Preparation of New 2-Amino- and 2,3-Diamino-pyridine Trifluoroacetyl Enamine Derivatives and Their Application to the Synthesis of Trifluoromethyl-containing 3*H*-Pyrido[2,3-*b*][1,4] diazepinols

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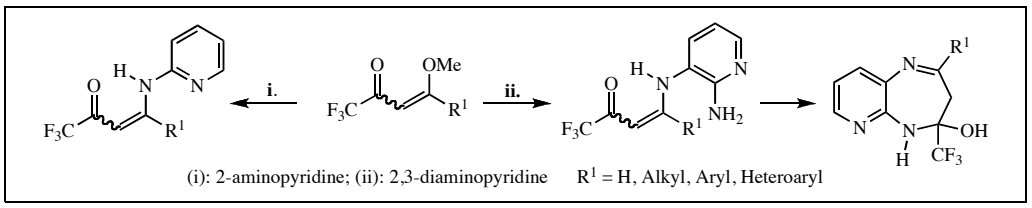

The synthesis of a novel series of the intermediates N^2(N^3)-[1-alkyl(aryl/heteroaryl)-3-oxo-4,4,4-trifluoroalk-1-en-1-yl]-2-aminopyridines [$F_3CC(O)CH=CR^1(2\text{-}NH\text{-}C_5H_3N)$] and 2,3-diaminopyridines [$F_3CC(O)CH=CR^1(2\text{-}NH_2\text{-}3\text{-}NH\text{-}C_5H_3N)$], where R^1 = H, Me, C_6H_5, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-$CH_3C_6H_4$, 4-$OCH_3C_6H_4$, 4,4'-biphenyl, 1-naphthyl, 2-thienyl, 2-furyl, is reported. The corresponding series of 2-aryl(heteroaryl)-4-trifluoromethyl-3*H*-pyrido[2,3-*b*][1,4]diazepin-4-ols obtained from intramolecular cyclization reaction of the respective trifluoroacetyl enamines or from the direct cyclocondensation reaction of 4-methoxy-1,1,1-trifluoroalk-3-en-2-ones with 2,3-diaminopyridine, under mild conditions, is also reported.

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INTRODUCTION

The presence of trifluoromethyl groups directly linked to acyclic and cyclic organic compounds confers special chemical, physical and biological properties to molecules, mostly due to the elevated electronegative and lipophilic character of fluorine atoms [1-11]. Thus, much attention has been given to the synthesis of trifluorinated compounds, many of which have been shown to be of notable pharmacologic value [12-13].

Although the reactions of 4-alkoxy-1,1,1-trifluoroalk-3-en-2-ones with primary and secondary amines have been well documented, there are few reports in the literature dealing with β-alkoxyvinyl trifluoromethyl ketones as electrophile precursors and 2-amino- or 2,3-diaminopyridine as nucleophiles [14-19].

Gerus *et al*. reported the reactions of 4-alkoxy-1,1,1-trifluorobut-3-en-2-ones with ammonia and primary amines to afford β-aminovinyl trifluoromethyl ketones [14]. Of particular importance, the synthesis of N^2-[3-oxo-4,4,4-trifluorobut-1-en-1-yl]-2-aminopyridine in a very satisfactory yield was reported in the same publication. The reaction of diamino compounds (ethylenediamine or *o*-phenylenediamine) with two equivalents of enones, giving the respective *N*,*N*-diaminovinyl trifluoromethyl ketones, was also described.

In 1991, protected amino acids were prepared by the reaction of β-ethoxyvinyl trifluoromethyl ketone with L-amino acids in aqueous sodium hydroxide solution [15].

Recently, we also reported an addition/elimination sequence leading to trifluoroacetyl- and trichloroacetyl-enamines from the reaction of *o*-phenylenediamine [16], *o*-aminophenol [17], 1-naphthylamine [18] and *S*,*S*-dimethylsulfoximide [19] with 4-alkyl(aryl)-1,1,1-trihalo-4-alkoxyalk-3-en-2-ones.

Considering the importance of developing new anticancer agents, in the last several years we have researched the possibility of using 4-alkoxy-1,1,1-trihaloalk-3-en-2-ones (**1**) for the synthesis of new structures with anti-cancer/chemotherapeutic potential. Thus, some acyclic trihaloacetyl enamines, derived from *o*-phenylenediamine and *o*-aminophenol, and submitted to *in vitro* anti-tumor screens have shown interesting results [17].

In 1989, Hojo *et al*. reported that 4-alkoxy-1,1,1-trifluoroalk-3-en-2-ones readily undergo *O*-*N* exchange reactions with various amines to give the corresponding *N*-[4,4,4-trifluoro-3-oxo-1-alkenyl]amines in high yields [20]. In 1992, the same author demonstrated that a series of *N*-[4,4,4-trifluoro-3-oxo-1-butenyl]amino acid esters, α-aminoacetophenones and aminacetonitriles were easily obtained in excellent yields by the *O*-*N* exchange reaction of 4-alkoxy-1,1,1-trifluoroalk-3-en-2-ones with some amino acid esters, α-amino-acetophenone and aminoacetonitrile [21].

Recently, we also reported attempts to obtain *N*-[1-alkyl(aryl)-3-oxo-4,4,4-trichloroalk-1-en-1-yl]-2-aminopyridine intermediates by the reaction of 4-alkoxy-1,1,1-trichloroalk-3-en-2-ones with 2-aminopyridine [22]. When these reactions were carried out in dichloromethane as solvent, under mild conditions, the respective trichloroacetyl enamines were isolated in very low yields (> 10%). Surprisingly, when the same reactions were carried out in a molar ratio of 1:1 respectively, in anhydrous ethanol as solvent under reflux for 5 hours, 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines were easily isolated in 45 – 81% yield, instead of *N*-[1-alkyl(aryl)-3-oxo-4,4,4-trichloroalk-1-en-1-yl]-2-aminopyridine intermediates.

A review of the literature showed that, except for the synthesis of N^2-[3-oxo-4,4,4-trifluorobut-1-en-1-yl]-2-aminopyridine (**2a**) [14], the preparation of trifluoroacetyl enamines (2-amino- and 2,3-diaminopyridine derivatives) (**2b, 2h-m** and **3b-k, 3o, 3q**) as precursors to obtain trifluoromethylated heterocycles has not been reported yet.

On the other hand, the reactions of 2,3-diaminopyridine with ethyl benzoylacetate and ethyl nicotinoylacetate were first reported in a communication in 1964 by Barchet and Merz [23]. However, no evidence was given to support the first 2-phenyl-1,3-dihydro-4*H*-pyrido[2,3-*b*][1,4]diazepin-4-one structure assignment.

Later, Israel *et al*. [24] found that different reaction conditions resulted in the preferential formation of dihydro-pyrido[2,3-*b*][1,4]diazepin-2-one or the 4-one isomer from the reaction of 2,3-diaminopyridine with ethyl acetoacetate. This reaction afforded 2-methyl-pyrido[2,3-*b*][1,4]diazepin-4-one as the major product when conducted in boiling xylene. In the absence of solvent, the mixture of 2,3-diaminopyridine with an excess of ethyl acetoacetate at 185 ºC furnished 4-methyl-pyrido[2,3-*b*][1,4]diazepin-2-one, which was obtained as an inseparable tautomeric mixture of 1,3- and 1,5-dihydro-4-methyl-2*H*-pyrido[2,3-*b*][1,4]diazepin-2-one.

Moreover, since the 60's various diamino-ketoester condensations [25-29] involving reactions of cyclic and acyclic β-ketoesters with non-symmetrical diaminopyridines have been studied in an attempt to develop generalized predictions regarding the direction of ring closure to form diazepinones as well as to find novel tricyclic ring systems which could be of interest in obtaining clozapine and pirenzapine analogues with psychotropic properties.

Surprisingly, since the first pyridodiazepinone was reported in 1964 [23], there have been no publications whose objective was to carry out a regiospecific and simultaneous introduction of a trifluoromethyl and substituted aryl groups at the pyrido[2,3-*b*][1,4]-diazepine derivatives starting from trifluoromethyl substituted 1,3-diketones or 4-methoxy-1,1,1-trihaloalk-3-en-2-ones. In addition, there is no data on reactions involving simple 1,3-diketones, such as acetylacetone or benzoylacetone, with 2,3-diaminopyridine.

