Synthesis of 1-Arylethyl-2-arylethylamino-5-trifluoroacetyl-1,2,3,4-tetrahydropyridines and Related Compounds with Potential Cell Efflux Pump Inhibition

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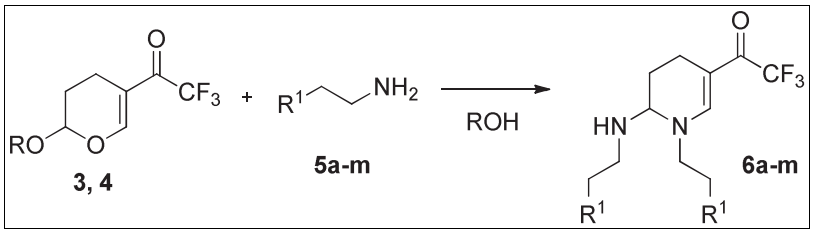

This study reports a simple, fast, and efficient method for the synthesis of a new series of 1-arylethyl-2-arylethylamino-5-trifluoroacetyl-1,2,3,4-tetrahydropyridines and related compounds from the reaction of 2-alkoxy-5-trifluoroacetyl-3,4-dihydro-2*H*-pyrans with 2-arylethanamines and related 2-ethanamines. The desired tetrahydropyridines were obtained in excellent yields (90–98%), through a reaction that can be described as an AAB′ three-component reaction protocol following an ANRORC-type mechanism.

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INTRODUCTION

Nitrogen heterocycles such as pyridines are present as basic skeleton of a series of compounds that exhibit significant medicinal properties [1,2]. Tetrahydropyridines, for example, are an important class of heterocycles that have potential therapeutic applications in the treatment of Parkinson's and Alzheimer's diseases [3]. Besides this, they possess anti-hyperglycemic [4], muscarinic [5], antipsychotic [6], antiproliferative [7], and antimalarial activity [8], and are also calcium ion efflux pump inhibitors [9].

Calcium channel antagonists [10] represent a heterogeneous group of drugs divided into four main families: dihydropyridine [11], phenylalkylamines [12], benzothiazepines [13], and tetralol [14]. Verapamil®, (shown in Fig. 1) [15], which belongs to the group known as phenylalkylamines, can inhibit P-glycoprotein mediated efflux and thus increase oral absorption of some compounds. In a previous study, we discovered a compound, which was designated as THP 124 (Fig. 1) that combines both phenylalkylamine and tetrahydropyridine scaffold and exhibited efflux pump inhibition four times higher than verapamil [16].

The most commonly used methods to synthesize tetrahydropyridines consist of reactions of imines with carbonyl compounds [17], the cyclocondensation of δ-haloimines [18], the hydrogenation of pyridine salts [19], Hantzsch cyclization reactions [20], and Diels-Alder reactions, as well as Michael Mukaiama reactions [20,21], which often consist of multistage reactions that lead to the desired tetrahydropyridines at low yields and with the formation of byproducts.

Although the syntheses of tetrahydropyridines have been reported since the late 19th century, methods to obtain 2-amino substituted tetrahydropyridines are scarce [22,22(a),22(b),23,24].

The introduction of a trifluoromethyl group into potentially bioactive compounds has become an important strategy to increase biological response [25] because the trifluoromethyl group has high electro-negativity, electron density, steric hindrance, and hydrophobic character, which can improve the pharmacokinetic profiles of potential drugs [26].

Although, many methods for trifluoromethylation of organic compounds have been developed [27], still the best methods for introducing a trifluoromethyl group into a molecule is through reactants containing the trifluoromethyl group, such as 4-alkoxy-1,1,1-trifluoroalk-3-en-2-ones (enones), which are easily obtained from the trifluoroacetylation of enol ethers or acetals [28]. The enones have proven to be useful precursor for the synthesis of a series of heterocycles [29] and other aliphatic compounds [30]. However, the synthetic potential of 2-alkoxy-5-trifluoroacetyl-3,4-dihydro-2*H*-pyrans as the starting material in organic synthesis has been explored very little [31,32]. Recently, our research group used 2-alkoxy-5-trifluoroacetyl-3,4-dihydro-2*H*-pyrans for the synthesis of an extensive series of tetrahydropyridines [23] and 6-trifluoroacetyl tetrahydropyridine oxa-geminated and aza-geminated heterocycles [24]. Many compounds of

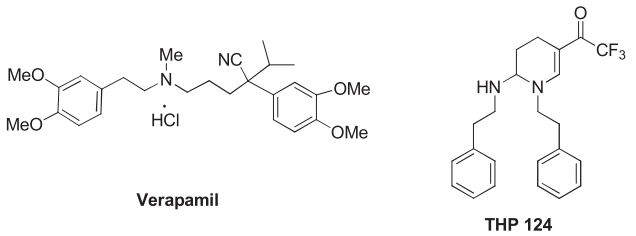


Figure 1. Structure of verapamil and tetrahydropyran-2-yl 124.

