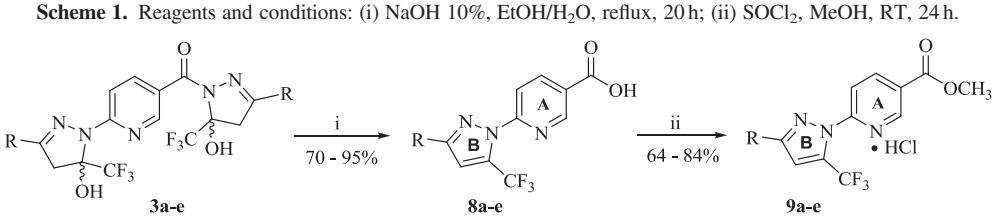
RESULTS AND DISCUSSION

In 2009, we described that the cyclocondensation reactions of 4-alkoxy-4-alkyl(aryl/heteroaryl)-1,1,1-trifluoroalk-3-en-2-ones (**2**) with 6-hydrazinylnicotinic acid hydrazide hydrate (**1**) regioselectively furnished a new trifluoromethylated system, namely 2-(1*H*-pyrazolyl)-5-(1*H*-1-carbonylpyrazol-1-yl)pyridines (**3**), at good yields (Fig. 2) [46a]. However, these reaction conditions do not lead to a chemoselective cyclization at the most reactive center (hydrazine moiety). Recently, in an attempt to demonstrate the reactivity differentiation between the two dinucleophilic centers in hydrazide hydrate **1**, we performed a reaction involving **1** and 1,1,1-tri ethoxyethane (**4**), which was also used as the reaction solvent. The hydrazine and the hydrazide moieties showed similar reactivity and only conducted to the not yet known structure of 3-methyl-6-(5-methyl-1,3,4-oxadiazol-2-yl)-[1,2,4]triazolo [4,3-a]pyridine (**5**) at 82% yield by a double [4 + 1] cyclocondensation reaction [46b]. On the basis of the literature data, we also performed several tests to differentiate the two nucleophilic centers of **1**. The most satisfactory results were obtained from the reaction of **1** with aryl aldehydes (**6**), which allowed to isolate a new series of 6-(methyli denehydrazinyl)nicotinohydrazides (**7**) [46b].

Conversely, it is widely known that acidic conditions can promote the hydrolysis of the *C*(*O*)-*N* function with the respective elimination of the carbamoyl group in some pyrazoles [46c–e].

The Japanese patent, published in 2005 by Kajino et al. [43], reported that 6-(1*H*-pyrazol-1-yl)nicotinic acid can be synthesized by a basic hydrolysis reaction of the ester methyl 6-(1*H*-pyrazol-1-yl)nicotinate using 1 M aqueous sodium hydroxide solution in methanol as the solvent at 60°C for 2.5 h. Previously, the respective ester was obtained at 64% yield when sodium hydride was added to a suspension of 1*H*-pyrazole in DMF, and after 5 h, methyl 6-chloronicotinate

Scheme 1. Reagents and conditions: (i) NaOH 10%, EtOH/H_2O, reflux, 20 h; (ii) $SOCl_2$, MeOH, RT, 24 h.



Scheme 2. Reagents and conditions: (i) $NH_2NH_2.H_2O$, EtOH, reflux, 20 h; (ii) $R^1C(OEt)_3$, 110°C, 16 h.

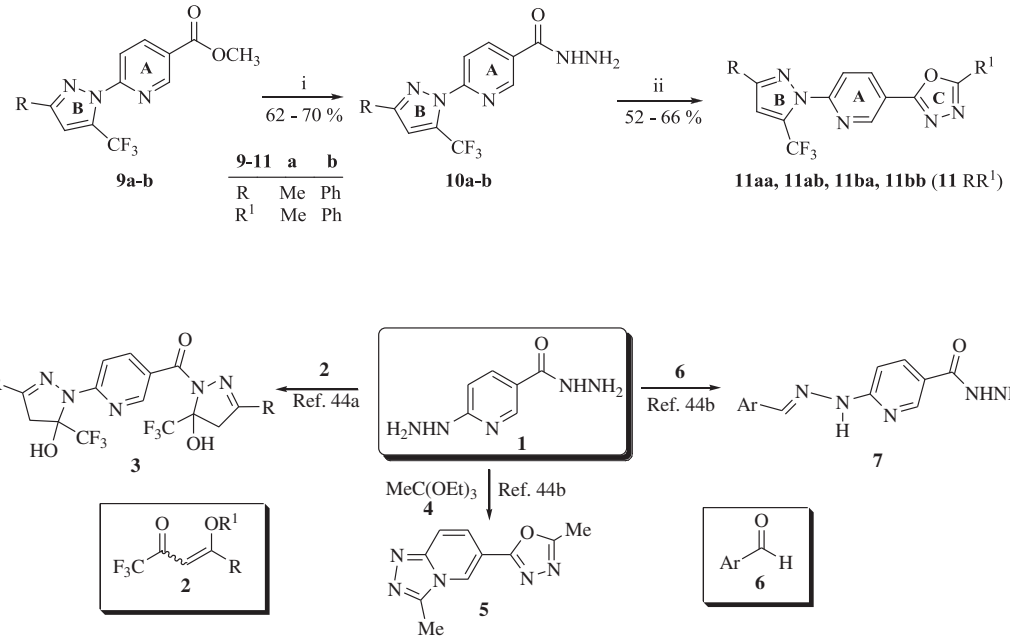


Figure 2. Synthetic derivatives of 6-hydrazinonicotinic acid hydrazide (**1**).

was also added to the mixture. After stirring for an additional 27 h, 6-(1*H*-pyrazolyl)nicotinic acid was isolated.