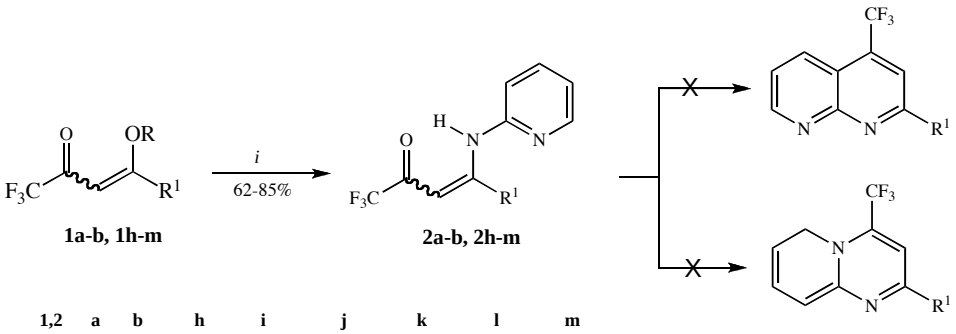
Recently, we communicated the first synthesis of 2-aryl(heteroaryl)-4-trifluoromethyl-3*H*-pyrido[2,3-*b*][1,4]-diazepin-4-ols from the direct cyclocondensation reaction of 4-methoxy-1,1,1-trifluoroalk-3-en-2-ones (**1**) with 2,3-diaminopyridine [30].

The purpose of this paper is to report the results of a chemical behavior study of the reactions of 4-alkoxy-1,1,1-trifluoroalk-3-en-2-ones (**1**) with 2-aminopyridine and with 2,3-diaminopyridine to obtain two series of trifluoroacetyl enamines and also to investigate the possibility of using these enamino ketones for the synthesis of new nitrogen-containg heterocycles with conventional procedures.

RESULTS AND DISCUSSION

Initially, we report the synthesis of a new series of N^2-[1-alkyl(aryl)-3-oxo-4,4,4-trifluoroalk-1-en-1-yl]-2-aminopyridines (**2**) (Scheme I) and N^3-[1-alkyl(aryl/heteroaryl)-3-oxo-4,4,4-trifluoroalk-1-en-1-yl]-2,3-diaminopyridines (**3**) (Scheme II) from the reaction of

Scheme I



1a-b, 1h-m **2a-b, 2h-m**

1,2	a	b	h	i	j	k	l	m
R	Et	Me	Me	Me	Me	Me	Me	Me
R1	H	Me	Ph	4-MePh	4-OMePh	4-FPh	4-ClPh	4-BrPh

(*i*): 2-Aminopyridine, EtOH, reflux, 2 h

4-alkoxy-1,1,1-trifluoroalk-3-en-2-ones (**1**) with 2-aminopyridine and 2,3-diaminopyridine, espectively. Second, we present the complete results and data of the first regiospecific preparation of a series of 2-aryl(heteroaryl)-4-trifluoromethyl-4,5-dihydro-3*H*-pyrido[2,3-*b*][1,4]diazepin-4-ols (**4**) from the intramolecular cyclization reaction of trifluoroacetyl enamines [$F_3CC(O)CH=CR^1(NH\text{-}C_5H_3N\text{-}NH_2$] (**3**), or from the direct cyclocondensation reaction of 4-methoxy-1,1,1-trifluoroalk-3-en-2-ones (**1**) with 2,3-diaminopyridine.

4-alkyl(aryl)-4-alkoxy-1,1,1-trifluoroalk-3-en-2-ones (**1**) were synthesized from the acylation reaction of the respective enolethers or ketone dimethyl acetals with trifluoroacetic anhydride according to a procedure developed previously [31].

The reactions of compounds **1** with 2-aminopyridine, in ethanol for 2 hours under reflux, led to N^2-[3-oxo-4,4,4-trifluoroalk-1-en-1-yl]-2-aminopyridines (**2a-b**, **2h-m**) in 62 to 85% yields. Although, 4*H*-pyrido[1,2-*a*]pyrimidin-4-one and 5*H*-thiazolo[3,2-*a*]pyrimidin-5-ones were synthesized previously in our laboratories from the reactions of 4-alkoxy-1,1,1-trichloroalk-3-en-2-ones with 2-aminopyridine [22] and 2-aminothiazole [32], respectively, the reactions of 1,1,1-trifluoroalk-3-en-2-ones (**1**) with 2-aminopyridine or *N*-[3-oxo-4,4,4-trifluoroalk-1-en-1-yl]-2-aminopyridines (**2**) in refluxing ethanol, *n*-butanol or an acidic media such as sulfuric acid or PPA at reflux or using $TiCl_4$ as catalyst at different temperatures in an attempt to obtain any heterocyclic structure, always resulted in the recovery of the precursors or complex mixtures of non identified products by ^{1}H- and ^{13}C-NMR spectroscopy.

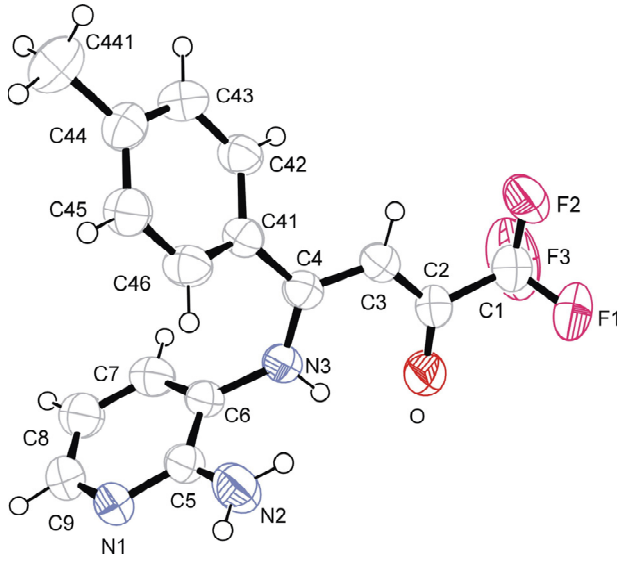
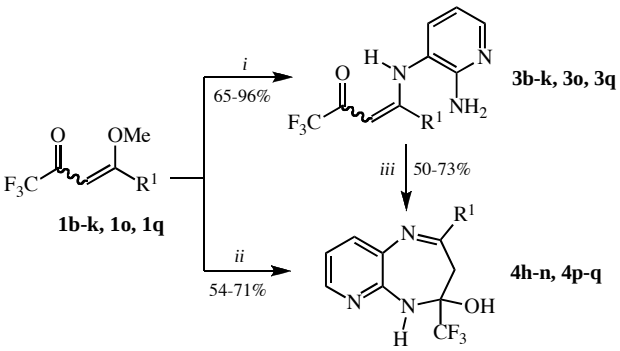


Figure 1. Perspective view of compound **3i**. Thermal ellipsoids correspond to 50% probability.

However, an extension of the reaction of ketones **1** with 2,3-diaminopyridine, a non-symmetrical heteroaromatic diamine, necessarily introduces the additional problem of two possible isomeric enaminones and subsequently diazepine products. The formation of the pyridodiazepine system presumably will depend on whether the initial reaction of the more nucleophilic 3-amino function to occur at the β-olefinic carbon of the vinyl ketones **1** or at the carbonyl carbon.

Fortunately, the reactions of compounds **1** with 2,3-aminopyridine, in methanol for 20 hours at 0ºC, led exclusively to N^3-[3-oxo-4,4,4-trifluoroalk-1-en-1-yl]-2,3-aminopyridine intermediates (**3b-k**, **3o**, **3q**) in 65 to 96% yields and its X-ray diffraction data is shown (Figure 1). Crystallographic data for compound **3i**, reported in this paper, have been deposited with the Cambridge Crystallographic Data Center (CCDC 687400) [33].

Scheme II



(*i*): 2,3-Diaminopyridine, MeOH, 0 ºC, 20 h; (*ii*): 2,3-Diaminopyridine, MeOH, 50 ºC, 24 h; (*iii*): MeOH, 50 ºC, 20 h.

