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Highly Chemoselective Synthesis of 6-Alkoxy-1-alkyl(aryl)-3-trifluoroacetyl-1,4,5,6-tetrahydropyridines and 1-Alkyl(aryl)-6-amino-3-trifluoroacetyl-1,4,5,6-tetrahydropyridines

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A simple and highly chemoselective method for the synthesis of a large series of novel 6-alkoxy-1-alkyl(aryl)-3-trifluoroacetyl-1,4,5,6-tetrahydropyridines and 1-alkyl(aryl)-6-amino-3-trifluoroacetyl-1,4,5,6-tetrahydropyridines, from the reaction of 6-alkoxy-3-trifluoroacetyl-4,5-dihydro-6*H*-pyrans with primary alkyl and arylamines, in good yields, is reported. Preliminary in vitro antimicrobial activity of the 1-alkyl(aryl)-6-amino-3-trifluoroacetyl-1,4,5,6-tetrahydropyridine series was assessed against a variety of microorganisms including yeast-like fungi, bacteria and algae, and some of these compounds exhibit significant antimicrobial activity.

Introduction

Tetrahydropyridines constitute an important class of organic compounds usually reported as potential therapeutic and pharmacological agents against Alzheimer's and Parkinson's[1] diseases and are used as experimental models for studying neurodegeneration.[2] In addition, tetrahydropyridines have been reported to exhibit important muscarinic,[1a,3] nicotinic,[4] analgesic,[5] hyperglycaemic,[5] antipsychotic[6] and antiproliferative[7] activity, as well as calcium ion flux regulation[4,8] and GABA inhibition.[6,9] Two tetrahydropyridines, 2-acetyl-1,4,5,6-tetrahydropyridine and 2-acetyl-3,4,5,6-tetrahydropyridine, reported as tautomeric structures and responsible for producing a mousy taint in wines, have been isolated from *Brettanomyces* and *Lactobacillus* yeasts.[10] Curiously enough, the same tautomeric tetrahydropyridines were recently identified as the major components of the cracker-like flavour in freshly baked bread.[11]

Tetrahydropyridines are usually prepared from the cyclocondensation of amines and carbonyl compounds,[12] cyclocondensation of δ-haloimines,[13] hydrogenation of pyridine salts,[14] Hantzsch's cyclisation[8a,15] as well as Diels–Alder[16] and Mukaiyama Michael reactions.[17] Most of these methods involve extensive synthetic routes, furnishing a mixture of products in low yields. Additionally, only few 1,4,5,6-tetrahydropyridines are described in the literature.[18]

Cyclic enones have been extensively used for the last few decades for obtaining a series of heterocyclic compounds such as isoxazoles,[19] pyrazoles,[20] pyrimidines,[21] 3-aminomethylene-dihydrofuran-2-ones,[22] analogues of cyclophosphamide,[23] furan-3-carboxamides[24] and 3-alkoxy-3-cyano carboxylic acids.[25] Although both the synthesis and applications of enones have been the subject of recent reviews,[26] 6-alkoxy-3-trifluoroacetyl-4,5-dihydro-6*H*-pyrans have been very little explored as starting reagents in organic synthesis. In a review of the literature, only four references were found. Three of them report Grignard reactions carried out with 6-alkoxy-3-trifluoroacetyl-4,5-dihydro-6*H*-pyrans **1** and **2** to obtain different compounds, depending on the nature of the Grignard reagent and the reaction conditions[27] and one reference reports the reactions of compounds **1** and **2** with hydroxylamine hydrochloride to selectively give fluorine-containing 4*H*-pyrano[3,2-*d*]isoxazoles or 4-(cyanoethyl)dihydroisoxazole in moderate to high yields.[28]

The use of cyclic enones such as 3-trihaloacetyl-4,5-dihydrofuran and 3-trihaloacetyl-5,6-dihydro-4*H*-pyran has been attracting much attention because these compounds can easily react with nucleophiles, generating new aliphatic or heterocyclic systems by a process that involves the opening of the furan or pyran ring by the nucleophile and the subsequent closure of the alkyl-hydroxy side chain.[9,27b,28,29] The two most widespread methods of introducing a trifluoroacetyl group in heterocycles are by direct trifluoroacetylation[30] and through a cyclocondensa-

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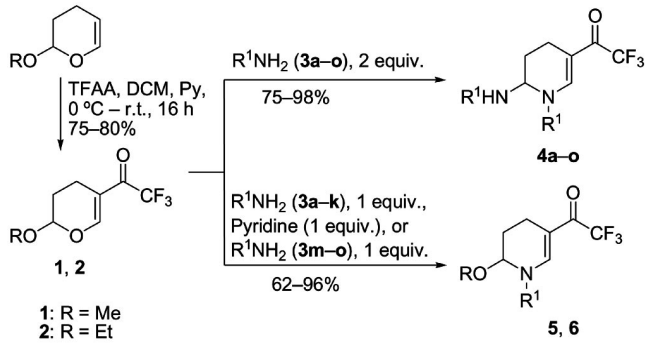
tion reaction of a bis(trifluoroacetyl)vinyl ether[31] or amine[32] with dinucleophiles. Other methods include oxidative dimerisation of 1,1,1-trifluoro-4-arylbut-3-yn-2-one, carried out by treatment with lead dioxide in a dichloromethane/trifluoroacetic acid mixture,[33] dipolar cycloaddition of diazo compounds[34] and azides[35] with α,β-unsaturated trifluoromethyl ketones,[36] photo-induced cyclisation of sulfimino uracil substituted with α,β-unsaturated trifluoromethyl ketones and intramolecular cyclisation of trifluoro(dimethoxyethylamino)alkenones.[37] Advances in the chemistry of α,β-unsaturated trifluoromethylketones have been the subject of a recent review.[26b]

In this study, a very simple and highly chemoselective method has been proposed for the synthesis of a wide range of 6-alkoxy-1-alkyl(aryl)-3-trifluoroacetyl-1,4,5,6-tetrahydropyridines and 1-alkyl(aryl)-6-amino-3-trifluoroacetyl-1,4,5,6-tetrahydropyridines from the reaction of the readily available 6-alkoxy-3-trifluoroacetyl-4,5-dihydro-6*H*-pyrans (cyclic enones) with primary alkyl and arylamines. In addition, a series of 1-alkyl(aryl)-6-amino-3-trifluoracetyl-1,4,5,6-tetrahydropyridines were assessed against a series of microorganisms including yeast-like fungi, bacteria and algae.

Results and Discussion

Scheme 1 outlines the synthesis of 1-alkyl(aryl)-6-amino-3-trifluoroacetyl-1,4,5,6-tetrahydropyridines **4** and 6-alkoxy-1-alkyl(aryl)-3-trifluoroacetyl-1,4,5,6-tetrahydropyridines **5** and **6** from the reaction of 6-alkoxy-3-trifluoroacetyl-4,5-dihydro-6*H*-pyrans **1** and **2** with primary alkyl and arylamines. In 2003, Zhu et al[38] reported the synthesis of pyrans **1** and **2** from a cyclocondensation reaction of β-alkoxyvinyl trifluoromethyl ketones with α,β-unsaturated carbonyl compounds. This reaction was carried out at high temperatures in a sealed tube for 8 hours and furnished low yields (30–42%). In this study, cyclic enones **1** and **2** were synthesised through the trifluoroacetylation of the parent 2-alkoxy-3,4-dihydro-2*H*-pyrans, in 75–80% yields, by a procedure similar to that described by Martins et al.[19]



Scheme 1. General scheme for the synthesis of all compounds.

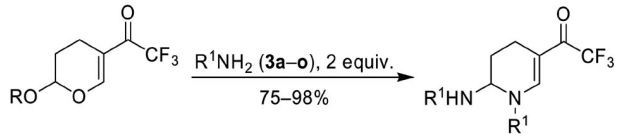
For the synthesis of compounds **4a**–**o**, reactions were carried out by stirring a mixture of enones **1** or **2** with primary amines in an appropriate solvent according to the conditions specified in Table 1. All reactions were tested with different solvents and reaction times and the yields and reaction conditions reported in Table 1 are the optimised results. The reactions were monitored by thin-layer chromatography by following the disappearance of the enones and formation of the products. It was observed that the more basic and volatile amines, such as methyl-, ethyl- and propylamines, gave better results in hexane while less reactive or bulkier amines furnished better results in more polar solvents, as shown in Table 1. Yields were very good for all amines tested. Table 1 shows that changing the 6-methoxy group to a 6-ethoxy group (compounds **1** and **2**) did not affect the reaction yields. Products **4** were isolated by evaporation of the solvent on a rotary evaporator and the resultant materials showed very good purity. The solid compounds were purified by recrystallisation from a mixture of dichloromethane and hexane and the oils were purified by filtration through a multilayer chromatography column composed (from the bottom to the top) of sodium sulfate, neutral alumina, active charcoal and neutral alumina. Although the solid compounds are stable, oily products are not very stable and they decomposed when purification was carried out using a silica gel chromatography column or if they were kept unrefrigerated for a few days.