In 1998, we reported the regioselective synthesis of 5-triflu oromethyl-4,5-dihydro-1*H*-pyrazoles by the cyclocondensation of ketones **2** with thiosemicarbazide, at excellent yields [47]. However, in an attempt to perform the dehydration of these 2-pyrazolines under acidic conditions, a degradation occurred (hydrolysis), and only 3(4)-alkyl- and 3-arylsubstituted 5-trifluoromethyl-1*H*-pyrazoles were furnished, without the presence of the thiocarbamoyl group attached to the N-1 atom of the pyrazole ring. Seven years later, we also reported the synthesis of 1-(isonicotinoyl)-3-phenyl-5-hydroxy-5-trifluor omethyl-4,5-dihydro-1*H*-pyrazole [45]. In agreement with the literature [48], this 2-pyrazoline was extremely resistant to dehydration reactions with chloroform/P_2O_5 under reflux for 48 h or with acetic acid under reflux for 4 h.

In 2008, we reported that not only the *C*(*O*)-*N* bond of 1-cy anoacetyl-4,5-dihydropyrazoles [49] but also that of 2-acety laminopyrimidines [50] can be cleaved under acidic and basic reaction conditions.

Because it is known that numerous nicotinic acid derivatives exhibit interesting properties and applications [4,36–42], we then attempted to obtain new pyrazolyl-nicotinic acids **8a–e** by hydrolyzing the *C*(*O*)-*N* linkage at position 5 of the pyridines **3a–e**. The best reaction conditions, in addition to selected physical and spectral data, are presented in the experimental part. As mentioned previously, the heterocyclic precursors **3a–e** were synthesized by the cyclocondensation reactions of 4-alkoxy-4-alkyl (aryl/heteroaryl)-1,1,1-trifluoroalk-3-en-2-ones (**2a–e**) with 6-hydrazinylnicotinic acid hydrazide hydrate **1** in ethanol as the solvent at 78°C for 4 h (78–97%), as described in the literature [46]. Thus, we attempted to perform the hydrolysis of the amide bond of some compounds of **3** using a procedure similar to that described by Bavetsias et al. [51], employing $Fe(NO_3)_3.9H_2O$ in methanol for 24 h at 40–50°C. However, this procedure, as well as more drastic acidic conditions described elsewhere, which employ concentrated HCl in ethanol and heat the mixture under reflux for 20 h [52], were unsuccessful. Subsequently, the *C*(*O*)-*N* bond hydrolysis was performed successfully under alkaline conditions, that is, 2.5 M NaOH aqueous solution in ethanol (7:3 v/v) at 100°C for 20 h [50], which furnished the nicotinic acid derivatives **8a–e** at a high degree of purity and at 70–95% yields. All compounds of **8** precipitated in the reaction course during the neutralization process using 37% HCl aqueous solution and were isolated by a simple filtration. It is important to mention that the alkaline condition allowed us to not only perform the expected hydrolysis reaction at position 5 but also the unexpected dehydration reaction at the 2-pyrazoline attached to position 2 of the pyridine ring, in a one-step procedure (Scheme 1).

After that, compounds **8a–e** underwent further esterification reactions using thionyl chloride in methanol as the solvent/reagent. The reactions were monitored by TLC; the optimal temperature and reaction time were RT for 24 h, according to methods described elsewhere [37,53]. Methyl

esters **9a** and **9c–e** began to precipitate after 1–2 h of the reaction course and were also isolated by a simple filtration at 64–84% yields and at a high purity grade, except for **9b**, which had to be purified by recrystallization from acetone (Scheme 1). In attempting to introduce another class of nitrogenated azoles into the pyrazolyl-pyridine system, two examples of the compounds of **9** were elected to react firstly with hydrazine hydrate under reflux of ethanol to give the hydrazides of **10a–b**. These hydrazides were submitted to a cyclocondensation reaction with $R^1C(OEt)_3$ (**4**), where R^1 = methyl (**4a**) and phenyl (**4b**), leading to the isolation of four examples of oxadiazolyl-pyrazolyl-pyridines (**11**), at moderate yields (Scheme 2).

As the reaction property, the orthoesters were used simultaneously as solvent and reagent and compounds of **11** precipitated steadily during the reaction time at 110°C. The new oxadiazoles **11** are purified to a high degree by reaction cooling, filtration under reduced pressure, washing with cold ethanol, and storage in a desiccator over P_2O_5. The structures of 6-[3-alkyl(aryl/heteroaryl)-5-trifluoromethyl-1*H*-pyrazol-1-yl]nicotinic acids (**8a–e**) were deduced from NMR experiments and by comparison with NMR data from other pyrazoles formerly synthesized in our laboratory [46]. Initially, the compounds of **3** showed ^{1}H-NMR chemical shifts for the diastereotopic methylene protons (H-4a, H-4b) characteristic of a pyrazoline system as doublets, at δ 3.73 and 3.35 ppm, with a geminal coupling constant in the range of ^2J 18 Hz [46]. After the dehydration reaction, the compounds of **8** showed ^{1}H-NMR chemical shifts in acetone-d_6 or DMSO-d_6 for the pyrazole H-4 as a characteristic singlet, in the range of δ 6.96–7.92 ppm. The pyridine protons appear in the range of δ 8.97–9.03 ppm ($H\text{-}2_A$), 8.50–8.55 ppm ($H\text{-}4_A$), and 8.05–8.17 ppm ($H\text{-}5_A$), with J = 9 Hz. Compounds **8a–e** also present the typical ^{13}C-NMR chemical shifts of the pyrazole ring in the range of δ 148.8–152.8 ppm($C\text{-}3_B$) and δ 109.3–114.5 ppm ($C\text{-}4_B$). Because of the presence of the CF_3 group, the $C\text{-}5_B$ presents a characteristic quartet in the range of δ 132.4–134.4 ppm with $^2J_{CF}$ = 40 Hz. Also, the CF_3 group shows a typical quartet in the range of δ 119.3–121.9 ppm with $^1J_{CF}$ = 268 Hz, and the carbonyl carbon of the acid moiety shows an NMR signal in the range of δ 164.9–166.7 ppm. The pyridine ring carbons appear in the range of δ 111.7–116.5 ppm ($C\text{-}5_A$), 125.6–126.9 ppm ($C\text{-}3_A$), 140.1–141.9 ppm ($C\text{-}4_A$), 145.5–151.9 ppm ($C\text{-}2_A$), and 152.5–160.1 ppm ($C\text{-}6_A$).