1,3-4	b	c	d	e	f	g	h	i	j	k
R¹	Me	*n*-Pr	*i*-Pr	*i*-Bu	*i*-Pen	*n*-Hex	Ph	4-MePh	4-OMePh	4-FPh

1,3-4	l	m	n	o	p	q
R¹	4-ClPh	4-BrPh	4,4'-BiPh	1-Naphthyl	2-Furyl	2-Thienyl

Subsequently, we found that trifluoromethylated ketones **1h-n**, **1p**, **1q** when treated with 2,3-diaminopyridine at a molar ratio of 1:1 respectively, in methanol as solvent for 24 hours, at 50 °C, produced regiospecifically 2-aryl(heteroaryl)-4-trifluoromethyl-4,5-dihydro-3*H*-pyrido[2,3-*b*][1,4]diazepin-4-ols (**4h-n**, **4p**, **4q**) in a one-step reaction and in 54 to 71% yield. The conditions described above allowed us to regiospecifically obtain the diazepinols (**4**) instead of the isomer analogues. As an extension of this study, compounds **3h-n**, **3q** were readily also converted into **4h-n**, **4q** by heating in methanol (50 ºC) for 20 hours in 50 to 73 % yields.

All reactions are presented in Scheme I and 2 and the best results, NMR spectral data, selected physical and analytical data are included in the experimental section.

In summary, it was observed that the reactions of 4-alkoxy-1,1,1-trifluoroalk-3-en-2-ones (**1**) with 2-amino-

pyridine and 2,3-diaminopyridine are regiospecific and when carried out in anhydrous ethanol under reflux or in methanol at 0 ºC give the enamino ketone intermediates *N*-[3-oxo-4,4,4-trifluoroalk-1-en-1-yl]-2-aminopyridines (**2**) or N^3-[3-oxo-4,4,4-trifluoroalk-1-en-1-yl]-2,3-aminopyridines (**3**), respectively. Moreover, we also developed the first efficient and regiospecific preparation of 3*H*-pyrido[2,3-*b*][1,4]diazepinol system (**4**) from intramolecular cyclization reaction of the respective trifluoroacetyl enamines (**3**) or from the direct cyclocondensation reaction of 4-methoxy-1,1,1-trifluoroalk-3-en-2-ones (**1**) with 2,3-diaminopyridine, under mild conditions by a conventional procedure in a moderate to good yields. A specific synthesis and the properties of trifluoromethyl substituted 4,5-dihydro-3*H*-pyrido[2,3-*b*]-[1,4]diazepin-4-ols are not yet known.

EXPERIMENTAL

Unless otherwise indicated, all common reagents and solvents were obtained from commercial suppliers without further purification. All melting points were determined on an Electrothermal Melt-Temp 3.0 apparatus and are uncorrected. Mass spectra were registered in a 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. ^{1}H and ^{13}C NMR spectra were acquired on a Bruker DPX 200 spectrometer (^{1}H at 200.13 MHz and ^{13}C at 50.32 MHz), 5 mm sample tubes, 298 K, digital resolution ±0.01 ppm, in chloroform-d_1 (for **2**, **3**) or DMSO-d_6 (for **4**) using TMS as internal reference. The CHN elemental analyses were performed on a Perkin Elmer 2400 CHN elemental analyzer (São Paulo University – USP / Brazil).

Synthetic Procedures.

General procedure for the Preparation of Substituted N^2-[3-oxo-4,4,4-trifluoroalk-1-en-1-yl]-2-aminopyridines (2a-b, 2h-m). To a stirred solution of 4-alkoxy-1,1,1-trifluoroalk-3-en-2-one **1a**, **1b**, **1h-m** (5 mmoles) in 15 mL of anhydrous ethanol, 2-aminopyridine (0.470 g, 5 mmoles) was added at 20 – 25 °C. The mixture was stirred for 5 hours at 80 – 85 °C (oil bath). After the reaction time, the solvent was evaporated under reduced pressure and the crude products **2a**, **2b**, **2h-m** were purified by recrystallization from ethyl acetate.

***N*-[3-Oxo-4,4,4-trifluorobut-1-en-1-yl]-2-aminopyridine** (**2a**). This compound was obtained as orange solid, yields 78%, Mp. 71-72°C (lit. [14]; Mp. 78-79ºC). ^{1}H NMR ($CDCl_3$) δ = 11.72 (s, 1H, NH), 8.45 (dd, *J* = 8, 1H, H-1), 8.35 (d, *J* = 5, 1H, PyH-6), 7.68 (t, *J* = 8, 1H, PyH-4), 7.07 (t, *J* = 7, 1H, PyH-5), 6.89 (d, *J* = 8, 1H, PyH-3), 5.73 (d, *J* = 8, 1H, H-2). ^{13}C NMR ($CDCl_3$) δ = 180.3 (C=O, $^2J_{CF}$ = 34), 150.17 (PyC-2), 148.7 (C-1), 147.9 (PyC-6), 138.7 (PyC-4), 120.2 (C-2), 116.7 (CF_3, $^1J_{CF}$ = 289), 112.1 (PyC-5), 90.9 (PyC-3). GC/MS (EI, 70eV): *m*/*z* (%) = 216 (M^+, 59), 147 (74), 119 (100), 78 (98), 51 (44)

***N*-[4-Oxo-5,5,5-trifluoropent-2-en-2-yl]-2-aminopyridine** (**2b**). This compound was obtained as white solid, yields 62%, Mp. 66-67°C. ^{1}H NMR ($CDCl_3$) δ = 12.91 (s, 1H, NH), 8.39 (d, *J* = 4.6, 1H, PyH-6), 7.71 (t, *J* = 7.7, 1H, PyH-4), 7.09 (t, *J* = 7.4, 1H, PyH-5), 7.01 (d, *J* = 7.9, 1H, PyH-3), 5.58 (s, 1H, H-2), 2.60 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ = 177.3 (C=O, $^2J_{CF}$ = 34), 167.2 (PyC-2), 151.6 (C-1), 148.3 (PyC-6), 138.3 (PyC-4), 120.3 (C-2), 117.2 (CF_3, $^1J_{CF}$ = 289), 115.8 (PyC-5), 93.4 (PyC-3), 22.4 (CH_3). GC/MS (EI, 70eV): *m*/*z* (%) = 230 (M^+, 6), 161 (20), 133 (100), 78 (71), 51 (17). *Anal*. Calcd. for $C_{10}H_9F_3N_2O$ (230.19): C, 52.18; H, 3.94; N, 12.17%. Found: C, 52.49; H, 3.94; N, 12.24%.

***N*-[1-Phenyl-3-oxo-4,4,4-trifluorobut-1-en-1-yl]-2-aminopyridine** (**2h**). This compound was obtained as yellow solid, yields 85%, Mp. 82-83°C. ^{1}H NMR ($CDCl_3$) δ = 12.23 (s, 1H, NH), 8.26 (d, *J* = 5, 1H, PyH-6), 7.39 (m, 6H, PyH-4, Ph), 6.98 (t, *J* = 7, 1H, PyH-5), 6.47 (d, *J* = 8, 1H, PyH-3), 5.74 (s, 1H, H-2). ^{13}C NMR ($CDCl_3$) δ = 178.3 (C=O, $^2J_{CF}$ = 34), 164.5 (C-1), 151.4 (PyC-2), 148.8 (PyC-6), 137.4 (PyC-4), 134.3 (Ph), 130.7 (Ph), 127.9 (Ph), 120.3 (C-2), 117.0 (CF_3, $^1J_{CF}$ = 289), 115.6 (PyC-5), 94.3 (PyC-3), 22.4 (CH_3). GC/MS (EI, 70eV): *m*/*z* (%) = 292 (M^+, 1), 223 (11), 195 (100), 78 (74), 51 (24). *Anal*. Calcd. for $C_{15}H_{11}F_3N_2O$ (292.26): C, 61.65; H, 3.79; N, 9.59%. Found: C, 61.43; H, 3.91; N, 9.92%.