Compound **4i** exhibited significant in vitro antimicrobial activity for most of the screened fungi and bacteria. In addition some compounds, such as **4f**, **4h**, **4j**, **4k** and **4l**, also exhibited relevant in vitro antimicrobial activity, though more selectively than compound **4i** for some kinds of fungi and/or bacteria.[39]

The structures of the 1-alkyl(aryl)-6-amino-3-trifluoroacetyl-1,4,5,6-tetrahydropyridines were examined by ^{1}H NMR spectroscopy and single-crystal X-ray diffraction. The interpretation of the coupling constants in the ^{1}H NMR spectra showed that the structure of **4d** is consistent with a half-chair conformation with the 6-amino group located at the axial position.[40] The position of the 6-amino group at the axial position is indicated by the coupling constant between H-6 and the vicinal H-5 and H-5′, where both coupling constants are very small and usually only a broad peak was observed for H-6. All other compounds obtained showed the same structural trend. The structure of **4d** was confirmed by single-crystal X-ray diffraction.[41]

Reactions of **1** or **2** with primary amines carried out in the same molar ratio furnished a mixture of disubstituted products **4**, monosubstituted compounds [6-alkoxy-1-alkyl(aryl)-3-trifluoroacetyl-1,4,5,6-tetrahydropyridines] as well as the starting enones. In this reaction, the formation of 6-amino-3-trifluoroacetyl-1,4,5,6-tetrahydropyrans was not observed. Much effort was made to stop the reaction at the first substitution in order to isolate pure 6-alkoxy-1-alkyl(aryl)-3-trifluoroacetyl-1,4,5,6-tetrahydropyridines. However, when the reaction of **1** or **2** with a series of pyridinylmethylamines (entries 13–18, Table 2) was carried out in an equivalent amount, the desired 6-alkoxy-1-(pyridinyl)-

Table 1. Optimised reaction conditions for the synthesis of **4a**–**o**.



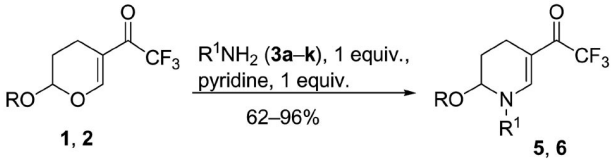
1, **2** **4a–o**

Entry	Enone[a]	R[1][b] and reaction conditions[c]	% Yield[d]	Product
1	**1**	Me	85	**4a**
2	**2**	Me	82	**4a**
3	**1**	Et	89	**4b**
4	**2**	Et	86	**4b**
5	**1**	Pr	95	**4c**
6	**2**	Pr	95	**4c**
7	**1**	C_6H_5	90	**4d**
8	**2**	C_6H_5	87	**4d**
9	**1**	$C_6H_5CH_2$	98	**4e**
10	**2**	$C_6H_5CH_2$	95	**4e**
11	**1**	$C_6H_5(CH_2)_2$	80	**4f**
12	**2**	$C_6H_5(CH_2)_2$	81	**4f**
13	**1**	2-Me-C_6H_5	95	**4g**
14	**2**	2-Me-C_6H_5	92	**4g**
13	**1**	4-Me-C_6H_5	92	**4h**
16	**2**	4-Me-C_6H_5	87	**4h**
17	**1**	2-OH-C_6H_5	89	**4i**
18	**2**	2-OH-C_6H_5	90	**4i**
19	**1**	4-MeO-C_6H_5	94	**4j**
20	**2**	4-MeO-C_6H_5	93	**4j**
21	**1**	4-Cl-C_6H_5	85	**4k**
22	**2**	4-Cl-C_6H_5	82	**4k**
23	**1**	pyridin-2-yl	75	**4l**
24	**2**	pyridin-2-yl	76	**4l**
25	**1**	(pyridin-2-yl)-CH_2	82	**4m**
26	**2**	(pyridin-2-yl)-CH_2	96	**4m**
27	**1**	(pyridin-3-yl)-CH_2	87	**4n**
28	**2**	(pyridin-3-yl)-CH_2	95	**4n**
29	**1**	(pyridin-4-yl)-CH_2	80	**4o**
30	**2**	(pyridin-4-yl)-CH_2	90	**4o**

[a] **1**: R = Me; **2**: R = Et. [b] Molar ratio enone/amine is 1:2, respectively. [c] Reaction conditions: entries 1–6: hexane, room temp., 4 h; entries 7–22: MeOH, room temp., 24 h; entries 23–24: MeCN, reflux, 24 h; entries 25, 27 and 29: EtOH, reflux, 24 h; entries 26, 28 and 30: MeOH, reflux, 24 h. [d] Yield of isolated product.

methyl-3-trifluoroacetyl-1,4,5,6-tetrahydropyridines **5m**–**o** and **6m**–**o** were isolated as pure compounds and in good yields. Amines **3m**–**o** bear a pyridine moiety which can capture an ionised hydrogen and act as a proton transfer agent. We therefore realised that in order to stop the reaction at the first substitution, when using amines **3a**–**k**, the addition of pyridine was necessary. Triethylamine was also used but failed to give the desired products **5** or **6**. Thus, when the reaction of 6-alkoxy-3-trifluoroacetyl-4,5-dihydro-6*H*-pyrans **1** or **2** with the other amines, such as **3a**–**k**, were carried out in the presence of an equivalent of pyridine, the corresponding products **5** or **6** were isolated, in good yields. Table 2 shows the optimised reaction conditions and yields for the synthesis of products **5** and **6**. Products **5** and **6** were isolated by evaporation of the solvent and the oils obtained were purified by filtration through a multilayer chromatography column as described for the purification of compounds **4**. The column was eluted with methanol or ethanol according to the alkoxy group present in the product **5** and **6**, respectively. Products **5** and **6** were obtained as oils and in good yields. The structures of the compounds **5** and **6** were confirmed by CG-MS as well as ^1H and ^{13}C NMR.

Table 2. Optimised reaction conditions for the synthesis of **5** and **6**.



1, **2** **5**, **6**

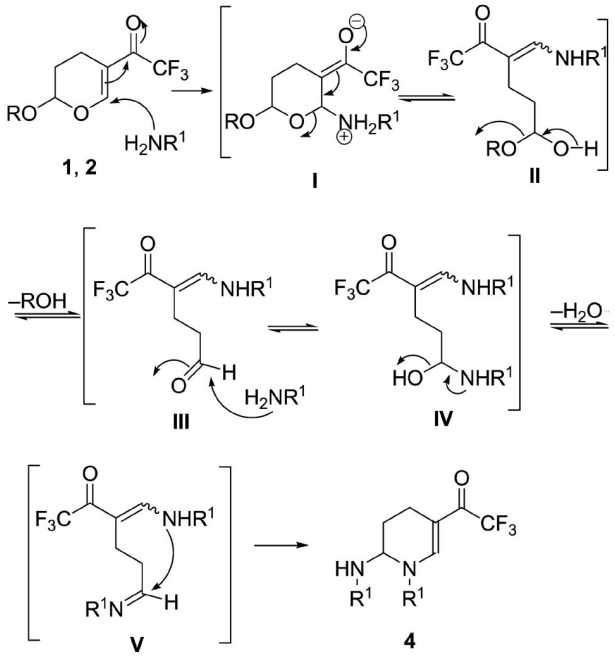
Entry	Enone[a]	R[1][b] and reaction conditions[c]	% Yield[d]	Product
1	**1**	Me	65	**5a**
2	**2**	Me	62	**6a**
3	**2**	Pr	67	**6c**
4	**1**	C_6H_5	69	**5d**
5	**2**	C_6H_5	68	**6d**
6	**1**	$C_6H_5CH_2$	82	**5e**
7	**1**	$C_6H_5(CH_2)_2$	71	**5f**
8	**2**	2-Me-C_6H_5	73	**6g**
9	**2**	4-Me-C_6H_5	62	**6h**
10	**1**	4-MeO-C_6H_5	70	**5j**
11	**2**	4-MeO-C_6H_5	67	**6j**
12	**2**	4-Cl-C_6H_5	68	**6k**
13	**1**	(pyridin-2-yl)-CH_2	82	**5m**
14	**2**	(pyridin-2-yl)-CH_2	96	**6m**
15	**1**	(pyridin-3-yl)-CH_2	87	**5n**
16	**2**	(pyridin-3-yl)-CH_2	95	**6n**
17	**1**	(pyridin-4-yl)-CH_2	80	**5o**
18	**2**	(pyridin-4-yl)-CH_2	90	**6o**

[a] **1**: R = Me; **2**: R = Et. [b] Molar ratio enone/amine/Py 1:1:1. [c] Reaction conditions: entries 1, 4, 6, 7 and 10: MeOH, Py, reflux, 48 h; entries 2, 3, 5, 8, 9, 11 and 12: EtOH, Py, reflux, 48 h; entries 13, 15 and 17: MeOH, reflux, 48 h; entries 14, 16 and 18: EtOH, reflux, 48 h. [d] Yield of isolated product.

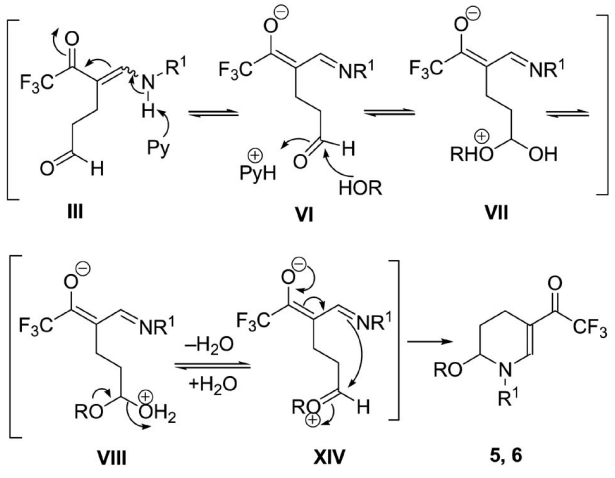
In further experiments, several compounds, **5**, were used as starting materials with the intention of carrying out substitution of the 6-methoxy group with alcohols and amines. First, we tried transetherification reactions in order to substitute the 6-methoxy group by other alkoxy groups. These reactions were carried out using alcohols such as 2-propanol, *tert*-butyl alcohol and propargyl alcohol as solvents and reflux times up to 70 hours. Similar reactions of compounds **5** with primary and secondary amines were carried out with solvents such as chloroform, methanol and acetonitrile, under reflux for up to 70 hours. Additionally, many reactions of compounds **5** with alcohols or primary and secondary amines were carried out in an appropriate solvent and in the presence of each one of these catalysts: *p*-toluenesulfonic acid, sulfuric acid, zinc chloride, zinc bromide, pyridine and triethylamine. In all these reactions, the desired products were not obtained and starting materials were always recovered.