Methyl esters **9a–e** show similar NMR chemical shifts in comparison with compounds **8a–e**, and present signals for the methoxy group, a feature of the ester, in the region of δ 3.92–3.98 ppm (^{1}H-NMR) and δ 52 ppm (^{13}C-NMR).

Complementarily, we performed X-ray diffraction measurements for a monocrystal of compound **9b** (Fig. 3). The crystallographic data showed that because of the possible steric effect from the phenyl and pyridine rings, the trifluoromethyl group occupies a position on the same side as the pyridine nitrogen. Crystallographic data reported in this paper for compound **9b** have been given to the Cambridge Crystallographic Data Center (CCDC 753328) [54].

Relative to the pyrazolyl-pyridine system, the ^{1}H and ^{13}C-NMR spectra registered in DMSO-d_6 for compounds **9**, **10**, and **11**, show signals with small variations in comparison to the compounds of **2**. Substantial variations in the chemical shifts are observed for position 5 of the pyridine due to the insertion of different substituents, namely, –COOMe (**9**), $–CONHNH_2$ (**10**), and an oxadiazole ring (**11**).

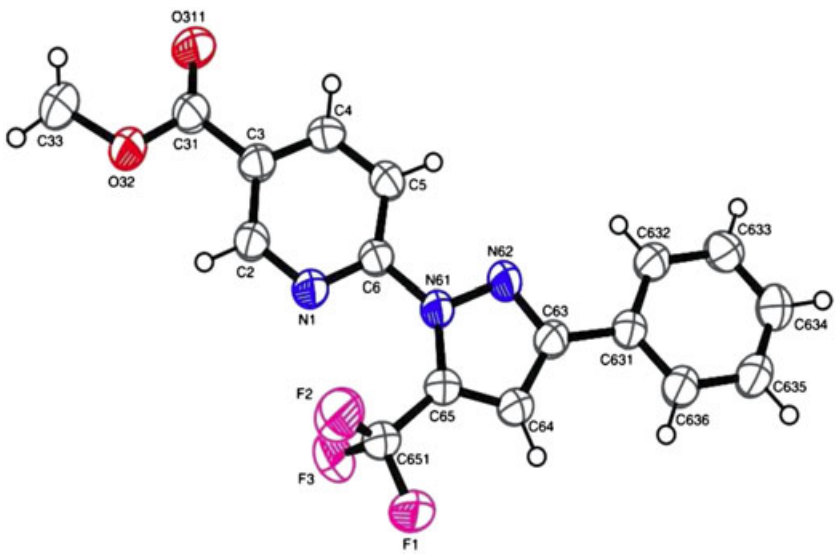


Figure 3. A perspective view of methyl 6-(3-phenyl-5-trifluoromethyl-1*H*-pyrazol-1-yl) nicotinate (**9b**) with atoms labeled (CCDC 753328). Displacement ellipsoids are drawn at the 50% probability level. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

The 6-(5-trifluoromethyl-1*H*-pyrazol-1-yl)nicotinohydrazides (**10**) presents important features observed in the ^{1}H-NMR spectra: broad singlets at an average of δ 10 ppm (NH) and δ 4.6 ppm (NH_2). In comparison to the esters of **9**, the ^{13}C-NMR spectra of **10** show a characteristic signal at an average of δ 163 ppm relative to the C=O. Oxadiazolyl-pyrazolyl-pyridines **11aa** and **11ba** (R^1=Me) exhibit the typical singlet for the methyl group in the region of δ 2.6–2.1 ppm (^{1}H-NMR) in relation to the oxadiazole substituent. In addition, signals of NH and NH_2 are absent near δ 10 and δ 4.6 ppm, respectively, a characteristic of **10**. Compounds **11ab** and **11bb** (R=R^1=Ph) show the typical signal range for phenyl protons at δ ~8.1 ppm as a doublet with J = 7 Hz and a multiplet in the range of δ 7.6–7.4 ppm. ^{13}C-NMR spectra also showed important features, for example, the absence of the signal of the C=O, which appeared in the range of δ 163 ppm for the hydrazides **10**. Triheterocycles **11** present two signals appearing in the region relative to the oxadiazole carbons C-2_C and C-5_C in the range of 164 and 162 ppm, respectively.

Furthermore, it should be noted that these compounds were not isolated as crystalline solids but rather in powder form, which prevented further study by X-ray diffraction.

CONCLUSIONS

In summary, we have developed a simple new convenient and one-pot procedure to obtain novel trifluoromethyl-substituted pyrazolyl-nicotinic acids (**8**). Methyl pyrazoly lnicotinate hydrochloride derivatives (**9**) were subsequently prepared with ease at good yields and high purity. To demonstrate the applicability of the esters of **9**, new hydrazides (**10**) and their oxadiazolyl-pyrazolyl-pyridines (**11**) were produced as a new triheterocyclic scaffold at moderate yields. The structures of the acids of **8** were checked by the synthesis of the esters of **9**. The structure of the esters of **9** was determined by NMR and X-ray diffraction, and the triheterocycles of **11** by NMR.