***N*-[1-(4-Methylphenyl)-3-oxo-4,4,4-trifluorobut-1-en-1-yl]-2-aminopyridine** (**2i**). This compound was obtained as yellow solid, yields 77%, Mp. 52-53°C. ^{1}H NMR ($CDCl_3$) δ = 12.11 (s, 1H, NH), 8.21 (d, *J* = 5, 1H, PyH-6), 7.38 (t, *J* = 8, 1H, PyH-4), 7.17 (m, 2H, Ph), 6.90 (t, *J* = 7, 1H, PyH-5), 6.42 (d, *J* = 8, 1H, PyH-3), 5.64 (s, 1H, H-2), 2.30 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ = 178.0 (C=O, $^2J_{CF}$ = 34), 164.6 (C-1), 151.5 (PyC-2), 148.7 (PyC-6), 141.4 (PyC-4), 137.3 (Ph), 131.2 (Ph), 129.5 (Ph), 127.8 (Ph), 120.2 (C-2), 117.0 (CF_3, $^1J_{CF}$ = 289), 116.7 (PyC-5), 93.9 (PyC-3), 21.3 (CH_3). GC/MS (EI, 70eV): *m*/*z* (%) = 305 (M^+, 1), 237 (5), 209 (100), 78 (27), 51 (5). *Anal*. Calcd. for $C_{16}H_{13}F_3N_2O$ (306.29): C, 62.74; H, 4.28; N, 9.15%. Found: C, 62.91; H, 4.43; N, 9.12%.

***N*-[1-(4-Methoxyphenyl)-3-oxo-4,4,4-trifluorobut-1-en-1-yl]-2-aminopyridine** (**2j**). This compound was obtained as yellow solid, yields 69%, Mp. 68-69°C. ^{1}H NMR ($CDCl_3$) δ = 12.18 (s, 1H, NH), 8.30 (d, *J* = 5, 1H, PyH-6), 7.45 (t, *J* = 8, 1H, PyH-4), 7.31 (d, *J* = 8.7, 2H, Ph), 6.99 (t, *J* = 7, 1H, PyH-5), 6.86 (d, *J* = 8.5, 2H, Ph), 6.52 (d, *J*=8, 1H, PyH-3), 5.73 (s, 1H, H-2), 3.84 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$) δ = 177.8 (C=O, $^2J_{CF}$ = 34), 164.3 (C-1), 161.8 (Ph), 151.8 (PyC-2), 148.8 (PyC-6), 137.3 (PyC-4), 129.7 (Ph), 126.2 (Ph), 120.2 (C-2), 117.1 (CF_3, $^1J_{CF}$ = 289), 116.8 (PyC-5), 93.7 (PyC-3), 55.3 (OCH_3). GC/MS (EI, 70eV): *m*/*z* (%) = 253 (M^+, 5), 225 (100), 78 (46), 51 (10). *Anal*. Calcd. for $C_{16}H_{13}F_3N_2O_2$ (322.29): C, 59.63; H, 4.07; N, 8.69%. Found: C, 59.26; H, 4.09; N, 8.02%.

***N*-[1-(4-Fluorophenyl)-3-oxo-4,4,4-trifluorobut-1-en-1-yl]-2-aminopyridine** (**2k**). This compound was obtained as yellow solid, yields 93%, Mp. 91-92°C. ^{1}H NMR ($CDCl_3$) δ = 12.20 (s, 1H, NH), 8.26 (d, *J* = 5, 1H, PyH-6), 7.49 (d, *J* = 8, 1H, PyH-4), 7.38 (m, 3H, PyH-5, Ph), 7.02 (m, 3H, Ph), 6.58 (m, 1H, PyH-3), 5.72 (s, 1H, H-2). ^{13}C NMR ($CDCl_3$) δ = 178.4 (C=O, $^2J_{CF}$ = 34), 163.9 (d, ^1J = 252, F-Ph), 163.4 (C-1), 151.3 (PyC-2), 148.8 (PyC-6), 137.7 (PyC-4), 130.5 (d, ^4J=3.5, F-Ph), 130.1 (d, ^3J = 9, F-Ph), 120.4 (C-2), 117.0 (CF_3, $^1J_{CF}$ = 289), 116.7 (PyC-5), 115.8 (d, ^2J = 23, F-Ph), 94.39 (PyC-3). GC/MS (EI, 70eV): *m*/*z* (%) = 310 (M^+, 1), 241 (11), 213 (100), 78 (70), 51 (14). *Anal*. Calcd. for $C_{15}H_{10}F_4N_2O$ (310.25): C, 58.07; H, 3.25; N, 9.03%. Found: C, 58.11; H, 3.37; N, 8.96%.

***N*-[1-(4-Chlorophenyl)-3-oxo-4,4,4-trifluorobut-1-en-1-yl]-2-aminopyridine** (**2l**). This compound was obtained as yellow solid, yields 85%, Mp. 96-97°C. ^{1}H NMR ($CDCl_3$) δ = 12.19 (s, 1H, NH), 8.24 (d, *J* = 5, 1H, PyH-6), 7.51 (d, *J* = 8, 1H, PyH-4),

7.33 (m, 4H, Ph), 7.01 (t, *J* = 7, 1H, PyH-5), 6.60 (d, *J* = 8, 1H, PyH-3), 5.72 (s, 1H, H-2). ^{13}C NMR ($CDCl_3$) δ = 183.9 (C=O, $^2J_{CF}$ = 34), 168.7 (C-1), 156.7 (PyC-2), 154.3 (PyC-6), 143.2 (PyC-4), 142.4 (Ph), 138.5 (Ph), 134.8 (Ph), 134.5 (Ph), 126.0 (C-2), 122.4 (CF_3, $^1J_{CF}$ = 289), 122.1 (PyC-5), 99.9 (PyC-3). GC/MS (EI, 70eV): *m/z* (%) = 326 (M^+, 1), 257 (9), 229 (100), 78 (14), 51 (6). *Anal*. Calcd. for $C_{15}H_{10}F_3N_2OCl$ (326.71): C, 55.15; H, 3.09; N, 8.57%. Found: C, 55.43; H, 3.31; N, 8.43%.

***N*-[1-(4-Bromophenyl)-3-oxo-4,4,4-trifluorobut-1-en-1-yl]-2-aminopyridine** (**2m**). This compound was obtained as yellow solid, yields 84%, Mp. 107-108°C. ^{1}H NMR ($CDCl_3$) δ = 12.18 (s, 1H, NH), 8.24 (d, *J* = 5, 1H, PyH-6), 7.51 (m, 3H, PyH-4, Ph), 7.24 (d, *J* = 8.7, 2H, Ph), 7.01 (t, *J* = 7, 1H, PyH-5), 6.61 (d, *J* = 8, 1H, PyH-3), 5.71 (s, 1H, H-2). ^{13}C NMR ($CDCl_3$) δ = 178.5 (C=O, $^2J_{CF}$ = 34), 163.2 (C-1), 151.1 (PyC-2), 148.7 (PyC-6), 137.7 (PyC-4), 134.4 (Ph), 131.9 (Ph), 129.4 (Ph), 125.1 (Ph), 120.4 (C-2), 116.9 (CF_3, $^1J_{CF}$ = 289), 115.4 (PyC-5), 94.4 (PyC-3). GC/MS (EI, 70eV): *m/z* (%) = 371 (M^+, 1), 302 (7), 273 (100), 78 (67), 51 (14). *Anal*. Calcd. for $C_{15}H_{10}F_3N_2OBr$ (371.16): C, 48.54; H, 2.72; N, 7.55%. Found: C, 48.89; H, 2.85; N, 7.38%.

General procedure for the Preparation of Substituted *N*^{3}-[3-oxo-4,4,4-trifluoroalk-1-en-1-yl]-2,3-aminopyridines (3b-k, 3o, 3q). To a stirred solution of 2,3-diaminopyridine (0.327 g, 3 mmol) in 10 mL of dry methanol, 4-alkoxy-4-aryl(alkyl)-1,1,1-trifluoroalk-3-en-2-ones (**1b-k**, **1o**, **1q**) (3 mmol) were added at 0°C. The mixture was stirred for 24 hours at 0°C. After the reaction time, the solvent was removed under reduced pressure and the crude solid products (**3b-k**, **3o**, **3q**) were recrystallized from hexane.