Reaction Mechanism

A possible mechanism for the formation 1-alkyl(aryl)-6-amino-3-trifluoroacetyl-1,4,5,6-tetrahydropyridines is shown in Scheme 1. Presumably the reaction starts with the Michael addition of the primary amine at the carbon-2 of the 6-alkoxy-3-trifluoroacetyl-4,5-dihydro-6*H*-pyran giving the addition intermediate **I** which is in equilibrium with the acyclic structure **II**.[28] The hemiacetal **II** eliminates an alcohol molecule to form a more stable aldehyde **III**[28] which is attacked by the second amine nitrogen to give the corresponding hemiaminal **IV** that eliminates a water molecule to give the imine **V**. Subsequent attack of the enamine nitrogen on the imino group, followed by a 1,3-H shift, furnishes compounds **4** in high yields (Scheme 2).



Scheme 2. Reaction mechanism for the formation of compounds **4**.



Scheme 3. Reaction mechanism for the formation of compounds **5** or **6**.

For the mechanism of formation of compounds **5** or **6**, shown in Scheme 3, we speculate that the aldehyde **VI** in the presence of a protonated pyridine, the alcohol, used as solvent, adds to the carbonyl of the aldehyde to give the hemiacetal **VII** which tautomerises to form the structure **VIII**. This eliminates a water molecule to give the oxonium ion **XIV**, which undergoes intramolecular attack at the enamino group furnishing compounds **5** or **6**, in good yields. We believe that the pyridine works as a proton transfer agent.

Conclusions

In summary, we have shown a simple and highly chemoselective method for the synthesis of a large series of 6-alkoxy-1-alkyl(aryl)-3-trifluoroacetyl-1,4,5,6-tetrahydropyridines and 1-alkyl(aryl)-6-amino-3-trifluoroacetyl-1,4,5,6-tetrahydropyridines, from the reaction of 6-alkoxy-3-trifluoroacetyl-4,5-dihydro-6*H*-pyrans with primary alkyl and arylamines in good yields. In addition, some of the 1-alkyl(aryl)-6-amino-3-trifluoroacetyl-1,4,5,6-tetrahydropyridines exhibited significant in vitro antimicrobial activity.[39]

Experimental Section

Unless otherwise indicated, all commercial reagents and solvents were obtained from commercial suppliers and used without further purification. Thin-layer chromatography (TLC) was performed using silica gel plates GF_{254}, 0.25 mm thickness. For visualisation, TLC plates were either placed under ultraviolet light, or stained with iodine vapour. All melting points were determined on a Reichert Thermovar apparatus and are uncorrected. Elemental analyses were performed on a Vario EL Elementar Analysensysteme. High resolution mass spectra were recorded in ESI-mode. Mass spectra were registered on EI mode (70 eV) on an HP 5973 MSD instrument connected to an HP 6890 GC and interfaced with a Pentium PC. The GC was equipped with a split-splitless injector, autosampler, cross-linked HP-5 capillary column (30 m, 0.32 mm ID) and helium was used as the carrier gas. ^1H and ^{13}C NMR spectra were recorded on a Bruker DPX 400 spectrometer (^1H at 400.13 MHz and ^{13}C at 100.62 MHz) in $[D_6]$DMSO or $CDCl_3$ using TMS as the internal reference. Crystallographic measurements were made on a Bruker Kappa Apex II CCD area detector with graphite-monochromated Mo-K_α radiation (λ = 0.71073 Å). The structure was solved by direct methods (SHELXS-97) and additional atoms were located in the difference Fourier map and refined on F^2 (SHELXL-97).

General Procedure for the Synthesis of 6-Alkoxy-3-trifluoroacetyl-4,5-dihydro-6*H*-pyrans 1 and 2: A solution of trifluoroacetic anhydride (21.2 mL; 165 mmol) in anhydrous dichloromethane (70 mL) was poured into a two-necked round-bottomed flask equipped with an addition funnel, drying tube and under argon atmosphere. To the stirred solution, cooled to 0 °C, a solution of the appropriate 6-alkoxy-4,5-dihydro-6*H*-pyran (150 mmol) in anhydrous pyridine (13.4 mL, 165 mmol) was added dropwise. After the addition was completed, the reaction mixture was kept stirring for 16 h while being allowed to warm to room temperature. The reaction mixture was washed with distilled water (4 × 30 mL) and the combined water phases were extracted with dichloromethane (1 × 30 mL). The dichloromethane layers were combined, dried with anhydrous

sodium sulfate, filtered and the solvent removed using a rotary evaporator. Products **1** and **2** were obtained as colourless oils in yields of 80 and 75%, respectively. Subsequent purification was not required for compounds **1** and **2**.

3-Trifluoroacetyl-6-methoxy-4,5-dihydro-6*H*-pyran (1): This product was obtained as a colourless oil, yield 25.2 g (80%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72 (s, 1 H), 5.15 (t, J = 3.6 Hz, 1 H), 3.54 (s, 3 H), 2.38–2.33 (m, 2 H), 2.05–2.00 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.3 (q, $^2J_{C,F}$ = 34.6 Hz), 159.2, 117.7 (q, $^1J_{C,F}$ = 290.4 Hz), 112.4, 100.2, 56.2, 25.1, 14.3 ppm. GC-MS (EI 70 eV): *m*/*z* (%) = 210 (14) $[M]^+$, 179 (15), 141 (16), 69 (21), 58 (100). $C_8H_9F_3O_3$ (210.15): calcd. C 45.72, H 4.32; found C 45.98, H 4.47.

6-Ethoxy-3-trifluoroacetyl-4,5-dihydro-6*H*-pyran (2): This product was obtained as a colourless oil, yield 25.2 g (75%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71 (s, 1 H), 5.24 (t, J = 6.4 Hz, 1 H), 3.94–3.87 (m, 1 H), 3.71–3.65 (m, 1 H), 2.37 (dd, J = 6.0, J = 5.6 Hz, 2 H), 2.03–1.97 (m, 1 H), 1.88–1.82 (m, 1 H), 1.23 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.2 (q, $^2J_{C,F}$ = 34.7 Hz), 159.4, 116.7 (q, $^1J_{C,F}$ = 290.1 Hz), 111.9, 99.1, 64.9, 25.4, 14.9, 14.5 ppm. GC-MS (EI 70 eV): *m*/*z* (%) = 224 (22) $[M^+]$, 178 (54), 127 (15), 72 (100). $C_9H_{11}F_3O_3$ (224.17): calcd. C 48.22, H 4.95; found C 48.53, H 5.10.

General Procedure for the Synthesis of Tetrahydropyridines 4a–c: To a stirred solution of 6-alkoxy-3-trifluoroacetyl-4,5-dihydro-6*H*-pyran **1** or **2** (2.0 mmol) in hexane (15 mL), amines **3b**–**c** (4.0 mmol) were added dropwise and the reaction was stirred at room temperature for 4 h. For methylamine (**3a**) an excess (4.0 mmol) was used because this amine is volatile and marketed as an aqueous solution. For this reaction, the solvent used was methanol (15 mL). At the end of the reaction, the solvent was removed using a rotary evaporator and the residue was dissolved in dichloromethane (20 mL) and washed with water (1 × 20 mL) and the organic phase was dried with anhydrous sodium sulfate and the solvents evaporated. Products were obtained as red oils in yields of 85% to 95%.

3-Trifluoroacetyl-1-methyl-6-methylamino-1,4,5,6-tetrahydropyridine (4a): This compound was obtained as a red oil; yield 0.38 g (85%) (from **1**) and 0.37 g (82%) (from **2**). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.48 (s, 1 H), 3.95 (t, J = 3.1 Hz, 1 H), 3.23 (s, 3 H), 2.63–2.50 (m, 4 H), 2.22–2.02 (m, 2 H), 1.76–1.58 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.54 (q, $^2J_{C,F}$ = 32.0 Hz), 151.17, 118.00 (q, $^1J_{C,F}$ = 289.8 Hz), 102.2, 72.2, 42.54, 32.5, 24.4, 14.5 ppm. GC-MS (EI 70 eV): *m*/*z* (%) = 222 (24) $[M]^+$; 207 (0.02), 192 (94), 176 (5), 153 (7), 125 (24), 110 (5), 94 (44), 57 (100). HRMS (ESI) *m*/*z* calcd. for $C_9H_{13}F_3N_2O$ $[M + H]^+$: 223.1058, found 223.1053.

1-Ethyl-6-ethylamino-3-trifluoroacetyl-1,4,5,6-tetrahydropyridine (4b): This compound was obtained as a red oil; yield 0.45 g (89%) (from **1**) and 0.43 g (86%). (from **2**). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.53 (s, 1 H), 4.13 (t, J = 2.9 Hz, 1 H), 3.60–3.32 (m, 2 H), 2.78–2.56 (m, 3 H), 2.24–2.02 (m, 2 H), 1.71–1.54 (m, 1 H), 1.30–1.00 (m, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.5 (q, $^2J_{C,F}$ = 33.5 Hz), 149.8, 118.1 (q, $^1J_{C,F}$ = 289.5 Hz), 102.3, 68.8, 49.5, 40.4, 27.9, 25.5, 15.3, 14.6 ppm. GC-MS (EI 70 eV): *m*/*z* (%) = 250 (28) $[M]^+$; 206 (100), 176 (30), 153 (27), 136 (21), 108 (42). HRMS (ESI) *m*/*z* calcd. for $C_{11}H_{17}F_3N_2O$ $[M + H]^+$ 251.1371, found 251.1375

3-Trifluoroacetyl-1-propyl-6-propylamino-1,4,5,6-tetrahydropyridine (4c): This compound was obtained as a red oil; yield 0.53 g (95%) (from **1**) and 0.53 g (95%) (from **2**). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.50 (s, 1 H), 4.10 (br. s, 1 H), 3.58–3.44 (m, 1 H), 3.30–3.16 (m, 1 H), 2.68–2.58 (m, 3 H), 2.22–2.03 (m, 2 H), 1.74–1.41 (m, 5 H), 0.94 (t, J = 7.4 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.7 (q, $^2J_{C,F}$ = 30.0 Hz), 150.3, 118.1 (q, $^1J_{C,F}$ = 289.4 Hz), 101.8, 69.3, 56.6, 48.0, 25.4, 23.5, 22.7, 14.7, 11.5, 10.8 ppm. GC-MS (EI 70 eV): *m*/*z* (%) = 278 (30) $[M]^+$; 249 (5), 220 (100), 181 (43), 150 (25), 122 (27). HRMS (ESI) *m*/*z* calcd. for $C_{13}H_{21}F_3N_2O$ $[M + H]^+$ 279.1684, found 279.1678.