EXPERIMENTAL

Unless otherwise indicated, all common reagents and solvents were used as obtained from commercial suppliers without further purification. The melting points were determined using coverslips on a Microquímica MQAPF – 302 apparatus and are uncorrected. ^{1}H and ^{13}C-NMR spectra were acquired on a Bruker DPX 200 (^{1}H at 200.13 MHz) and Bruker DPX 400 (^{1}H at 400.13 MHz and ^{13}C at 100.61 MHz) spectrometer (Bruker Co., Germany), 5 mm sample tubes, 298 K, digital resolution ±0.01 ppm, in $CDCl_3$, DMSO-d_6 or acetone- d_6, and using TMS as an internal reference. Mass spectra were registered in an HP 5973 MSD connected to a HP 6890 GC and interfaced by a Pentium PC. The GC was equipped with a split-splitless injector, auto sampler, cross-linked HP-5 capillary column (30 m, 0.32 mm internal diameter), and helium was used as the carrier gas. Mass spectra were registered in an Agilent 6460 Triple Quad LC/MS (Agilent Technologies, Inc., Wilmington, DE) connected to a 1200 series LC and equipped with a solvent degasser, binary pump, column oven, and autosampler. The CHN elemental analyses were performed on a Perkin-Elmer 2400 CHN elemental analyzer (University of São Paulo, Brazil), the high resolution mass spectrometry was performed in an Agilent-QTOF 6530 spectrometer (UFSM, Brazil) and Micro TOF Bruker Daltonic (University of São Paulo, Brazil). The diffraction measurements were done by graphite-monochromatized Mo Kα radiation with λ = 0.71073 Å on a Bruker SMART CCD diffractometer [55]. The structure of **3b** was solved with direct methods using the SHELXS-97 program [56], and refined on F^2 by full-matrix least-squares using the SHELXL-97 package [57]. The absorption correction was performed by Gaussian methods [58]. Anisotropic displacement parameters for non-hydrogen atoms were applied. The hydrogen atoms were placed at calculated positions with 0.96 Å (methyl CH_3) and 0.93 Å (aromatic CH) using a riding model. The hydrogen isotropic thermal parameters were kept equal to Uiso(H) = χUeq (carrier C atom), with χ = 1.5 for methyl groups and χ = 1.2 for others. The valence angles C–C–H and H–C–H of methyl groups were set to 109.5º, and the H atoms were allowed to rotate around the C–C bond. The molecular graph was prepared using ORTEP-3 for Windows [59].

General procedure for the synthesis of 6-[3-alkyl(aryl/heteroaryl)-5-trifluoromethyl-1*H*-pyrazol-1-yl]nicotinic acids (8a–e). To a stirred solution of pyrazolyl-pyridines **3a–e** (2 mmol) in a mixture of ethanol: water (7:3 v/v) (10 mL) kept at RT (20–25°C), was added in one portion 2.5 M aqueous NaOH solution (5 mL). The mixture was then refluxed for 20 h. After cooling (<5°C), the reaction was neutralized with 37% HCl. The solids **8a–e** were collected by filtration, washed with ice-water (20 mL), and dried under reduced pressure in a P_2O_5-containing desiccator.

6-(5-Trifluoromethyl-3-methyl-1H-pyrazol-1-yl)nicotinic acid (8a). White solid, yield: 70%; mp 192–194°C. ^{1}H-NMR (acetone-d_6): δ 9.03 (s, 1H, 2_A); 8.52–8.54 (m, 1H, 4_A); 8.05 (d, 1H, 5_A, J = 9 Hz); 6.96 (s, 1H, 4_B); 2.37 (s, 3H, CH_3).

^{13}C-NMR (acetone-d_6): δ 166.7 (CO); 155.4 (C-6_A); 152.6 (C-3_B); 151.2 (C-2_A); 141.9 (C-4_A); 134.4 (q, $^2J_{C-F}$ = 40 Hz, C-5_B); 126.9 (C-3_A); 121.9 (q, $^1J_{C-F}$ = 267 Hz, CF_3); 116.5 (C-5_A); 114.5 (C-4_B); 14.4 (CH_3). MS (ESI) m/z: [(M + H)$^+$, 272.1]. Anal. Calcd for $C_{11}H_8F_3N_3O_2$ (271.19): C, 48.72; H, 2.97; N, 15.49%. Found: C, 48.33; H, 2.59; N, 15.24%.

6-(5-Trifluoromethyl-3-phenyl-1H-pyrazol-1-yl)nicotinic acid (8b). White solid; yield 95%; mp 215–217°C. ^{1}H-NMR (DMSO-d_6): δ 8.98 (s, 1H, 2_A); 8.51–8.53 (m, 1H, 4_A); 8.13 (d, 1H, 5_A, J = 9 Hz); 8.01–8.03 (m, 2H, Ph); 7.8 (s, 1H, 4_B); 7.45–7.53 (m, 3H, Ph). ^{13}C-NMR (DMSO-d_6): δ 165.0 (CO); 152.6 (C-6_A); 151.9 (C-3_B); 148.8 (C-2_A); 140.1 (C-4_A); 132.6 (q, $^2J_{C-F}$ = 40 Hz, C-5_B); 130.3 (Ph); 129.0 (Ph); 128.6 (Ph); 125.8 (Ph); 125.6 (C-3_A); 119.4 (q, $^1J_{C-F}$ = 268 Hz, CF_3); 115.3 (C-5_A); 110.0 (C-4_B). MS (ESI) m/z: [(M + H)$^+$, 334.1] Anal. Calcd for $C_{16}H_{10}F_3N_3O_2$ (333.26): C, 57.66; H, 3.02; N, 12.61%. Found: C, 57.43; H, 3.37; N, 12.22%.

6-[5-Trifluoromethyl-3-(4-methoxyphenyl)-1H-pyrazol-1-yl]nicotinic acid (8c). Yellow solid; yield 83%; mp 226–228°C. ^{1}H-NMR (DMSO-d_6): δ 8.97 (s, 1H, 2_A); 8.50–8.52 (m, 1H, 4_A); 8.12 (d, 1H, 5_A, J = 9 Hz); 7.96 (d, 2H, Ph, J = 9 Hz); 7.77 (s, 1H, 4_B); 7.06 (d, 2H, Ph, J = 9 Hz); 3.82 (s, 3H, OCH_3). ^{13}C-NMR (DMSO-d_6): δ 165.4 (CO); 160.1 (C-6_A); 152.8 (C-3_B); 151.9 (C-2_A); 149.0 (Ph); 140.3 (C-4_A); 132.5 (q, $^2J_{C-F}$ = 40 Hz, C-5_B); 127.3 (Ph); 125.6 (C-3_A);

123.0 (Ph); 119.7 (q, $^1J_{C-F}$ = 267 Hz, CF_3); 115.1 (C-5_A); 114.3 (Ph); 110.0 (C-4_B). MS (ESI) *m/z*: [(M + H)$^+$,364.1] Anal. Calcd for $C_{17}H_{12}F_3N_3O_3$ (363.29): C, 56.20; H, 3.33; N, 11.57%. Found: C, 55.87; H, 3.14; N, 11.28%.