***N*^{3}-[3-Oxo-4,4,4-trifluoropent-2-en-2-yl]-2,3-diaminopyridine** (**3b**). This compound was obtained as yellow solid, yields 88%, Mp. 106-107°C. ^{1}H NMR ($CDCl_3$) δ = 11.93 (s, 1H, NH), 8.04 (d, 1H, *J* = 5, PyH-6), 7.28 (d, 1H, *J* = 7.5, PyH-4), 6.69 (dd, 1H, *J*=7.5, *J*=7.5, PyH-5), 5.58 (s, 1H, H-2), 5.21 (s, 2H, NH_2), 2.01 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ = 177.0 (q, $^2J_{CF}$ = 34, C=O), 169.9 (C-1), 154.9 (PyC-2), 147.9 (PyC-6), 135.4 (PyC-4), 117.5 (PyC-3), 117.2 (q, $^1J_{CF}$ = 288, CF_3), 113.7 (PyC-5), 91.0 (C-2), 19.7 (CH_3). *Anal*. Calcd. for $C_{10}H_{10}F_3N_3O$ (245.08): C, 48.98; H, 4.11; N, 17.14%. Found: C, 49.15; H, 4.21; N, 17.14%.

***N*^{3}-[6-Oxo-7,7,7-trifluorohept-4-en-4-yl]-2,3-diamino-pyridine** (**3c**). This compound was obtained as yellow solid, yields 71%, Mp. 128-130°C. ^{1}H NMR ($CDCl_3$) δ = 12.01 (s, 1H, NH), 8.05 (d, 1H, *J* = 5, PyH-6), 7.28 (d, 1H, *J* = 7.5, PyH-4), 6.69 (dd, 2H, *J* = 7.5, *J* = 7.5, PyH-5), 5.60 (s, 1H, H-2), 5.23 (s, 2H, NH_2), 2.21 (q, 2H, *J* = 7, CH_2), 1.52 (sex, 2H, *J* = 8, CH_2), 0.88 (t, 3H, *J* = 7, CH_3). ^{13}C NMR ($CDCl_3$) δ = 177.2 (q, $^2J_{CF}$ = 34, C=O), 174.1 (C-1), 155.0 (PyC-2), 147.9 (PyC-6), 135.6 (PyC-4), 117.2 (PyC-3), 117.1 (q, $^1J_{CF}$ = 288, CF_3), 113.5 (PyC-5), 89.7 (C-2), 34.1 (CH_2), 20.9 (CH_2), 13.6 (CH_3). *Anal*. Calcd. for $C_{12}H_{14}F_3N_3O$ (273.11): C, 52.75; H, 5.16; N, 15.38%. Found: C, 52.77; H, 4.82; N, 15.30%.

***N*^{3}-[2-Methyl-5-oxo-6,6,6-trifluorohex-3-en-3-yl]-2,3-diaminopyridine** (**3d**). This compound was obtained as yellow solid, yields 66%, Mp. 146-148°C. ^{1}H NMR ($CDCl_3$) δ = 12.17 (s, 1H, NH), 8.07 (d, 1H, *J* = 5, PyH-6), 7.27 (d, 1H, *J* = 7.5, PyH-4), 6.72-6.69 (m, 1H, PyH-5), 5.92 (s, 1H, H-2), 5.87 (s, 2H, NH_2), 2.63 (sept, 1H, *J* = 7, CH), 1.14 (d, 6H, *J* = 6, $2CH_3$). ^{13}C NMR ($CDCl_3$) δ = 180.4 (C-1), 177.6 (q, $^2J_{CF}$ = 34, C=O), 155.1 (PyC-2), 148.2 (PyC-6), 135.8 (PyC-4), 117.3 (q, $^1J_{CF}$ = 288, CF_3), 117.0 (PyC-3), 113.9 (PyC-5), 86.4 (C-2), 29.7 (CH), 21.3 (CH_3). *Anal*. Calcd. for $C_{12}H_{14}F_3N_3O$ (273.11): C, 52.75; H, 5.16; N, 15.38%. Found: C, 52.37; H, 5.15; N, 15.23%.

***N*^{3}-[2-Methyl-6-oxo-7,7,7-trifluorohept-4-en-4-yl]-2,3-diaminopyridine** (**3e**). This compound was obtained as yellow solid, yields 73%, Mp. 123-125°C. ^{1}H NMR ($CDCl_3$) δ = 11.51 (s, 1H, NH), 8.07 (d, 1H, *J* = 5, PyH-6), 7.28 (d, 1H, *J* = 7.5, PyH-4), 6.72-6.66 (m, 1H, PyH-5), 5.92 (s, 1H, H-2), 5.37 (s, 2H, NH_2), 2.20 (d, 2H, *J* = 8, CH_2), 1.80 (sept, 1H, *J* = 7, CH), 0.87 (d, 6H, *J* = 6, $2CH_3$). ^{13}C NMR ($CDCl_3$) δ = 176.8 (q, $^2J_{CF}$ = 34, C=O), 173.2 (C-1), 155.0 (PyC-2), 147.8 (PyC-6), 135.7 (PyC-4), 117.2 (PyC-3), 117.0 (q, $^1J_{CF}$ = 288, CF_3), 113.3 (PyC-5), 90.4 (C-2), 40.9 (CH_2), 27.4 (CH), 22.0 ($2CH_3$). *Anal*. Calcd. for $C_{13}H_{16}F_3N_3O$ (287.12): C, 54.35; H, 5.61; N, 14.63%. Found: C, 54.09; H, 5.42; N, 14.31%.

***N*^{3}-[2-Methyl-7-oxo-8,8,8-trifluorooct-5-en-5-yl]-2,3-diaminopyridine** (**3f**). This compound was obtained as yellow solid, yields 65%, Mp. 122-124°C. ^{1}H NMR ($CDCl_3$) δ = 12.00 (s, 1H, NH), 8.07 (d, 1H, *J* = 5, PyH-6), 7.29 (d, 1H, *J* = 7.5, PyH-4), 6.71 (m, 1H, PyH-5), 5.60 (s, 1H, H-2), 5.04 (s, 2H, NH_2), 2.23 (t, 2H, *J* = 8, CH_2), 1.47 (m, 1H, CH), 1.37 (m, 2H, CH_2), 0.77 (d, 6H, *J* = 6, $2CH_3$). ^{13}C NMR ($CDCl_3$) δ = 177.6 (q, $^2J_{CF}$ = 34, C=O), 174.7 (C-1), 155.0 (PyC-2), 147.9 (PyC-6), 135.6 (PyC-4), 117.2 (PyC-3), 117.0 (q, $^1J_{CF}$ = 288, CF_3), 113.4 (PyC-5), 89.8 (C-2), 36.7 (CH_2), 30.2 (CH), 27.6 (CH_2), 21.7 ($2CH_3$). *Anal*. Calcd. for $C_{14}H_{18}F_3N_3O$ (301.14): C, 55.81; H, 6.02; N, 13.95%. Found: C, 55.50; H, 5.87; N, 13.72%.

***N*^{3}-[9-Oxo-10,10,10-trifluorodec-7-en-7-yl]-2,3-diaminopyridine** (**3g**). This compound was obtained as yellow solid, yields 96%, Mp. 122-124°C. ^{1}H NMR ($CDCl_3$) δ = 12.01 (s, 1H, NH), 8.06 (d, 1H, *J* = 5, PyH-6), 7.29 (d, 1H, *J* = 7.5, PyH-4), 6.71 (dd, 2H, *J* = 7.5, *J* = 7.5, PyH-5), 5.61 (s, 1H, H-2), 5.05 (s, 2H, NH_2), 2.40 (t, 2H, *J* = 8, CH_2), 1.48 (quint., 2H, *J* = 7.5, CH_2), 1.25-1.14 (m, 6H, $3CH_2$), 0.83 (t, 3H, *J* = 7, CH_3). ^{13}C NMR ($CDCl_3$) δ = 177.4 (q, $^2J_{CF}$ = 34, C=O), 174.3 (C-1), 155.0 (PyC-2), 148.1 (PyC-6), 135.9 (PyC-4), 117.4 (PyC-3), 117.1 (q, $^1J_{CF}$ = 288, CF_3), 113.8 (PyC-5), 90.0 (C-2), 32.4 (CH_2), 31.2 (CH_2), 28.8 (CH_2), 27.7 (CH_2), 22.3 (CH_2), 13.9 (CH_3). *Anal*. Calcd. for $C_{15}H_{20}F_3N_3O$ (315.16): C, 57.13; H, 6.39; N, 13.33%. Found: C, 56.70; H, 6.28; N, 13.08%.