General Procedure for the Synthesis of Tetrahydropyridines 4d–k: To a stirred solution of pyran **1** or **2** (2.0 mmol) in methanol (15 mL), amines **3d**–**k** (4.0 mmol) were added dropwise. Amines such as **3j** and **3k** (4.0 mmol), which are solid, were dissolved in methanol (5 mL) and added to the solution of pyran through an addition funnel. The reactions were stirred at room temperature for 24 h. The solvent was removed using a rotary evaporator and the residue was dissolved in dichloromethane (20 mL) and washed with water (1 × 20 mL). The organic phase was dried with anhydrous sodium sulfate and the solvents evaporated. Product **4e** was obtained as an orange oil and products **4d**, **4f**–**k** were obtained as solids and were purified by recrystallisation from a mixture of hexane and dichloromethane. Compound **4e** was purified by filtration through a multilayer chromatography column composed (from the bottom to the top) of sodium sulfate, neutral alumina, active charcoal and neutral alumina. The column was eluted with methanol or ethanol.

1-Phenyl-6-phenylamino-3-trifluoroacetyl-1,4,5,6-tetrahydropyridine (4d): This compound was obtained as a white solid, yield 0.56 g (81%) (from **1**) and 0.52 g (75%) (from **2**), mp. 144–145 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.90 (s, 1 H), 7.37–7.33 (m, 2 H), 7.24–7.16 (m, 5 H), 6.78 (t, J = 7.6 Hz, 1 H), 6.64 (d, J = 7.6 Hz, 2 H), 5.47 (br. s, 1 H), 2.71 (dd, J_1 = 14.0, J_2 = 5.3 Hz, 1 H), 2.39–2.31 (m, 2 H), 1.92–1.83 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 176.8 (q, $^2J_{C,F}$ = 32.3 Hz), 146.4, 144.7, 144.4, 129.8, 129.5, 126.1, 120.9, 119.1, 114.1, 117 ppm. 7 (q, $^1J_{C,F}$ = 289.2 Hz), 105.7, 66.9, 25.1, 14.4. GC-MS (EI 70 eV): *m*/*z* (%) = 346 (9) $[M]^+$; 277 (0.05), 254 (100), 184 (3), 173 (0.02), 156 (33), 93 (11), 77 (35). $C_{19}H_{17}F_3N_2O$ (346.35): calcd. C 65.89, H 4.95, N 8.09; found C 65.68, H 5.00, N 8.22.

1-Benzyl-6-benzylamino-3-trifluoroacetyl-1,4,5,6-tetrahydropyridine (4e): This compound was obtained as a yellow solid, yield 0.67 g (90%) (from **1**) and 0.65 g (87%) (from **2**), mp. 103–104 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.64 (s, 1 H), 7.38–7.24 (m, 8 H), 7.06–7.02 (m, 2 H), 4.59 (d, J = 15.0 Hz, 1 H), 4.48 (d, J = 15.0 Hz, 1 H), 3.98 (t, J = 2.9 Hz, 1 H), 3.88 (d, J = 13.4 Hz, 1 H), 3.75 (d, J = 13.4 Hz, 1 H), 2.67–2.58 (m, 1 H), 2.27–1.98 (m, 2 H), 1.60–1.43 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 175.21 (q, $^2J_{C,F}$ = 31.6 Hz), 150.6, 139.3, 135.6, 128.9, 128.5, 128.2, 128.0, 127.5, 127.3, 118.0 (q, $^1J_{C,F}$ = 289.7 Hz), 102.4, 67.2, 58.2, 49.9, 24.7, 14.6 ppm. CG−MS (EI, 70 eV): *m*/*z* (%) = 374 (1) $[M]^+$; 305 (0.02), 283 (18), 198 (2), 176 (11), 108 (17), 91 (100). $C_{21}H_{21}F_3N_2O$ (374.40): calcd. C 67.37, H 5.65, N 7.48; found C 67.30, H 5.58, N 7.40.

1-(2-Phenylethyl)-6-(2-phenylethylamino)-3-trifluoroacetyl-1,4,5,6-tetrahydropyridine (4f): This compound was obtained as an orange oil, yield 0.79 g (98%) (from **1**) and 0.76 g (95%) (from **2**). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.34–7.16 (m, 9 H), 7.11–7.07 (m, 2 H), 3.89 (br. s, 1 H), 3.67 (dd, J = 14.0, J = 7.0 Hz, 1 H), 3.44 (dd, J = 14.0, J = 7.0 Hz, 1 H), 2.95–2.72 (m, 6 H), 2.48 (m, 1 H,), 2.08–1.83 (m, 2 H), 1.56–1.38 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 174.7 (q, $^2J_{C,F}$ = 31.7 Hz), 150.1, 139.3, 137.3, 128.6, 128.6, 128.4, 128.4, 126.8, 126.3, 117.9 (q, $^1J_{C,F}$ = 289.8 Hz), 102.1, 69.5, 55.8, 47.1, 36.5, 36.1, 25.1, 14.7 ppm. GC-MS (EI, 70 eV): *m*/*z* (%) = 402 (3) $[M]^+$; 333 (2), 305 (13), 282 (96), 212 (2),

105 (100), 91 (50), 79 (21). $C_{23}H_{25}F_3N_2O$ (402.45): calcd. C 68.64, H 6.26, N 6.96; found C 68.23, H 5.82, N 7.03.

1-(2-Methylphenyl)-6-(2-methylphenylamino)-3-trifluoroacetyl-1,4,5,6-tetrahydropyridine (4 g): This compound was obtained as a white solid, yield 0.71 g (95%) (from **1**) and 0.69 (92%) (from **2**), mp. 108–109 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.54 (s, 1 H), 7.21 (dd, J = 10.3, J = 3.3 Hz, 4 H), 7.02 (d, J = 7.4 Hz, 1 H), 6.86 (t, J = 7.5 Hz, 1 H), 6.63 (t, J = 7.3 Hz, 1 H), 6.22 (d, J = 8.0 Hz, 1 H), 5.31 (d, J = 9.6 Hz, 1 H), 4.02 (d, J = 9.4 Hz, 1 H), 2.92–2.83 (m, 1 H), 2.46–2.07 (m, 9 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 176.2 (q, $^2J_{C,F}$ = 32.1 Hz), 149.8, 143.8, 142.7, 134.2, 131.6, 130.5, 128.3, 127.2, 127.0, 126.8, 122.5, 118.6, 111.4, 117.7 (q, $^1J_{C,F}$ = 289.70 Hz), 103.0, 67.3, 26.3, 17.6, 17.3, 14.5 ppm. GC-MS (EI, 70 eV): m/z (%) = 374 (5) $[M]^+$; 345 (0.02), 305 (0.05), 268 (100), 198 (3), 170 (29), 91 (40). $C_{21}H_{21}F_3N_2O$ (374.40): calcd. C 67.37, H 5.65, N 7.48; found C 67.34, H 5.36, N 7.04.

1-(4-Methylphenyl)-6-(5-methylphenylamino)-3-trifluoroacetyl-1,4,5,6-tetrahydropyridine (4h): This compound was obtained as a yellow solid, yield 0.69 g (92%) (from **1**) and 0.65 g (87%) (from **2**), mp. 101–102 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.86 (s, 1 H), 7.14 (s, 4 H), 6.99 (d, J = 8.0 Hz, 2 H), 6.55 (d, J = 8.2 Hz, 2 H), 5.39 (br. s, 1 H), 3.93 (s, 1 H), 2.71 (m, 1 H), 2.33–2.24 (m, 8 H), 1.92–1.76 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 176.5 (q, $^2J_{C,F}$ = 32.0 Hz), 146.7, 142.4, 142.0, 136.1, 130.3, 130.0, 128.5, 120.9, 114.4, 117.7 (q, $^1J_{C,F}$ = 289.8 Hz), 105.2, 67.4, 25.0, 20.7, 20.3, 14.3 ppm. GC-MS (EI, 70 eV): m/z (%) = 374 (5) $[M]^+$; 345 (0.02), 268 (100), 198 (2), 170 (37), 91 (39). $C_{21}H_{21}F_3N_2O$ (374.40): calcd. C 67.37, H 5.65, N 7.48; found C 67.21, H 5.42, N 7.11.