6-[3-(4,4′-Biphenyl)-5-trifluoromethyl-1H-pyrazol-1-yl]nicotinic acid (8d). Yellow solid; yield 87%; mp 244–246°C. ^{1}H-NMR (DMSO-d_6): δ 8.99 (s,1H, 2_A); 8.52–8.55 (m, 1H, 4_A); 8.17 (d, 1H, 5_A, *J* = 9 Hz); 8.13 (d, 2H, BiPh, *J* = 8 Hz); 7.92 (s, 1H, 4_B); 7.82 (d, 2H, BiPh, *J* = 8 Hz); 7.75–7.76 (m, 2H, BiPh); 7.48–7.52 (m, 3H, BiPh). ^{13}C-NMR (DMSO-d_6): δ 164.9 (CO); 152.5 (C-6_A); 151.5 (C-3_B); 148.7 (C-2_A); 140.7 (C-4_A); 140.0 (BiPh); 139.19 (BiPh), 132.6 (q, $^2J_{C-F}$ = 40 Hz, C-5_B); 129.3 (BiPh); 128.6 (BiPh); 127.3 (BiPh); 126.7 (BiPh); 126.2 (BiPh); 125.8 (C-3_A); 119.3 (q, $^1J_{C-F}$ = 267 Hz, CF_3); 115.2 (C-5_A); 110.0 (C-4_B). MS (ESI) *m/z*: [(M + H)$^+$,410] Anal. Calcd for $C_{22}H_{14}F_3N_3O_2$ (409.36): C, 64.55; H, 3.45; N, 10.26%. Found: C, 64.41; H, 3.66; N, 9.88%.

6-[5-Trifluoromethyl-3-(fur-2-yl)-1H-pyrazol-1-yl]nicotinic acid (8e). Brown solid; yield 76%; mp 205–207°C. ^{1}H-NMR (DMSO-d_6): δ 8.97 (s, 1H, 2_A); 8.51–8.53 (m, 1H, 4_A); 8.07 (d, 1H, 5_A, *J* = 9 Hz); 7.86–7.87 (m, 1H, furyl); 7.64 (s, 1H, 4_B); 7.12–7.13 (m, 1H, furyl); 6.68–6.69 (m, 1H, furyl). ^{13}C-NMR (DMSO-d_6): δ 165.0 (CO); 152.5 (C-6_A); 148.8 (C-3_B); 145.5 (C-2_A); 144.3 (furyl); 143.9 (furyl); 140.3 (C-4_A); 132.4 (q, $^2J_{C-F}$ = 41 Hz, C-5_B); 126.0 (C-3_A); 119.3 (q, $^1J_{C-F}$ = 268 Hz, CF_3); 115.4 (furyl); 111.7 (C-5_A); 109.7 (furyl); 109.3 (C-4_B). MS (ESI) *m/z*: [(M + H)$^+$, 324] Anal. Calcd for $C_{14}H_8F_3N_3O_3$ (323.22): C, 52.02; H, 2.49; N, 13.00%. Found: C, 51.74; H, 3.66; N, 12.75%.

General procedure for the synthesis of methyl 6-[3-alkyl(aryl/heteroaryl)-5-trifluoromethyl-1*H*-pyrazol-1-yl]nicotinate hydrochlorides (9a–e). Pyrazolyl-nicotinic acids **8** (1 mmol) were added to a stirred solution of methanol (10 mL) and $SOCl_2$ (15 mmol). After stirring the reaction mixture at RT for 24 h, the solids **9a–e** were isolated by filtration, washed with cold methanol and in the case of **9b** purified by recrystallization from acetone.

Methyl 6-(5-trifluoromethyl-3-methyl-1H-pyrazol-1-yl)nicotinate hydrochloride (9a). White solid; yield 61%; mp 110–112°C. ^{1}H-NMR ($CDCl_3$): δ 9.08 (s, 1H, 2_A); 8.38–8.43 (m, 1H, 4_A); 7.93 (d, 1H, 5_A, *J* = 9 Hz); 6.71 (s, 1H, 4_B); 3.96 (s, 3H, OCH_3); 2.38 (s, 3H, CH_3). ^{13}C-NMR ($CDCl_3$): δ 165.3 (CO); 152.7 (C-6_A); 150.5 (C-3_B); 148.9 (C-2_A); 140.2 (C-4_A); 131.5 (q, $^2J_{C-F}$ = 40 Hz, C-5_B); 125.4 (C-3_A); 119.6 (q, $^1J_{C-F}$ = 267 Hz, CF_3); 114.9 (C-5_A); 112.9(C-4_B); 52.4 (OCH_3); 13.0 (CH_3). MS: *m/z* (%) = 285 (M$^+$, 100); 254 (90); 216 (23); 149 (14). Anal. Calcd for $C_{12}H_{11}ClF_3N_3O_2$ (321.68): C, 44.80; H, 3.45; N, 13.06%. Found: C, 45.19; H, 3.07; N, 13.44%.