***N*^{3}-[1-Phenyl-3-oxo-4,4,4-trifluorobut-1-en-1-yl]-2,3-diaminopyridine** (**3h**). This compound was obtained as yellow solid, yields 77%, Mp. 152-154°C. ^{1}H NMR ($CDCl_3$) δ = 12.01 (s,1H, NH), 7.84 (d, 1H, *J* = 5, PyH-6), 7.39-7.29 (m, 5H, Ph), 6.73 (d, 1H, *J* = 7.5, PyH-4), 6.39-6.37 (dd, 1H, *J* = 7.5, *J* = 7.5, PyH-5), 5.79 (s,1H, H-2), 5.26 (s, 2H, NH_2). ^{13}C NMR ($CDCl_3$) δ = 178.1 (q, $^2J_{CF}$ = 34, C=O), 168.7 (C-1), 153.8 (PyC-2), 146.2 (PyC-6), 134.9 (PyC-4), 133.2 (Ph), 130.9 (Ph), 128.7 (Ph), 127.8 (Ph), 119.4 (PyC-3), 117.5 (q, $^1J_{CF}$ = 288, CF_3), 113.6 (PyC-5), 92.9 (C-2). *Anal*. Calcd. for $C_{15}H_{12}F_3N_3O$ (307.09): C, 58.63; H, 3.94; N, 13.68%. Found: C, 58.27; H, 3.52; N, 13.73%.

***N*^{3}-[1-(4-Methylphenyl)-3-oxo-4,4,4-trifluorobut-1-en-1-yl]-2,3-diaminopyridine** (**3i**). This compound was obtained as yellow solid, yields 78%, Mp. 156-158°C. ^{1}H NMR ($CDCl_3$) δ = 12.01 (s, 1H, NH), 7.83 (d, 1H, *J* = 5, PyH-6), 7.18 (d, 2H, *J* = 7.5, Ph), 7.10 (d, 2H, *J* = 7.5, Ph), 6.76 (d, 1H, *J* = 7.5, PyH-4), 6.40 (m, 1H, PyH-5), 5.78 (s, 1H, H-2), 5.31 (s, 2H, NH_2), 2.32 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ = 177.9 (q, $^2J_{CF}$ = 34, C=O), 168.8 (C-1), 164.4 (Ph), 153.8 (PyC-2), 145.8 (PyC-6), 135.7 (PyC-4), 130.2 (Ph), 129.4 (Ph), 127.8 (Ph), 118.7 (PyC-3), 117.2 (q, $^1J_{CF}$ = 288, CF_3), 115.8 (PyC-5), 92.7 (C-2), 21.3 (CH_3). *Anal*. Calcd. for $C_{16}H_{14}F_3N_3O$ (321.11): C, 59.81; H, 4.39; N, 13.08%. Found: C, 60.06; H, 4.13; N, 13.37%.

***N*^{3}-[1-(4-Methoxylphenyl)-3-oxo-4,4,4-trifluorobut-1-en-1-yl]-2,3-diaminopyridine** (**3j**). This compound was obtained as yellow solid, yields 91%, Mp. 127-129°C. ^{1}H NMR ($CDCl_3$) δ = 12.02 (s, 1H, NH), 7.85 (d, 1H, *J* = 5, PyH-6), 7.24 (d, 2H, *J* = 9, Ph), 6.79 (m, 3H, Ph, PyH-4), 6.42-6.40 (dd, 1H, *J* = 7.5, *J* = 7.5, PyH-5), 5.77 (s, 1H, H-2), 5.25 (s, 2H, NH_2), 3.78 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$) δ = 177.5 (q, $^2J_{CF}$ = 34, C=O), 168.5 (C-1), 161.7 (Ph), 153.9 (PyC-2), 146.1 (PyC-6), 134.8 (PyC-4), 129.7 (Ph), 125.1 (Ph), 119.7 (PyC-3), 117.2 (q, $^1J_{CF}$ = 288, CF_3), 114.1 (Ph), 113.7 (PyC-5), 92.4 (C-2), 55.2 (OCH_3). *Anal.* Calcd. for $C_{16}H_{14}F_3N_3O_2$ (337.1): C, 56.97; H, 4.18; N, 12.46%. Found: C, 57.26; H, 3.99; N, 11.94%.

***N*^{3}-[1-(4-Fluorophenyl)-3-oxo-4,4,4-trifluorobut-1-en-1-yl]-2,3-diaminopyridine** (**3k**). This compound was obtained as yellow solid, yields 82%, Mp. 152-154°C. ^{1}H NMR ($CDCl_3$) δ = 11.96 (s,1H, NH), 7.89 (d, 1H, *J* = 5, PyH-6), 7.32 (d, 2H, *J* = 9, Ph), 7.01 (t, 2H, *J* = 8.5, Ph), 6.77 (d, 1H, *J* = 7.5, PyH-4), 6.44-6.42 (dd, 1H, *J* = 7.5, *J* = 7.5, PyH-5), 5.76 (s, 1H, H-2), 5.31 (s, 2H, NH_2). ^{13}C NMR ($CDCl_3$) δ = 178.1 (q, $^2J_{CF}$ = 34, C=O), 167.6 (C-1), 165.2-162.7 (d, ^1J = 252, F-Ph), 153.9 (PyC-2), 146.5 (PyC-6), 135.1 (PyC-4), 130.1-130.0 (^2J = 29, F-Ph), 129.3 (Ph), 119.2 (PyC-3), 116.6 (q, $^1J_{CF}$ = 288, CF_3), 116.1-115.9 (d, ^3J = 9, F-Ph), 115.3 (PyC-5), 92.8 (C-2). *Anal.* Calcd. for $C_{15}H_{11}F_4N_3O$ (325.08): C, 55.38; H, 3.41; N, 12.92%. Found: C, 55.34; H, 3.23; N, 13.13%.

***N*^{3}-[1-(1-Naphthyl)-3-oxo-4,4,4-trifluorobut-1-en-1-yl]-2,3-diaminopyridine** (**3o**). This compound was obtained as yellow solid, yields 73%, Mp. 161-163°C. ^{1}H NMR ($CDCl_3$) δ = 12.48 (s, 1H, NH), 7.91 (d, *J* = 5, 1H, PyH-6), 7.80 (m, 2H, nf), 7.67 (m, 1H, nf), 7.46 (m, 2H, naph), 7.38 (m, 2H, naph), 6.55 (d, *J* = 7.5, *J* = 7.5, 1H, PyH-4), 6.08-6.06 (dd, *J* = 7.5, *J* = 7.5, 1H, PyH-5) 5.85 (s, 1H, H-2), 5.19 (s, 2H, NH_2). ^{13}C NMR ($CDCl_3$) δ = 177.9 (q, $^2J_{CF}$ = 34, C=O),167.9 (C-1), 153.1 (PyC-2), 146.4 (PyC-6), 133.2 (naph), 132.6 (PyC-4), 130.8-124.1 (naph), 118.8 (PyC-3), 115.3 (q, $^2J_{CF}$ = 288, CF_3), 114.9 (PyC-5), 94.7 (C2). *Anal.* Calcd. for $C_{19}H_{14}F_3N_3O$ (357.11): C, 63.86; H, 3.95; N, 11.76%. Found: C, 63.55; H, 3.87; N, 11.53%

***N*^{3}-[1-(2-Thienyl)-3-oxo-4,4,4-trifluorobut-1-en-1-yl]-2,3-diaminopyridine** (**3q**). This compound was obtained as yellow solid, yields 76%, Mp. 158-160°C. ^{1}H NMR ($CDCl_3$) δ = 12.18 (s, 1H, NH), 8.05 (d, *J* = 5, 1H, PyH-6), 7.48 (d, *J* = 5.0, 1H, tn), 7.29 (d, *J* = 3.0, 1H, tn), 7.15 (d, *J* = 7.0, 1H, tn), 7.00 (dd, *J* = 7.5, *J* = 7.5, 1H, PyH-4), 6.64-6.62 (dd, *J* = 5.0, *J* = 5.0, 1H, PyH-5) 6.02 (s, 1H, H-2), 4.79 (s, 2H, NH_2). ^{13}C NMR ($CDCl_3$) δ = 176.6 (q, $^2J_{CF}$ = 34, C=O), 161.3 (C-1), 154.7 (PyC-2), 147.7 (tn), 136.1 (PyC-6), 133.6 (PyC-3), 131.7 (tn), 131.6 (tn), 127.7 (PyC-4), 118.7 (tn), 117.3 (q, $^1J_{CF}$ = 288, CF_3), 114.1 (PyC-5), 91.1 (C-2). *Anal.* Calcd. for $C_{13}H_{10}F_3N_3OS$ (313.05): C, 49.84; H, 3.22; N, 13.41%. Found: C, 49.73; H, 2.96; N, 12.69%.