1-(2-Hydroxyphenyl)-6-(2-hydroxyphenylamino)-3-trifluoroacetyl-1,4,5,6-tetrahydropyridine (4i): This compound was obtained as a brown solid, yield 0.67 g (89%) (from **1**) and 0.68 g (90%) (from **2**), mp. 143–144 °C. ^{1}H NMR (DMSO–d_6, 200 MHz): δ = 10.07 (s, 1 H), 9.34 (s, 1 H), 7.59 (s, 1 H), 7.28 (d, J = 7.8 Hz, 1 H), 7.12 (t, J = 7.6 Hz, 1 H), 6.93 (d, J = 8.0 Hz, 1 H), 6.78 (t, J = 7.5 Hz, 1 H), 6.64 (d, J = 7.0 Hz, 1 H), 6.47 (s, 3 H), 5.53 (d, J = 8.8 Hz, 1 H), 4.94 (d, J = 9.4 Hz, 1 H), 2.63–2.55 (m, 1 H), 2.34–2.09 (m, 2 H), 2.00–1.85 (m, 1 H) ppm. ^{13}C NMR ([D_6]DMSO, 100 MHz): δ = 174.0 (q, $^2J_{C,F}$ = 30.9 Hz), 152.0, 144.3, 134.0, 131.6, 128.6, 126.84, 119.5, 119.4, 117.7, 116.6, 114.1, 111.9, 151.1, 117.8 (q, J = 288.8 Hz), 102.4, 66.3, 25.5, 14.5 ppm. GC-MS (EI, 70 eV): m/z (%) = 377 (1) $[M - 1]^+$; 269 (100), 200 (99), 172 (25), 93 (9). $C_{19}H_{17}F_3N_2O_3$ (378.35): calcd. C 60.32, H 4.53, N 7.40; found C 60.12, H 4.67, N 7.23.

1-(4-Methoxyphenyl)-6-(4-methoxyphenylamino)-3-trifluoroacetyl-1,4,5,6-tetrahydropyridine (4j): This compound was obtained as a white solid, yield 0.76 g (94%) (from **1**) and 0.75 g (93%) (from **2**), mp. 110–111 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.78 (s, 1 H), 7.13 (d, J = 8.0 Hz, 2 H), 6.85 (d, J = 8.2 Hz, 2 H), 6.74 (d, J = 7.8 Hz, 2 H), 6.57 (d, J = 8.2 Hz, 2 H), 5.27 (br. s, 1 H), 3.78 (s, 3 H), 3.73 (s, 3 H), 2.78–2.67 (m, 1 H), 2.38–2.26 (m, 2 H), 1.94–1.81 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 176.3 (q, $^2J_{C,F}$ = 32.3 Hz), 158.1, 153.4, 138.5, 138.3, 123.4, 116.4, 115.0, 114.9, 147.4, 117.8 (q, $^1J_{C,F}$ = 290.0 Hz), 104.6, 69.0, 55.6, 55.5, 25.4, 14.3 ppm. GC-MS (EI, 70 eV): m/z (%) = 406 (7) $[M]^+$, 284 (100), 186 (34), 123 (73), 107 (13), 92 (9), 77 (17). $C_{21}H_{21}F_3N_2O_3$ (406,40): calcd. C 62.06, H 5.21, N 6.89; found C 61.85, H 5.24, N 6.86.

1-(4-Chlorophenyl)-6-(4-chlorophenylamino)-3-trifluoroacetyl-1,4,5,6-tetrahydropyridine (4k): This compound was obtained as a white solid, yield 0.71 g (85%) (from **1**) and 0.66 g (80%) (from **2**), mp. 128–129 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.79 (s, 1 H), 7.32 (d, J = 9.0 Hz, 2 H), 7.17–7.10 (m, 4 H), 6.58 (d, J = 8.6 Hz, 2 H), 5.38 (br. s, 1 H), 2.74–2.64 (m, 1 H), 2.37–2.25 (m, 2 H), 1.95–1.83 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 176.8 (q, $^2J_{C,F}$ = 31.3 Hz), 146.1, 143.1, 142.9, 129.9, 129.4, 129.0, 123.8, 122.3, 115.1, 117.5 (q, $^1J_{C,F}$ = 289.8 Hz), 106.0, 66.9, 25.1, 14.3 ppm. GC-MS (EI, 70 eV): m/z (%) = 414 (3) $[M]^+$; 288 (100), 207 (2), 190 (26), 111 (21). $C_{19}H_{15}Cl_2F_3N_2O$ (415.24): calcd. C 54.96, H 3.64, N 6.75; found C 54.94, H 3.75, N 6.79.

General Procedure for the Synthesis of Tetrahydropyridine 4l: To a stirred solution of pyran **1** or **2** (2.0 mmol) in acetonitrile (15 mL) was added a solution of amine **3l** (4.0 mmol) in acetonitrile (5 mL) dropwise and the reaction was heated to reflux for 24 h. The solvent was removed using a rotary evaporator and the residue was dissolved in dichloromethane (20 mL), washed with water (1 × 20 mL) and the organic phase was dried with anhydrous sodium sulfate and the solvents evaporated. Product **4l** was obtained as a solid and purified by recrystallisation from a mixture of hexane and dichloromethane.

6-(Aminopyrid-2-yl)-1-(pyrid-2-yl)-3-trifluoroacetyl-1,4,5,6-tetrahydropyridine (4l): This compound was obtained as a yellow solid, yield 0.57 g (82%) (from **1**) and 0.58 g (84%) (from **2**), mp. 150–152 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 9.15 (s, 1 H), 8.36–8.34 (m, 1 H), 8.17 (d, J = 4.0 Hz, 1 H), 7.68–7.59 (m, 1 H), 7.48–7.40 (m, 1 H), 7.27 (d, J = 8.2 Hz, 1 H), 7.05–7.00 (m, 1 H), 6.71–6.65 (m, 1 H), 6.53–6.49 (m, 2 H), 5.14 (d, J = 8.8 Hz, 1 H), 2.80–2.70 (m, 1 H), 2.40–2.28 (m, 2 H), 2.00–1.82 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 178.1 (q, $^2J_{C,F}$ = 32.8 Hz), 155.9, 152.5, 148.2, 147.7, 138.8, 137.7, 119.5, 114.2, 110.6, 109.2, 142.8, 117.5 (q, $^1J_{C,F}$ = 289.7 Hz), 107.5, 59.8, 25.79, 14.8 ppm. GC-MS (EI, 70 eV): m/z (%) = 348 (3) $[M]^+$, 254 (98), 157 (48), 78 (100). $C_{17}H_{15}F_3N_4O$ (348.32): calcd. C 58.62, H 4.34, N 16.08; found C 58.60, H 4.20, N 15.68.

General Procedure for the Synthesis of Tetrahydropyridines 4m–o: To a stirred solution of pyran **1** (0.42 g, 2.0 mmol) in methanol (8 mL) or pyran **2** (0.45 g, 2.0 mmol) in ethanol (8 mL), amines **3m–o** (0.43 g, 4.0 mmol) were added dropwise and the reaction was stirred at room temperature for 24 h. The solvent was removed using a rotary evaporator and the products were purified by filtration through a multilayer chromatography column composed (from the bottom to the top) of sodium sulfate, neutral alumina, active charcoal and neutral alumina and the column was eluted with methanol or ethanol. Products **4m–o** should be stored in a refrigerator to avoid decomposition.

2-(Aminopyrid-2-yl)methyl-1-(pyrid-2-yl)methyl-3-trifluoroacetyl-1,4,5,6-tetrahydropyridine (4m): This compound was obtained as a brown oil, yield 0.62 g (82%) (from **1**) and 0.68 g (90%) (from **2**). ^{1}H NMR (DMSO–d_6, 400 MHz): δ = 8.54 (d, J = 1.2 Hz, 1 H), 8.47 (d, J = 0.8 Hz, 1 H), 7.78–7.74 (m, 4 H), 7.44 (s, 1 H), 7.31–7.24 (m, 4 H), 4.82 (s, 2 H), 4.16 (br. s, 1 H), 3.94 (d, J = 14 Hz, 1 H); 3.89 (d, J = 4.0 Hz, 1 H), 2.36–2.35 (m, 1 H), 2.25–2.21 (m, 1 H), 1.98–1.93 (m, 1 H), 1.52–1.49 (m, 1 H) ppm. ^{13}C NMR ([D_6]-DMSO, 100 MHz): δ = 174.2 (q, $^2J_{C,F}$ = 31.6 Hz), 150.2, 150.0, 149.8, 146.3, 122.3, 146.3, 117.7 (q, $^1J_{C,F}$ = 292.7 Hz), 103.5, 85.1, 56.3, 55.1, 23.6, 13.7 ppm. GC-MS (EI, 70 eV): m/z (%) = 376 (3) $[M]^+$, 284 (13), 268 (10), 176 (9), 92 (100). HRMS (ESI) m/z calcd. for $C_{19}F_3H_{19}N_4O$ $[M + H]^+$ 377.1589, found 377.1580.

2-(Aminopyrid-3-yl)methyl-1-(pyrid-3-yl)methyl-3-trifluoraocetyl-1,4,5,6-tetrahydropyridine (4n): This compound was obtained as a brown oil, yield 0.62 g (83%) (from **1**) and 0.63 g (84%) (from **2**). ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 8.54 (s, 1 H), 8.52 (d, J = 4.0 Hz, 1 H), 8.42 (s, 1 H), 3.71–7.77 (d, J = 7.2 Hz, 2 H), 7.60 (s, 1 H), 7.39–7.35 (m, 2 H), 4.82 (d, J = 15.6 Hz, 1 H), 4.70 (d, J = 15.4 Hz, 1 H), 4.01 (br. s, 1 H), 3.86 (d, J = 13.6 Hz, 1 H), 3.76 (d,

J = 13.6 Hz, 1 H), 2.40–2.25 (m, 2 H), 2.24–1.98 (m, 1 H), 1.44 (br. s, 1 H) ppm. ^{13}C NMR ([D$_6$]DMSO, 100 MHz): δ = 173.1 (q, $^2J_{C,F}$ = 30.6 Hz), 151.4, 149.3, 148.9, 135.8, 135.6, 135.3, 132.4, 123.6, 123.2, 147.9, 117.9 (q, $^1J_{C,F}$ = 292.1 Hz), 102.2, 67.9, 54.0, 46.4, 24.7, 14.6 ppm. GC-MS (EI, 70 eV): m/z (%) = 376 (3) [M]$^+$, 284 (11), 268 (5), 176 (10), 92 (100). HRMS (ESI) m/z calcd. for $C_{19}F_3H_{19}N_4O$ [M + H]$^+$ 377.1589, found 377.1576.