Methyl 6-(5-trifluoromethyl-3-phenyl-1H-pyrazol-1-yl)nicotinate hydrochloride (9b). White solid; yield 74%; mp 179–181°C. ^{1}H-NMR ($CDCl_3$): δ 9.09 (s, 1H, 2_A); 8.41–8.44 (m, 1H, 4_A); 8.07 (d, 1H, 5_A, *J* = 9 Hz); 7.87–7.89 (m, 2H, Ph); 7.39–7.47 (m, 3H, Ph); 7.2 (s, 1H, 4_B); 3.96 (s, 3H, OCH_3). ^{13}C-NMR ($CDCl_3$): δ 165.0 (CO); 153.9 (C-6_A); 152.6 (C-3_B); 149.7 (C-2_A); 139.6 (C-4_A); 134.3 (q, $^2J_{C-F}$ = 42 Hz, C-5_B); 131.3 (Ph); 129.1 (Ph); 128.8 (Ph); 126.1 (Ph); 124.8 (C-3_A); 119.9 (q, $^1J_{C-F}$ = 267 Hz, CF_3); 114.9 (C-5_A); 109.7 (C-4_B); 52.3 (OCH_3). MS: *m/z* (%) = 347 (M$^+$, 100); 316 (23); 287 (5); 77 (5). Anal. Calcd for $C_{17}H_{13}ClF_3N_3O_2$ (383.75): C, 53.21; H, 3.41; N, 10.95%. Found: C, 53.18; H, 3.53; N, 10.59%.

Methyl 6-[5-trifluoromethyl-3-(4-methoxyphenyl)-1H-pyrazol-1-yl]nicotinate hydrochloride (9c). Yellow solid; yield 84%; mp 202–204°C. ^{1}H-NMR (DMSO-d_6): δ 8.97 (s, 1H, 2_A); 8.48–8.53 (m, 1H, 4_A); 8.11 (d, 1H, 5_A, *J* = 8 Hz); 7.96 (d, 2H, Ph, *J* = 9 Hz); 7.76 (s, 1H, 4_B); 7.06 (d, 2H, Ph, *J* = 8 Hz); 3.92 (s, 3H, OCH_3); 3.83 (s, 3H, $OCH_{3\text{-}B}$). ^{13}C-NMR (DMSO-d_6): δ 165.3 (CO); 160.1 (C-6_A); 152.7 (C-3_B); 151.9 (C-2_A); 148.9 (C-4_A); 140.3 (Ph); 132.4 (q, $^2J_{C-F}$ = 40 Hz, C-5_B); 127.3 (Ph); 125.6 (C-3_A); 122.9 (Ph); 119.6 (q, $^1J_{C-F}$ = 268 Hz, CF_3); 115.1 (C-5_A); 114.2 (Ph); 110.0 (C-4_B); 55.1 (OCH_3); 52.4 ($OCH_{3\text{-ester}}$). MS: *m/z* (%) = 377 (M$^+$, 100); 362 (14); 46 (5); 207 (33); 173 (11). Anal. Calcd for $C_{18}H_{15}Cl\,F_3N_3O_3$ (413.78): C, 52.25; H, 3.65; N, 10.16%. Found: C, 52.44; H, 3.24; N, 10.06%.

Methyl 6-[3-(4,4′-biphenyl)-5-trifluoromethyl-1H–pyrazol-1-yl]nicotinate hydrochloride (9d). Yellow solid; yield 57%; mp 242–244°C. ^{1}H-NMR ($CDCl_3$): δ 9.11 (s, 1H, 2_A); 8.45–8.47 (m, 1H, 4_A); 8.12 (d, 1H, 5_A, *J* = 9 Hz); 7.97 (d, 2H, BiPh, *J* = 8 Hz); 7.70 (d, 2H, BiPh, *J* = 8 Hz); 7.64–7.65 (m, 3H, BiPh + 4_B) 7.45–7.47 (m, 2H, BiPh); 7.37–7.39 (m, 1H, BiPh); 3.98 (s, 3H, OCH_3). ^{13}C-NMR (DMSO-d_6): 165.2 (CO); 152.7 (C-6_A); 151.7 (C-3_B); 148.9 (C-2_A); 140.9 (BiPh); 140.3 (C-4_A); 139.2 (BiPh); 132.8 (q, $^2J_{C-F}$ = 40 Hz, C-5_B); 129.5 (C-3_A); 129.5 (BiPh); 128.8 (BiPh); 127.6 (BiPh); 127.0 (BiPh); 126.5 (BiPh); 126.4 (BiPh); 126.0 (BiPh); 119.5 (q, $^1J_{C-F}$ = 268 Hz, CF_3); 115.5 (C-5_A); 110.4 (C-4_B); 52.4 (OCH_3). MS: *m/z* (%) = 423 (M$^+$, 100); 392 (5); 317 (9); 196 (31); 153 (11). Anal. Calcd for $C_{23}H_{17}Cl\,F_3N_3O_2$ (459.85): C, 60.07; H, 3.73; N, 9.14%. Found: C, 60.37; H, 3.43; N, 8.75%.

Methyl 6-[5-trifluoromethyl-3-(fur-2-yl)-1H-pyrazol-1-yl]nicotinate hydrochloride (9e). Brown solid; yield 72%; mp 151–152°C. ^{1}H-NMR ($CDCl_3$): δ 9.10 (s, 1H, 2_A); 8.42–8.47 (m, 1H, 4_A); 8.05 (d, 1H, 5_A, *J* = 9 Hz); 7.54 (m, 1H, furyl); 7.14 (s, 1H, 4_B); 6.85–6.87 (m, 1H, furyl); 6.52–6.54 (m, 1H, furyl); 6.52–6.54 (m, 1H, furyl); 3.97 (s, 3H, OCH_3). ^{13}C-NMR ($CDCl_3$): δ 165.0 (CO); 153.5 (C-6_A); 149.6 (C-3_B); 146.5 (C-2_A); 144.9 (furyl); 143.2 (furyl); 139.7 (C-4_A); 133.9 (q, $^2J_{C-F}$ = 40, C-5_B); 124.8 (C-3_A); 119.4 (q, $^1J_{C-F}$ = 268 Hz, CF_3); 115.0 (furyl); 111.6 (C-5_A); 109.5 (furyl); 108.3 (C-4_B); 52.4 (OCH_3). MS: *m/z* (%) = 337 (M$^+$, 100); 306 (19); 283 (17); 153 (31); 136 (11). Anal. Calcd for $C_{15}H_{11}ClF_3N_3O_3$ (373.71): C, 48.21; H, 2.97; N, 11.24%. Found: C, 48.21; H, 2.63; N, 11.13%.