General Procedures for the Preparation of 2-aryl(heteroaryl)-4-trifluoromethyl-3*H*-pyrido[2,3-*b*][1,4]diazepin-4-ols (4).

Method A. From *N*^{3}-[1-Aryl(heteroaryl)-3-oxo-4,4,4-trifluorobut-1-en-1-yl]-2,3-diaminopyridine (3). A stirred solution of *N*^{3}-[1-aryl(heteroaryl)-3-oxo-4,4,4-trifluorobut-1-en-1-yl]-2,3-diaminopyridines (**3h-n**, **3q**) (3 mmol) in 5 mL of dry ethanol was stirred at 50 °C during 16 h. After the reaction time the solvent was removed under reduced pressure and the crude solid products were washed with chloroform, obtaining pure dark or gray solids (**4h-n**, **4q**) (yields 50 - 73 %).

Method B. From 4-Aryl(heteroaryl)-4-methoxy-1,1,1-trifluorobut-3-en-2-ones [30]. A stirred solution of 2,3-diaminopyridine (0.218 g, 2 mmol) with 4-aryl(heteroaryl)-4-methoxy-1,1,1-trifluorobut-3-en-2-ones (**1h-n**, **1p**, **1q**) (2 mmol) in 6 mL of dry methanol was stirred at 50 °C during 24 h. After the reaction time the solvent was removed under reduced pressure and the crude solid products were washed with chloroform, obtaining pure dark or gray solids (**4h-n**, **4p**, **4q**) (yields 54 – 71 %).

2-Phenyl-4-trifluoromethyl-4,5-dihydro-3*H*-pyrido[2,3-*b*]-diazepin-4-ol (**4h**). This compound was obtained as gray solid, yields 54%, Mp. 141-143°C. ^{1}H NMR (DMSO-d_6) δ = 8.12 (d, *J* = 5, 1H, H-7), 8.04-8.0 (m, 2H, Ph), 7.66 (s, 1H, OH), 7.63 (d, *J* = 7.5, H-9), 7.52-7.49 (m, 3H, Ph), 7.13-7.09 (dd, *J* = 7.5, *J* = 7.5, 1H, H-8), 6.42 (s, 1H, NH), 3.45 (d, *J* = 14.5, 1H, H-3a), 2.91 (d, *J* = 14.5, 1H, H-3b). ^{13}C NMR (DMSO-d_6) δ = 162.7 (C-2), 147.3 (C-5a), 145.5 (C-7), 138.2 (Ph), 136.8 (C-9a), 131.9 (C-9), 130.5 (Ph), 128.4 (Ph), 127.3 (Ph), 123.6 (q, CF_3, $^1J_{CF}$ = 288), 117.6 (C-8), 92.4 (q, C-4, $^2J_{CF}$ = 29), 34.2 (C-3). *Anal.* Calcd. for $C_{15}H_{12}F_3N_3O$ (307.09): C, 58.63; H, 3.94; N, 13.68%. Found: C, 58.18; H, 3.53; N, 14.15%.

2-(4-Methylphenyl)-4-trifluoromethyl-4,5-dihydro-3*H*-pyrido[2,3-*b*]diazepin-4-ol (**4i**). This compound was obtained as gray solid, yields 57%, Mp. 140-142°C. ^{1}H NMR (DMSO-d_6) δ = 8.11 (d, *J* = 5, 1H, H-7), 8.03 (d, *J* = 8, 2H, Ph), 7.67 (m, 2H, OH, H-9), 7.55 (d, *J* = 8, 2H, Ph), 7.11 (m, 1H, H-8), 6.44 (s, 1H, NH), 3.40 (d, *J* = 14.5, 1H, H-3a), 2.91 (d, *J* = 14.5, 1H, H-3b), 2.13 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6) δ = 161.6 (C-2), 147.3 (C-5a), 145.7 (C-7), 136.9 (Ph), 136.8 (C-9a), 135.4 (C-9), 128.6 (Ph), 128.4 (Ph), 123.5 (q, CF_3, $^1J_{CF}$ = 288), 117.8 (C-8), 92.3 (q, C-4, $^2J_{CF}$ = 29), 33.9 (C-3). *Anal.* Calcd. for $C_{16}H_{14}F_3N_3O$ (321.11): C, 59.81; H, 4.39; N, 13.08%. Found: C, 59.71; H, 4.37; N, 13.20%.

2-(4-Methoxyphenyl)-4-trifluoromethyl-4,5-dihydro-3*H*-pyrido[2,3-*b*]diazepin-4-ol (**4j**). This compound was obtained as gray solid, yields 67%, Mp. 137-139°C. ^{1}H NMR (DMSO-d_6) δ = 8.07 (d, *J* = 5, 1H, H-7), 7.97 (d, 2H, *J* = 9, Ph), 7.59 (d, *J* = 7.5, H-9), 7.48 (s, 1H, NH), 7.09-7.07 (dd, 1H, *J* = 7.5, *J* = 7.5, H-8), 7.03 (d, 2H, *J* = 9, Ph), 6.07 (s, 1H, NH), 3.83 (s, 3H, OCH_3), 3.39 (d, 1H, *J* = 14.5, H-3a), 2.85 (d, 1H, *J* = 14.5, H-3b). ^{13}C NMR (DMSO-d_6) δ = 161.9 (Ph), 161.2 (C-2), 147.3 (C5a), 144.9 (C-7), 136.3 (Ph), 132.3 (C-9a), 130.7 (C-9), 129.0 (Ph), 129.6 (q, $^1J_{CF}$ = 288, CF_3), 117.7 (C-8), 113.6 (Ph), 92.4 (q, $^2J_{CF}$ = 29, C-4), 55.2 (OCH_3), 33.9 (C-3). *Anal.* Calcd. for $C_{16}H_{14}F_3N_3O_2$ (337.1): C, 56.97; H, 4.18; N, 12.46%. Found: C, 56.66; H, 3.82; N, 12.15%.

2-(4-Fluorophenyl)-4-trifluoromethyl-4,5-dihydro-3*H*-pyrido[2,3-*b*]diazepin-4-ol (**4k**). This compound was obtained as gray solid, yields 69%, Mp. 160-162°C. ^{1}H NMR (DMSO-d_6) δ = 8.11 (d, *J* = 5, 1H, H-7), 8.07-8.05 (d, 2H, *J* = 6, Ph), 7.63 (d, *J* = 7.5, H-9), 7.53 (s, 1H, OH), 7.30 (t, 2H, *J* = 9, Ph), 7.10-7.09 (dd, 1H, *J* = 7.5, *J* = 7.5, H-8), 6.21 (s, 1H, NH), 3.38 (d, 1H, *J* = 14.5, H-3a), 2.92 (d, 1H, *J* = 14.5, H-3b). ^{13}C NMR (DMSO-d_6) δ = 164.8 (Ph), 162.4 (C-2), 161.7 (C-5a), 147.3 (C-7), 145.5 (C-9), 136.7 (Ph), 134.8 (Ph), 131.8 (C-9a), 129.8 (d, ^3J = 9, F-Ph), 124.1 (q, $^1J_{CF}$ = 288, CF_3), 117.7 (C-8), 115.2 (d, ^2J = 21, F-Ph), 92.3 (q, $^2J_{CF}$ = 29, C-4), 34.2 (C-3). *Anal.* Calcd. for $C_{15}H_{11}F_4N_3O$ (325.08): C, 55.39; H, 3.41; N, 12.92%. Found: C, 55.72; H, 3.76; N, 12.60%.