6-(Aminopyrid-4-yl)methyl-1-(pyrid-4-yl)methyl-3-trifluoroacetyl-1,4,5,6-tetrahydropyridine (4o): This compound was obtained as a brown oil, yield 0.56 g (74%) (from **1**) and 0.57 g (76%) (from **2**). ^{1}H NMR ([D$_6$]DMSO, 400 MHz): δ = 8.54 (d, J = 1.6 Hz, 2 H), 8,46 (d, J = 1.2 Hz, 2 H), 7.79 (s, 1 H), 7.33 (d, J = 4.0 Hz, 2 H), 7.19 (d, J = 4.0 Hz, 2 H), 4.83 (d, J = 16.0 Hz, 1 H), 4.73 (d, J = 16.2 Hz, 1 H), 3.99 (br. s, 1 H), 3.85 (d, J = 15.2 Hz, 1 H), 3.75 (d, J = 15.2 Hz, 1 H), 2.43–2.28 (m, 2 H), 2.02–2.00 (m, 1 H), 1.56 (br. s, 1 H) ppm. ^{13}C NMR ([D$_6$]DMSO, 50 MHz): δ = 173.8 (q, $^2J_{C,F}$ = 31.0 Hz), 151.7, 150.9, 149.9, 149.3, 122.9, 122.3, 146.3, 117.9 (q, $^1J_{C,F}$ = 290.1 Hz), 103.6, 85.1, 68.4, 56.4, 23.6, 13.7 ppm. GC-MS (EI, 70 eV): m/z (%) = 376 (3) [M]$^+$, 284 (24), 268 (28), 176 (12), 107 (16), 92 (100). HRMS (ESI) m/z calcd. for $C_{19}F_3H_{19}N_4O$ [M + H]$^+$ 377.1589, found 377.1580.

General Procedure for the Synthesis of Tetrahydropyridines 5a, 5d–f, 5j and 6a, 6c–d, 6 g–h, 6j–k: To a stirred solution of pyran **1** (0.42 g, 2.0 mmol) in methanol (8 mL) or pyran **2** (0.45 g, 2.0 mmol) in ethanol (8 mL) and pyridine (0.17 mL, 2.0 mmol), the desired amines **3** (2.0 mmol) were added and the reaction was stirred and heated to reflux for 48 h. The solvent was partially evaporated and the residue was dissolved in chloroform (20 mL) and washed with water (2 × 20 mL). The combined organic phases were dried with anhydrous sodium sulfate and evaporated with a rotary evaporator. Products were purified by filtration through a multilayer chromatography column composed (from the bottom to the top) of sodium sulfate, neutral alumina, active charcoal and neutral alumina and the column was eluted with methanol or ethanol.

6-Methoxy-1-methyl-3-trifluoroacetyl-1,4,5,6-tetrahydropyridine (5a): This compound was obtained as a orange oil, yield 0.29 g (65%). ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 7.42 (s, 1 H), 4.38 (br. s, 1 H), 3.44 (s, 3 H), 3.23 (s, 3 H), 2.57–2.53 (m, 1 H), 2.20–2.16 (m, 2 H), 1.57–1.49 (m, 1 H,) ppm. ^{13}C NMR (CDCl$_3$, 100 MHz): δ = 175.2 (q, J = 32.2 Hz), 150.3, 117.7 (q, J = 292.1 Hz), 103.8, 86.8, 55.5, 43.3, 26.6, 13.4 ppm. GC-MS (EI, 70 eV): m/z (%) = 223 (23) [M]$^+$, 208 (3), 192 (46), 154 (43), 94 (100), 69 (63). HRMS (ESI) m/z calcd. for $C_9H_{12}F_3NO_2$ [M + H]$^+$ 224.0898, found 224.0887.

6-Methoxy-1-phenyl-3-trifluoroacetyl-1,4,5,6-tetrahydropyridine (5d): This compound was obtained as a brown oil, yield 0.38 g (67%). ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 7.83 (s, 1 H), 7.44–7.38 (m, 2 H), 7.32–7.26 (m, 3 H), 5.02 (br. s, 1 H), 3.37 (s, 3 H), 2.67–2.59 (m, 1 H), 2.39–2.32 (m, 2 H), 1.78–1.63 (m, 1 H) ppm. ^{13}C NMR (CDCl$_3$, 100 MHz): δ = 177.0 (q, J = 32.5 Hz), 146.5 (C-2), 145.3, 129.9, 126.1, 121.1, 117.5 (q, J = 291.7 Hz), 107.5, 86.5, 55.32, 23.95, 14.08 ppm. GC-MS (EI, 70 eV): m/z (%) = 285 (14) [M]$^+$, 270 (4), 192 (46), 254 (20), 216 (4), 184 (9), 156 (29), 77 (100). HRMS (ESI) m/z calcd. for $C_{14}H_{14}F_3NO_2$ [M + H]$^+$ 286.1055, found 286.1051.

1-Benzyl-6-methoxy-3-trifluoroacetyl-1,4,5,6-tetrahydropyridine (5e): This compound was obtained as a orange oil, yield 0.40 g (68%). ^{1}H NMR (CDCl$_3$, 200 MHz): δ = 7.56 (s, 1 H), 7.36 (m, 3 H), 4.64 (d, J = 15.2 Hz, 1 H), 4.50 (d, J = 15.2 Hz, 1 H), 4.36 (br. s, 1 H), 3.37 (s, 3 H), 2.63–2.51 (m, 1 H,), 2.30–2.11 (m, 2 H), 1.54–1.38 (m, 1 H) ppm. ^{13}C NMR (CDCl$_3$, 100 MHz): δ = 175.9 (q, J = 32.5 Hz), 149.9, 135.5, 129.1, 128.4, 127.6, 117.8 (q, J = 291.7 Hz), 104.5, 84.6, 58.5, 55.4, 23.9, 13.9 ppm. GC-MS (EI, 70 eV): m/z (%) = 299 (30) [M]$^+$, 268 (17), 230 (30), 208 (14), 176 (10), 108 (10), 91 (100). HRMS (ESI) m/z calcd. for $C_{15}H_{16}F_3NO_2$ [M + H]$^+$ 300.1211, found 300.1208.

1-Phenetyl-6-methoxy-3-trifluoroacetyl-1,4,5,6-tetrahydropyridine (5f): This compound was obtained as a brown oil, yield 0.51 g (82%). ^{1}H NMR (CDCl$_3$, 200 MHz): δ = 7.32–7.24 (m, 4 H), 7.17–7.13 (m, 2 H), 4.28 (br. s, 1 H), 3.69–3.58 (m, 2 H), 3.36 (s, 3 H), 2.91 (t, J = 7.0 Hz, 2 H), 2.55–2.46 (m, 1 H), 2.12–2.06 (m, 2 H), 1.42–1.26 (m, 1 H) ppm. ^{13}C NMR (CDCl$_3$, 100 MHz): δ = 175.6 (q, J = 31.8 Hz), 149.53, 137.3, 128.7, 126.9, 117.7 (q, J = 291.7 Hz), 104.1, 86.1, 56.7, 55.1, 36.4, 23.7, 13.7 ppm. GC-MS (EI, 70 eV): m/z (%) = 281 (74); 105 (100), 77 (48). $C_{16}H_{18}F_3NO_2$ (313.13): calcd. C 61.33, H 5.79, N 4.47; found C 61.34, H 5.68, N 4.36.

1-(4-Methoxyphenyl)-6-methoxy-3-trifluoroacetyl-1,4,5,6-tetrahydropyridine (5j): This compound was obtained as a brown oil, yield 0.48 g (77%). ^{1}H NMR (CDCl$_3$, 200 MHz): δ = 7.73 (s, 1 H), 7.17 (d, J = 9.0 Hz, 2 H), 6.94 (d, J = 9.0 Hz, 2 H), 4.92 (br. s, 1 H), 3.83 (s, 3 H), 3.35 (s, 3 H), 2.69–2.59 (m, 1 H), 2.37–2.30 (m, 2 H), 1.68–1.64 (m, 1 H) ppm. ^{13}C NMR (CDCl$_3$, 100 MHz): δ = 176.7 (q, J = 31.8 Hz), 147.3, 150.1, 138.8, 123.3, 116.4, 117.7 (q, J = 291.05 Hz), 106.6, 87.02, 55. 6, 24.12, 13.93 ppm. GC-MS (EI, 70 eV): m/z (%) = 315 (72) [M]$^+$, 300 (6), 284 (69), 122 (89), 107 (24), 58 (100). $C_{15}H_{16}F_3NO_3$ (315.11): calcd. C 57.14, H 5.12, N 4.44; found C 57.07, H 5.21, N 4.48.

6-Ethoxy-1-methyl-3-trifluoroacetyl-1,4,5,6-tetrahydropyridine (6a): This compound was obtained as an orange oil, yield 0.29 g (62%). ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 7.41 (s, 1 H), 4.45 (br. s, 1 H), 3.61 (m, 2 H,), 3.21 (s, 3 H), 2.58–2.54 (m, 1 H), 2.16–2.12 (m, 2 H), 1.57–1.53 (m, 1 H) e 1.25 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (CDCl$_3$, 100 MHz): δ = 174.9 (q, J = 31.7 Hz), 150.4, 117.7 (q, J = 291.7 Hz), 103.5, 85.3, 63.6, 42.0, 24.3, 15.0, 13.4 ppm. GC-MS (EI, 70 eV): m/z (%) = 237 (22) [M]$^+$, 208 (9), 192 (60), 168 (22), 140 (8), 94 (100), 69 (51). $C_{10}H_{14}F_3NO_2$ (237.22): calcd. C 50.63, H 5.95, N 5.90; found C 50.36, H 5.53, N 5.45.