General procedure for the synthesis of 6-[3-alkyl(aryl)-5-trifluoromethyl-1*H*-pyrazol-1-yl]nicotinohydrazides (10a–b). Methyl nicotinate hydrochlorides **9a–b** (1 mmol) were added to a stirred solution of ethanol (5 mL) and 24% aqueous solution of hydrazine hydrate (1 mL). After stirring the reaction mixture at reflux temperature for 20 h, the solids **10a–b** were isolated by filtration, washed with cold ethanol, and dried under reduced pressure in a P_2O_5-containing desiccator.

6-(5-Trifluoromethyl-3-methyl-1H-pyrazol-1-yl) nicotinohydrazide (10a). White solid; yield 70%; mp 154–156°C. ^{1}H-NMR (DMSO-d_6): δ 9.98 (s, 1H, NH); 8.87 (s, 1H, 2_A); 8.39 (dd, 1H, 4_A, *J* = 8 Hz); 7.92 (d, 1H, 5_A, *J* = 9 Hz); 7.04 (s, 1H, 4_B); 4.58 (s, 2H, NH_2); 2.34 (s, 3H, CH_3). ^{13}C-NMR (DMSO-d_6): δ 163.3 (CO); 151.7 (C-6_A); 150.2 (C-3_B); 146.5 (C-2_A); 138.1 (C-4_A); 131.5 (q, $^2J_{C-F}$ = 40 Hz, C-5_B); 127.9 (C-3_A); 119.7 (q, $^1J_{C-F}$ = 268 Hz, CF_3); 115.1 (C-5_A); 112.3 (q, $^3J_{C-F}$ = 3, C-4_B); 12.9 (CH_3). HRMS (ESI): *m/z* calcd for $C_{11}H_{10}F_3N_5O$: 286.0915(M + H), found: 286.0987.

6-(5-Trifluoromethyl-3-phenyl-1H-pyrazol-1-yl) nicotinohydrazide (10b). White solid; yield 62%; mp 218–219°C. ^{1}H-NMR (DMSO-d_6): δ 10.06 (s, 1H, NH); 8.93 (s, 1H, 2_A); 8.47 (dd, 1H, 4_A, *J* = 8 Hz); 8.11 (d, 1H, 5_A, *J* = 9 Hz); 8.02–8.04 (m, 2H, Ph); 7.82 (s, 1H, 4_B); 7.44–7.54 (m, 3H, Ph); 4.60 (s, 2H, NH_2). ^{13}C-NMR (DMSO-d_6): δ 163.1 (CO); 151.8 (C-6_A); 151.73 (C-3_B); 146.5 (C-2_A); 138.2 (C-4_A); 132.5 (q, $^2J_{C-F}$ = 40 Hz, C-5_B); 130.5 (Ph); 129.1 (Ph); 128.8 (Ph); 128.3 (C-3_A); 125.7 (Ph); 119.6 (q, $^1J_{C-F}$ = 267 Hz, CF_3); 115.5 (C-5_A); 109.8 (q, $^3J_{C-F}$ = 3, C-4_B). HRMS (ESI): *m/z* calcd for $C_{16}H_{12}F_3N_5O$: 348.1072 (M + H), found: 348.1064.

General procedure for the synthesis of 5-[5-Methyl(phenyl)-1,3,4-oxadiazol-2-yl]-2-(3-alquil(aril)-5-trifluoromethyl-1*H*-pyrazol-1-yl) pyridine (11aa, **11ab**, **11ba**, **11bb**). A mixture of pyrazolylnicotino hydrazides **10** (1 mmol) and 1,1,1-triethoxyethane (**4a**) or 1-(triethoxymethyl)benzene (**4b**) (6 mmol) was stirred for 16 h at 110°C. After the reaction time, the solids were isolated by filtration, washed with cold ethanol, and drying in desiccators under reduced pressure over P_2O_5, furnished **11** in high degree of purity (HRMS).

5-(5-Methyl-1,3,4-oxadiazol-2-yl)-2-(3-methyl-5-trifluoromethyl-1H-pyrazol-1-yl) pyridine (11aa). Yellow solid; yield 52%; mp 147–149°C. ^{1}H-NMR (DMSO-d_6): δ 9.00 (d, 1H, 6_A, J = 2 Hz); 8.53 (dd, 1H, 4_A, J = 8 Hz); 8.05 (d, 1H, 3_A, J = 8 Hz); 7.08 (s, 1H, 4_B); 2.62 (s, 3H, $CH_{3\text{-}C}$); 2.36 (s, 3H, $CH_{3\text{-}B}$). ^{13}C-NMR (DMSO-d_6): δ 164.3 (C-2_C); 161.4 (C-5_C); 151.8 (C-2_A); 150.5 (C-3_B); 145.4 (C-6_A); 137.1 (C-4_A); 131.5 (q, $^2J_{C-F}$ = 40 Hz, C-5_B); 118.92 (C-5_A); 119.6 (q, $^1J_{C-F}$ = 268 Hz, CF_3); 115.7 (C-3_A); 112.7 (q, $^3J_{C-F}$ = 3 Hz, C-4_B); 12.9 ($CH_{3\text{-}B}$); 10.4 ($CH_{3\text{-}C}$). ^{19}F-NMR (C_6H_5F): −55.96 (CF_3). MS: *m/z* (%) (EI) = 309 (M^+, 100); 254 (44); 184 (11); 149 (7). HRMS (ESI): *m/z* calcd for $C_{13}H_{10}F_3N_5O$ 310.0915 (M + H), found 310.0908.