2-(4-Chlorophenyl)-4-trifluoromethyl-4,5-dihydro-3*H*-pyrido[2,3-*b*]diazepin-4-ol (**4l**). This compound was obtained as gray solid, yields 70%, Mp. 148-150°C. ^{1}H NMR (DMSO-d_6) δ = 8.13 (d, *J* = 5, 1H, H-7), 7.96 (d, 2H, *J* = 9, Ph), 7.70 (d, 2H, *J* = 9, Ph, 1H, OH), 7.65 (d, *J* = 7.5, H-9), 7.11-7.10 (dd, 1H, *J* =

7.5, *J* = 7.5, H-8), 6.45 (s, 1H, NH), 3.40 (d, 1H, *J* = 14.5, H-3a), 2.91 (d, 1H, *J* = 14.5, H-3b). ^{13}C NMR (DMSO-d_6) δ = 161.6 (C-2), 147.2 (C-5a), 145.7 (C-7), 137.0 (Ph), 136.8 (Ph), 135.4 (C-9a), 131.1 (Ph), 129.1 (Ph), 128.4 (C-9), 123.5 (q, ^1J = 288, CF_3), 117.7 (C-8), 92.3 (q, ^2J = 29, C-4), 34.1 (C-3). *Anal.* Calcd. for $C_{15}H_{11}ClF_3N_3O$ (341.05): C, 52.72; H, 3.24; N, 12.30%. Found: C, 52.34; H, 2.89; N, 12.25%.

2-(4-Bromophenyl)-4-trifluoromethyl-4,5-dihydro-3*H*-pyrido-[2,3-*b*]diazepin-4-ol (**4m**). This compound was obtained as gray solid, yields 66%, Mp. 145-147°C. ^{1}H NMR (DMSO-d_6) δ = 8.13 (d, *J* = 5, 1H, H-7), 7.96 (d, 2H, *J* = 9, Ph), 7.70 (d, 2H, *J* = 9, Ph, 1H, OH), 7.65 (d, *J* = 7.5, H-9), 7.12-7.10 (dd, 1H, *J* = 7.5, *J* = 7.5, H-8), 6.43 (s, 1H, NH), 3.40 (d, 1H, *J* = 14.5, H-3a), 2.92 (d, 1H, *J* = 14.5, H-3b). ^{13}C NMR (DMSO-d_6) δ = 161.7 (C-2), 147.2 (C-7), 145.7 (C-5a), 137.4 (Ph), 136.9 (C-9a), 131.7 (Ph), 131.3 (Ph), 129.3 (C-9), 124.4 (Ph), 123.6 (q, $^1J_{CF}$ = 288, CF_3), 117.7 (C-8), 92.3 (q, $^2J_{CF}$ = 29, C-4), 34.1 (C-3). *Anal.* Calcd. for $C_{15}H_{11}BrF_3N_3O$ (385.0): C, 46.65; H, 2.87; N, 10.88%. Found: C, 46.70; H, 2.54; N, 11.18%.

2-(4,4'-Biphenyl)-4-trifluoromethyl-4,5-dihydro-3*H*-pyrido-[2,3-*b*]diazepin-4-ol (**4n**). This compound was obtained as gray solid, yields 71%, Mp. 134-136°C. ^{1}H NMR (DMSO-d_6) δ = 8.14 (d, *J* = 5, 1H, H-7), 8,10 (Ph), 7.81 (d, *J* = 8, 3H, Ph), 7.76 (d, *J* = 8, 2H, Ph), 7.68 (m, 1H, Ph, 1H, OH), 7.50 (m, 3H, Ph), 7.42 (d, *J* = 7.5, H-9), 7.14-7.10 (dd, *J* = 7.5, *J* = 7.5, 1H, H-8), 6.45 (s, 1H, NH), 3.48 (d, *J* = 14, 1H, H-3a), 2.94 (d, *J* = 14, 1H, H-3b). ^{13}C NMR (DMSO-d_6) δ = 168.1 (Ph), 162.1 (C-2), 154.9 (Ph), 147.3 (C-5a), 145.4 (C-7), 141.9 (Ph), 139.3 (Ph), 137.1 (Ph), 136.7 (C-9a), 131.9 (C-9), 128.8 (Ph), 127.9 (Ph), 126.6 (Ph), 126.5 (Ph), 126.4 (Ph), 123.6 (q, CF_3, $^1J_{CF}$ = 288), 117.6 (C-8), 92.3 (q, C-4, $^2J_{CF}$ = 29), 34.1 (C-3). *Anal.* Calcd. for $C_{21}H_{16}F_3N_3O$ (383.12): C, 65.79; H, 4.21; N, 10.96%. Found: C, 65.45; H, 3.88; N, 11.13%.

2-(2-Furyl)-4-trifluoromethyl-4,5-dihydro-3*H*-pyrido[2,3-*b*]-diazepin-4-ol (**4p**). This compound was obtained as gray solid, yields 64%, Mp. 151-153°C. ^{1}H NMR (DMSO-d_6) δ = 8.08 (m, 1H, H-7), 7.90 (s, 1H, fr), 7.71 (s, 1H, H-9), 7,58 (d, *J* = 7.5, 1H, fr), 7.21 (m, 1H, H-6), 7.09 (dd, *J*= 7.5, *J*= 7.5, 1H, H-8), 6.68 (s, 1H, fr), 6.35 (s, 1H, fr), 3.37 (d, *J* = 14.5, 1H, H-3a), 2.87 (d, *J* = 14.5, 1H, H-3b). ^{13}C NMR (DMSO-d_6) δ = 152.8 (C-2), 147.3 (C-5a), 146.0 (C-7), 145.3 (fr), 136.6 (C-9a), 131.7 (C-9a), 123.7 (q, CF_3, $^1J_{CF}$ = 288), 117.7 (C-8), 113.9 (fr), 112.5 (fr), 92.0 (q, CF_3, $^2J_{CF}$ = 29), 34.6 (C-3). *Anal.* Calcd. for $C_{13}H_{10}F_3N_3O_2$ (297.07): C, 52.53; H, 3.39; N, 14.14%. Found: C, 52.21; H, 3.17; N, 13.97%.

2-(2-Thienyl)-4-trifluoromethyl-4,5-dihydro-3*H*-pyrido-[2,3-*b*]diazepin-4-ol (**4q**). This compound was obtained as gray solid, yields 67%, Mp. 129-131°C. ^{1}H NMR (DMSO-d_6) δ = 8.10 (d, *J* = 5, 1H, H-7), 7.75 (d, *J* = 5, 1H, tn), 7.68 (m, 2H, OH, tn), 7.57 (d, *J* = 7.5, H-9), 7.17 (t, *J* = 4.5, 1H, tn), 7.09-7.07 (dd, *J* = 7.5, *J* = 7.5, 1H, H-8), 3.50 (d, *J* = 14.5, 1H, H-3a), 2.90 (d, *J* = 14.5, 1H, H-3b). ^{13}C NMR (DMSO-d_6) δ = 157.4 (C-2), 147.4 (C-5a), 145.3 (C-7), 145.1 (tn), 136.4 (C-9a), 131.6 (C-9), 131.3 (tn), 129.9 (tn), 128.1 (tn), 123.6 (q, CF_3, $^1J_{CF}$ = 288), 117.6 (C-8), 91.8 (q, C-4, $^2J_{CF}$ = 29), 35.2 (C-3). *Anal.* Calcd. for $C_{13}H_{10}F_3N_3OS$ (313.05): C, 49.84; H, 3.22; N, 13.41%. Found: C, 49.60; H, 2.96; N, 13.07%.

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[33] Crystallographic data for compound **3i**, reported in this paper, have been deposited with the Cambridge Crystallographic Data Center (CCDC 687400). Copies of the data can be obtained, free of charge, on application to CCDC 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).