6-Ethoxy-1-propyl-3-trifluoroacetyl-1,4,5,6-tetrahydropyridine (6c): This compound was obtained as an orange oil, yield 0.37 g (70%). ^{1}H NMR (CDCl$_3$, 200 MHz): δ = 7.46 (s, 1 H), 4.53 (br. s, 1 H), 3.63–3.5 (m, 2 H), 3.45–3.38 (m, 1 H), 3.30–3.23 (m, 1 H), 2.64–2.54 (m, 1 H), 2.25–2.06 (m, 2 H), 1.70–1.64 (m, 2 H), 1.53–1.44 (m, 1 H), 1.24 (t, J = 7.0 Hz, 3 H), 0.94 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (CDCl$_3$, 50 MHz): δ = 175.2 (q, J = 31.7 Hz), 150.2, 117.8 (q, J = 291.4 Hz), 103.5, 84.0, 63.2, 56.8, 24.41, 22.6, 15.1, 13.7, 10.62 ppm. GC-MS (EI, 70 eV): m/z (%) = 265 (29) [M]$^+$, 236 (11), 220 (100), 196 (29), 177 (28), 69 (57). HRMS (ESI) m/z calcd. for $C_{12}H_{18}F_3NO_2$ [M + H]$^+$ 266.1368, found 266.1361.

6-Ethoxy-1-phenyl-3-trifluoroacetyl-1,4,5,6-tetrahydropyridine (6d): This compound was obtained as a brown oil, yield 0.41 g (69%). ^{1}H NMR (CDCl$_3$, 200 MHz): δ = 7.83 (s, 1 H), 7.46–7.39 (m, 2 H), 7.32–7.22 (m, 3 H), 5.10 (s, 1 H), 3.60–3.49 (m, 2 H), 2.69–2.57 (m, 1 H), 2.43–2.28 (m, 2 H), 1.77–1,61 (m, 1 H), 1.21 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (CDCl$_3$, 50 MHz): δ = 176.9 (q, J = 32.3 Hz), 145.3, 146.7, 129.8, 126.1, 121.1, 117.6 (q, J = 291.7 Hz), 107.3, 85.2, 63.4, 24.6, 15.3, 14.14 ppm. GC-MS (EI, 70 eV): m/z (%) = 299 (90) [M]$^+$, 270 (28), 254 (100), 230 (22), 202 (7), 177 (57), 77 (98). HRMS (ESI) m/z calcd. for $C_{15}H_{16}F_3NO_2$ [M + H]$^+$ 300.1211, found 300.1207.

6-Ethoxy-1-(2-tolyl)-3-trifluoroacetyl-1,4,5,6-tetrahydropyridine (6g): This compound was obtained as an orange oil, yield 0.52 g (83%). ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 7.45 (s, 1 H), 7.29–7.26

(m, 4 H), 4.80 (br. s, 1 H), 3.47 (m, 2 H), 2.71–2.66 (m, 1 H), 2.41–2.33 (m, 1 H), 2.28 (s, 3 H), 1.80–1.69 (m, 2 H), 1.10 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 176.5 (q, J = 32.3 Hz), 149.5, 144.3, 134.3, 131.7, 128.2, 127.2, 126.9, 117.7 (q, J = 291.7 Hz), 105.2, 86.4, 64.6, 25.6, 17.9, 15.3, 14.0 ppm. GC-MS (EI, 70 eV): m/z (%) = 313 (27) $[M]^+$, 284 (7), 268 (45), 244 (6), 108 (100), 91 (43). HRMS (ESI) m/z calcd. for $C_{16}H_{18}F_3NO_2$ $[M + H]^+$ 314.1367, found 314.1364.

6-Ethoxy-1-(4-tolyl)-3-trifluoroacetyl-1,4,5,6-tetrahydropyridine (6h): This compound was obtained as an orange oil, yield 0.44 g (71%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.78 (s, 1 H), 7.22 (d, J = 8.8 Hz, 2 H), 7.12 (d, J = 8.4 Hz, 2 H), 5.07 (br. s, 1 H), 3.54–3.50 (m, 2 H), 2.66–2.61 (m, 1 H), 2.37 (s, 3 H), 2.33–2.29 (m, 1 H), 1.71–1,63 (m, 2 H), 1.20 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 176.7 (q, J = 32.5 Hz), 147.0, 143.0, 136.1, 130.3, 121.3, 117.6 (q, J = 291.7 Hz), 106.8, 85.3, 63.6, 24.74, 20.7, 15.3, 14.1 ppm. GC-MS (EI, 70 eV): m/z (%) = 313 (31) $[M]^+$, 298 (2), 284 (9), 268 (47), 170 (39), 107 (100). HRMS (ESI) m/z calcd. for $C_{16}H_{18}F_3NO_2$ $[M + H]^+$ 314.1367, found 314.1361.

6-Ethoxy-1-(4-methoxyphenyl)-3-trifluoroacetyl-1,4,5,6-tetrahydropyridine (6j): This compound was obtained as a brown oil, yield 0.41 g (63%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.72 (s, 1 H), 7.17 (d, J = 9 Hz, 2 H), 6.93 (d, J = 9 Hz, 2 H), 5.00 (br. s, 1 H), 3.83 (s, 3 H), 3.56–3.48 (m, 2 H), 2.66–2,61 (m, 1 H), 2.38–2.26 (m, 2 H), 1.72–1.63 (m, 1 H), 1.19 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 176.6 (q, J = 32.5 Hz), 147.6, 158, 138.7, 123.4, 114.8, 117.7 (q, J = 291.7 Hz), 106.4, 85.7, 63.7, 55.5, 24.8, 15.4, 14.0 ppm. GC-MS (EI, 70 eV): m/z (%) = 329 (55) $[M]^+$, 300 (13), 284 (53), 123 (100), 107 (9), 77 (20). HRMS (ESI) m/z calcd. for $C_{16}H_{18}F_3NO_3$ $[M + H]^+$ 330.1317, found 330.1308.

1-(4-Chlorophenyl)-6-ethoxy-3-trifluoroacetyl-1,4,5,6-tetrahydropyridine (6k): This compound was obtained as an orange oil, yield 0.49 g (73%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.74 (s, 1 H), 7.39 (d, J = 9.2 Hz, 2 H), 7.17 (d, J = 8.8 Hz, 2 H), 5.04 (br. s, 1 H), 3.59–3.49 (m, 2 H), 2.65–2,60 (m, 1 H), 2.39–2.32 (m, 2 H), 1.72–1,64 (m, 1 H), 1.22 (t, J = 6.8 Hz, 3 H,) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 177.1 (q, J = 32.7 Hz), 146.0, 143.8, 131.6, 129.9, 122.4, 117.5 (q, J = 289.9 Hz), 107.8, 85.2, 63., 24.5, 15.3, 14.0 ppm. GC-MS (EI, 70 eV): m/z (%) = 333 (24) $[M]^+$, 304 (8), 288 (46), 264 (6), 127 (100) [PB], 111 (34). HRMS (ESI) m/z calcd. for $C_{15}H_{15}ClF_3NO_3$ $[M + H]^+$ 334.0821, found 334.0812.

General Procedure for the Synthesis of Tetrahydropyridines 5m–o, 6m–o: To a stirred solution of pyran **1** (0.42 g, 2.0 mmol) in methanol (8 mL) or pyran **2** (0.45 g, 2.0 mmol) in ethanol (8 mL), amines **3m**–**o** (0.22 g, 2.0 mmol) were added and the reaction was stirred and heated to reflux for 24 h for the compounds **5m**–**o** and for 48 h for the compounds **6m**–**o**. The solvent was partially evaporated and the products were purified by filtration through a multilayer chromatography column composed upwards from sodium sulfate, neutral alumina, active charcoal and neutral alumina and the column was eluted with methanol or ethanol. Compounds **5m**–**o** and **6m**–**o** must be stored in a refrigerator to avoid decomposition.

6-Methoxy-1-(pyrid-2-yl)methyl-3-trifluoroacetyl-1,4,5,6-tetrahydropyridine (5m): This compound was obtained as a brown oil, yield 0.49 g (82%). ^{1}H NMR ([D$_6$]DMSO, 200 MHz): δ = 8.57 (d, J = 3.8 Hz, 1 H), 7.83 (dd, J = 7.6, J = 1.6 Hz, 2 H), 7.37 (s, 1 H), 7.33 (t, J = 7.8 Hz, 1 H), 4.92 (d, J = 15.4 Hz, 1 H), 4.78 (d, J = 15.6 Hz, 1 H), 4.64 (br. s, 1 H), 3.32 (s, 3 H), 2.42–2.35 (m, 1 H), 2.10–2.02 (m, 2 H), 1.44–1.40 (m, 1 H) ppm. ^{13}C NMR ([D$_6$]DMSO, 100 MHz): δ = 173.8 (q, $^2J_{C,F}$ = 31.1 Hz), 156.3, 151.2, 137.0, 122.8, 122.1, 151.1, 117.7 (q, $^1J_{C,F}$ = 292.3 Hz), 103.0, 85.3, 59.1, 55.0, 23.7, 13.8 ppm. GC-MS (EI, 70 eV): m/z (%) = 300 (24) $[M]^+$, 269 (15), 231 (19), 208 (20), 176 (54), 92 (100), 80 (5). HRMS (ESI) m/z calcd. for $C_{14}F_3H_{15}N_2O_2$ $[M + H]^+$ 301.1164, found 301.1159.