5-(5-Phenyl-1,3,4-oxadiazol-2-yl)-2-(3-methyl-5-trifluoromethyl-1H-pyrazol-1-yl) pyridine (11ab). White solid; yield 56%; mp 166–168°C. ^{1}H-NMR (DMSO-d_6): δ 9.15 (s, 1H, 6_A); 8.65 (dd, 1H, 4_A, J = 8 Hz); 8.14 (d, 2H, Ph, J = 7 Hz); 8.05 (d, 1H, 3_A, J = 8 Hz); 7.65–7.60 (m, 3H, Ph); 7.04 (s, 1H, 4_B); 2.34 (s, 3H, CH_3). ^{13}C-NMR (DMSO-d_6): δ 164.4 (C-2_C); 161.79 (C-5_C); 152.0 (C-2_A); 150.6 (C-3_B); 145.9 (C-6_A); 137.4 (C-4_A); 131.2 (q, $^2J_{C-F}$ = 40 Hz, C-5_B); 132.1(Ph); 129.0 (Ph); 128.7 (Ph); 126.7 (Ph); 128.4 (C-5_A); 119.6 (q, $^1J_{C-F}$ = 268 Hz, CF_3); 115.7 (C-3_A); 112.8 (q, $^3J_{C-F}$ = 3, C-4_B); 12.9 (CH_3). ^{13}C-NMR ($CDCl_3$): δ 165.1 (C-2_C); 162.1 (C-5_C); 152.9 (C-2_A); 150.6 (C-3_B); 146.2 (C-6_A); 136.6 (C-4_A); 133.2 (q, $^2J_{C-F}$ = 40 Hz, C-5_B); 132.0 (Ph); 129.4 (Ph); 129.1(Ph); 127.0 (Ph); 128.2 (C-5_A); 119.8 (q, $^1J_{C-F}$ = 268 Hz, CF_3); 115.4 (C-3_A); 112.5 (q, $^3J_{C-F}$ = 3 Hz, C-4_B); 13.4 (CH_3). MS: *m/z* (%) (EI) = 371 (M^+, 100); 254 (31); 105 (28); 77 (14). HRMS (ESI): *m/z* calcd for $C_{18}H_{12}F_3N_5O$ 372.1072 (M + H), found 372.1087.

5-(5-Methyl-1,3,4-oxadiazol-2-yl)-2-(5-trifluoromethyl-3-phenyl-1H-pyrazol-1-yl)pyridine (11ba). Yellow solid; yield 60%; mp 208–210°C. ^{1}H-NMR (DMSO-d_6): δ 8.94 (s, 1H, 6_A); 8.45 (dd, 1H, 4_A, J = 8 Hz); 8.10 (d, 1H, 3_A, J = 8 Hz); 8.02 (d, 2H, Ph, J = 7 Hz); 7.78 (s, 1H, 4_B); 7.53–7.45 (m, 3H, Ph); 2.1 (s, 3H, $CH_{3\text{-}C}$). ^{13}C-NMR (DMSO-d_6): δ 164.3 (C-2_C); 163.16 (C-5_C); 151.8 (C-2_A); 151.7 (C-3_B); 146.5 (C-6_A); 138.2 (C-4_A); 132.5 (q, $^2J_{C-F}$ = 40 Hz, C-5_B); 130.5 (Ph); 129.0 (Ph); 128.7 (Ph); 128.3 (C-5_A); 125.7 (Ph); 119.6 (q, $^1J_{C-F}$ = 268 Hz, CF_3); 115.6 (C-3_A); 109.8 (q, $^3J_{C-F}$ = 3 Hz, C-4_B); 10.3 (CH_3). MS: *m/z* (%) (EI) = 371 (M^+, 100); 316 (27); 207 (34); 103 (9); 77 (9). HRMS (ESI): *m/z* calcd for $C_{18}H_{12}F_3N_5O$ 372.1072 (M + H), found 372.1085.

5-(5-Phenyl-1,3,4-oxadiazol-2-yl)-2-(3-phenyl-5-trifluoromethyl-1H-pyrazol-1-yl) pyridine (11bb). Yellow solid; yield 66%; mp 204–206°C. ^{1}H-NMR (DMSO-d_6): δ 9.26 (s, 1H, 6_A); 8.76 (dd, 1H, 4_A, J = 8 Hz); 8.26 (d, 1H, 3_A, J = 8 Hz); 8.19 (d, 2H, Ph, J = 7 Hz); 8.04 (d, 2H, Ph, J = 7 Hz); 7.83 (s, 1H, 4_B); 7.67–7.65 (m, 3H, Ph); 7.54–7.46 (m, 3H, Ph). ^{1}H-NMR ($CDCl_3$): δ 9.21 (s, 1H, 6_A); 8.59 (dd, 1H, 4_A, J = 8 Hz); 8.20 (d, 1H, 3_A, J = 8 Hz); 8.16 (d, 2H, Ph, J = 7 Hz); 7.90 (d, 2H, Ph, J = 7 Hz); 7.59–7.54 (m, 3H, Ph); 7.49–7.42 (m, 3H, Ph); 7.24 (s, 1H, 4_B). ^{13}C-NMR ($CDCl_3$): δ 165.1 (C-2_C); 162.1 (C-5_C); 153.0 (C-2_A); 152.6 (C-3_B); 146.2 (C-6_A); 136.7 (C-4_A); 134.1 (q, $^2J_{C-F}$ = 40 Hz, C-5_B); 132.1(Ph); 131.1 (Ph); 129.3 (C-5_A); 129.2 (Ph); 128.9 (Ph); 127.1 (Ph); 126.0 (Ph); 123.5 (Ph); 119.1 (Ph); 120.5 (q, $^1J_{C-F}$ = 268 Hz, CF_3); 115.6 (C-3_A); 109.8 (q, $^3J_{C-F}$ = 3 Hz, C-4_B). MS: *m/z* (%) (EI) = 433 (M^+, 100); 376 (14); 316 (31); 105 (35); 77 (19). HRMS (ESI): *m/z* calcd for $C_{23}H_{14}F_3N_5O$ 434.1228 (M + H), found 434.1222.

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