6-Methoxy-1-(pyrid-3-yl)methyl-3-trifluoroacetyl-1,4,5,6-tetrahydropyridine (5n): This compound was obtained as a brown oil, yield 0.49 g (87%). ^{1}H NMR ([D$_6$]DMSO, 200 MHz): δ = 8.57 (s, 1 H), 8.53 (d, J = 1.4 Hz, 1 H), 7.76 (d, J = 4.0 Hz, 1 H), 7.71 (s, 1 H), 7.42 (dd, J = 7.6, J = 4.6 Hz, 1 H), 4.87 (d, J = 15.4 Hz, 1 H), 4.74 (d, J = 15.4 Hz, 1 H), 4.60 (br. s, 1 H), 3.31 (s, 3 H), 2.49–2.33 (m, 1 H), 2.13–1.97 (m, 2 H), 1.44–1.34 (m, 1 H,) ppm. ^{13}C NMR ([D$_6$]-DMSO, 100 MHz): δ = 173.9 (q, $^2J_{C,F}$ = 31.9 Hz), 150.3, 139.5, 132.5, 123.6, 149.0, 117.6 (q, $^1J_{C,F}$ = 292.6 Hz), 103.4, 84.8, 55, 54.9, 23.5, 13.7 ppm. GC-MS (EI, 70 eV): m/z (%) = 300 (28) $[M]^+$, 268 (29), 231 (21), 208 (18), 176 (13), 92 (100). HRMS (ESI) m/z calcd. for $C_{14}F_3H_{15}N_2O_2$ $[M + H]^+$ 301.1164, found 301.1156.

6-Methoxy-1-(pyrid-4-yl)methyl-3-trifluoroacetyl-1,4,5,6-tetrahydropyridine (5o): This compound was obtained as a brown oil, yield 0.48 g (80%). ^{1}H NMR ([D$_6$]DMSO, 200 MHz): δ = 8.57 (d, J = 5.8 Hz, 2 H), 7.75 (s, 1 H), 7.28 (d, J = 5.4 Hz, 2 H), 4.92 (d, J = 16.2 Hz, 1 H), 4.76 (d, J = 16.0 Hz, 1 H), 4.56 (br. s, 1 H), 3.30 (s, 3 H), 2.39–2.36 (m, 1 H), 2.16–1.91 (m, 2 H), 1.53–1.44 (m, 1 H) ppm. ^{13}C NMR ([D$_6$]DMSO, 100 MHz): δ = 174.1 (q, $^2J_{C,F}$ = 31.9 Hz), 150.6, 149.8, 122.2, 146.2, 117.4 (q, $^1J_{C,F}$ = 291.8 Hz), 103.5, 84.9, 56.3, 54.9, 23,5, 13.7 ppm. GC-MS (EI, 70 eV): m/z (%) = 300 (23) $[M]^+$, 268 (29), 231 (21), 208 (18), 176 (13), 92 (100). HRMS (ESI) m/z calcd. for $C_{14}F_3H_{15}N_2O_2$ $[M + H]^+$ 301.1164, found 301.1156.

6-Ethoxy-1-(pyrid-2-yl)methyl-3-trifluoroacetyl-1,4,5,6-tetrahydropyridine (6m): This compound was obtained as a brown oil, yield 0.60 g (96%). ^{1}H NMR ([D$_6$]DMSO, 400 MHz): δ = 8.58 (d, J = 0.8 Hz, 1 H), 7.86–7.81 (m, 2 H), 7.42 (s, 1 H), 7.40–7.34 (m, 1 H), 4.90 (d, J = 15.6 Hz, 1 H), 4.79 (d, J = 15.6 Hz, 1 H), 4.72 (br. s, 1 H), 3.61–3.50 (m, 2 H), 2.43–2.38 (m, 1 H), 2.08–2.00 (m, 2 H, 4-H), 1.49–1.44 (m, 1 H) e 1.07 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR ([D$_6$]DMSO, 100 MHz): δ = 174.2 (q, $^2J_{C,F}$ = 30.9 Hz), 154.7, 151.7, 137.4, 123.2, 122.6, 149.7, 118.1 (q, $^1J_{C,F}$ = 292.7 Hz), 103.3, 84.3, 63.3, 59.4, 24.7, 15.5, 14.2 ppm. GC-MS (EI, 70 eV): m/z (%) = 314 (14) $[M]^+$, 269 (15), 245 (7), 222 (18), 177 (15), 92 (100). HRMS (ESI) m/z calcd. for $C_{15}F_3H_{17}N_2O_2$ $[M + H]^+$ 315.1320, found 315.1325.

6-Ethoxy-1-(pyrid-3-yl)methyl-3-trifluoroacetyl-1,4,5,6-tetrahydropyridine (6n): This compound was obtained as a brown oil, yield 0.60 g (95%). ^{1}H NMR ([D$_6$]DMSO, 400 MHz): δ = 8.57 (s, 1 H), 8.54 (d, J = 4.8 Hz, 1 H), 7.74 (d, J = 7.6 Hz, 1 H), 7.43 (t, J = 8 Hz, 1 H), 6.66 (s, 1 H), 4.82–4.78 (m, 2 H), 4.67 (br. s, 1 H), 3.59–3.43 (m, 2 H), 2.41–2.37 (m, 2 H), 1.51–1.39 (m, 2 H), 1.05 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR ([D$_6$]DMSO, 100 MHz): δ = 173.5 (q, $^2J_{C,F}$ = 30.3 Hz), 150.4, 150.3, 135.4, 132.4, 123.5, 148.9, 117.7 (q, $^1J_{C,F}$ = 292.0 Hz), 103.0, 83.6, 62.6, 54.8, 27.2, 14.9, 13.8 ppm. GC-MS (EI, 70 eV): m/z (%) = 314 (15) $[M]^+$, 269 (12), 245 (7), 222 (15), 177 (12), 92 (100). HRMS (ESI) m/z calcd. for $C_{15}F_3H_{17}N_2O_2$ $[M + H]^+$ 315.1320, found 315.1324.

6-Ethoxy-1-(pyrid-4-yl)methyl-3-trifluoroacetyl-1,4,5,6-tetrahydropyridine (6o): This compound was obtained as a brown oil, yield 0.57 g (90%). ^{1}H NMR ([D$_6$]DMSO, 400 MHz): δ = 8.57 (d, J = 5.6 Hz, 2 H), 7.75 (s, 1 H), 7.29 (d, J = 5.2 Hz, 2 H), 4.87 (d, J = 16.4 Hz, 1 H), 4.77 (d, J = 16.4 Hz, 1 H), 4.63 (br. s, 1 H), 3.59–3.45 (m, 2 H), 2.44–2.40 (m, 1 H), 2.10–2.06 (m, 2 H), 1.53–1.47 (m, 1 H), 1.06 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR ([D$_6$]DMSO, 100 MHz): δ = 173.9 (q, $^2J_{C,F}$ = 31.3 Hz), 150.4, 149.6, 122.2, 145.8, 117.4 (q, $^1J_{C,F}$ = 292.6 Hz), 102.5, 83.7, 62.8, 56.0, 24.2,

14.8, 13.7 ppm. GC-MS (EI, 70 eV): *m/z* (%) = 314 (31) $[M]^+$, 269 (46), 245 (15), 222 (32), 177 (26), 92 (100). HRMS (ESI) *m/z* calcd. for $C_{15}F_3H_{17}N_2O_2$ $[M + H]^+$ 315.1320, found 315.1317.

Biological Assays: The in vitro antimicrobial activity of the 1-alkyl(aryl)-6-amino-3-trifluoroacetyl-1,4,5,6-tetrahydropyridines was assessed against a selection of microorganisms including yeast-like fungi, algae and bacteria. The minimal inhibitory concentration (MIC) and minimal fungicidal, bactericidal and algacidal concentrations were determined by broth microdilution methods according to NCCLS standards.[42–44] Compounds were dissolved in DMSO and the solutions were diluted with a culture medium. By further progressive dilutions with the test medium, the required concentrations (320, 160, 80, 40, 20, 10, 5, 2.5 and 1.25 $\mu g\,mL^{-1}$) were obtained. The antimicrobial activities were evaluated based on the minimal inhibitory concentration (MIC) according to the NCCLS M27-A2 procedures[42] for yeast-like fungi and algae. For bacteria, the procedures described in NCCLS M7-A4[44] were employed. Bacteria were initially inoculated into Mueller-Hinton agar and, after overnight growth, four or five colonies were directly suspended in saline solution until the turbidity matched the turbidity of the McFarland standard (approximately 108 $cfu\,mL^{-1}$). The suspensions were diluted to 1:100 in saline followed by a new dilution to 1:20 in Mueller-Hinton broth, resulting in a final inoculum concentration of 5×104 $cfu\,mL^{-1}$ per well. Yeasts and *P. zopfii* were inoculated on potato dextrose agar and the procedures of inoculum standardisation were similar; the test medium was RPMI 1640 broth. Briefly, each well of the microdilution tray was filled with 100 µL of compound diluted in 100 µL of the inoculum. The plates were incubated at 35 °C / 24 h for the bacteria and *Candida* species; *S. cerevisae*, *C. neoformans* and *P. zopfii* required up to 72 h of incubation. Growth or a lack of growth in the wells containing the antimicrobial agent was determined by comparison with the growth control, indicated by turbidity. The lowest concentration that completely inhibited visible growth of the organism was recorded as the MIC. All tests were carried out in duplicate and accepted when coincident. When the tests were not coincident they were repeated in duplicate once more. The minimal fungicidal, bactericidal and algacidal concentrations were determined by subculture of 20 µL of the content of each well that remained clear. The media employed were Sabouraud dextrose agar for fungi and *P. zopfii* and Mueller–Hinton agar for bacteria. The plates were incubated at 35 °C during the same time periods for MIC determination and the lowest concentration required to demonstrate complete growth absence was named cidal. The interpretation of the results was based on fluconazole and amphotericin B breakpoints for the fungi and based on imipenem for bacterial pathogens all according to M27-A2,[42] M38-A[43] and M7-A4[44] techniques, respectively.

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