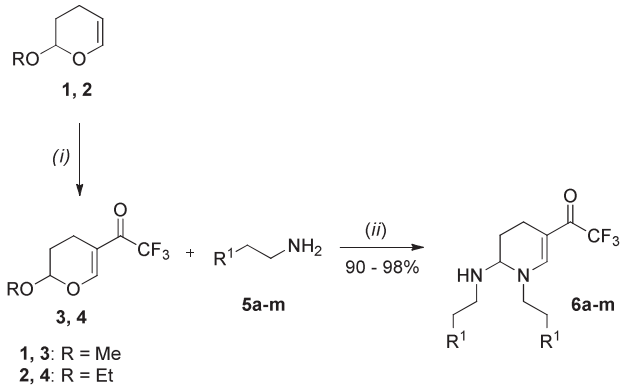
these two series showed cell efflux inhibition double that of the control drug verapamil and, in particular, the compound known as THP 124 (shown in Fig. 1) exhibited cell efflux inhibition four times higher than the control drug [16]. Thus, we decide to investigate how different substituents on the phenyl ring of the 2-arylethanamines and related 2-ethanamines portion could affect both the reactivity of the reaction and the biological response. Thus, in this study, we focus on a specific class of compounds that have similar structure of the model compound THP 124. This study allowed optimizing the reaction conditions and yields for the reaction of this specific class of amines with 2-alkoxy-5-trifluoroacetyl-3,4-dihydro-2*H*-pyrans that in the previous paper [23] was described, as a general procedure and carried out in 24 h. In the present study, the reaction time was optimized to 5 min. at room temperature and rendering excellent yields (≥90%).

RESULTS AND DISCUSSION

The cyclic enones **3** and **4** were obtained by acylation of 2-methoxy(ethoxy)-3,4-dihydro-2*H*-pyran (**1** and **2**) by trifluoroacetic anhydride under basic conditions as described by Okada et al. [30] and more recently by our research group [23,24]. The reaction of cyclic enones **3** and **4** with 2-substituted ethanamines was carried out in either methanol (for enone **3**) or ethanol (for enone **4**), at a molar ration 1:2 (enone:amine, respectively) at room temperature for 5 min, as shown in Scheme 1. The choosing of the solvent was carried out according to previous work reported by Zanatta et al., [23] in which methanol or ethanol was used as the ideal solvent. To avoid the mixture of products, methanol was used for the reaction of enone **3,** and ethanol was used for enone **4**. When a low polar solvent such as chloroform was used, the reaction time increased by approximately 75%. We speculate that polar solvents such as methanol and ethanol, besides solubilizing all the amines and enones used, increase the reaction rate by stabilizing the polar transition state.

Excellent yields of the expected 1-arylethyl-2-arylethylamino-5-trifluoroacetyl-1,2,3,4-tetrahydropyridines and related compounds **6a–m** was obtained for both enones **3** and **4** as shown in Table 1.

Scheme 1



1, 3: R = Me
2, 4: R = Et

i) TFAA, Py, $CHCl_3$, 0 - 25 ºC, 16 h. ref. [31]
ii) Reaction conditions: enone (1 equiv.), amine (2 equiv.), MeOH or EtOH, r.t., 5 min.
R^1 See Table 1.

Table 1

Optimized yields for the synthesis of tetrahydropyridines **6a–m.**

Entry	Enone[a]	Ethanamines (R^1)[b] (**3a–m**)	Yield[c] (%)	Product
1	**3**	2-$OMeC_6H_4$	90	**6a**
2	**4**	2-$OMeC_6H_4$	92	**6a**
3	**3**	4-$OMeC_6H_4$	97	**6b**
4	**4**	4-$OMeC_6H_4$	98	**6b**
5	**3**	3,4-$OMeC_6H_3$	91	**6c**
6	**4**	3,4-$OMeC_6H_3$	92	**6c**
7	**3**	4-FC_6H_4	90	**6d**
8	**4**	4-FC_6H_4	91	**6d**
9	**3**	2-ClC_6H_4	98	**6e**
10	**4**	2-ClC_6H_4	92	**6e**
11	**3**	3-ClC_6H_4	93	**6f**
12	**4**	3-ClC_6H_4	93	**6f**
13	**3**	4-ClC_6H_4	92	**6g**
14	**4**	4-ClC_6H_4	97	**6g**
15	**3**	2,4-ClC_6H_3	95	**6h**
16	**4**	2,4-ClC_6H_3	94	**6h**
17	**3**	4-OHC_6H_4	94	**6i**
18	**4**	4-OHC_6H_4	90	**6i**
19	**3**	2-Cyclohexenyl	94	**6j**
20	**4**	2-Cyclohexenyl	94	**6j**
21	**3**	*N*-morpholyl	95	**6k**
22	**4**	*N*-morpholyl	92	**6k**
23	**3**	$N(CH_2CH_3)_2$	95	**6l**
24	**4**	$N(CH_2CH_3)_2$	96	**6l**
25	**3**	1*H*-Indol-3-yl	92	**6m**
26	**4**	1*H*-Indol-3-yl	90	**6m**

[a]**3**: R = Me; **4**: R = Et.
[b]Reaction conditions: enone (1 equiv.), amine (2 equiv.), ROH, RT, 5 min.
[c]Yield of isolated products.

The reaction that furnishes the compounds **6** can be described as an AAB′ three-component reaction protocol [33], which follows an ANRORC-type mechanism [34]. The detailed mechanism of a similar reaction has been presented elsewhere and will not be discussed further in this study [23].

The products **6** were isolated by evaporation of the solvent on a rotary evaporator, and the resulting materials showed very good purity. The solid compounds were further purified by recrystallization from a mixture of chloroform and methanol (5:1), 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.

Tetrahydropyridines **6a–m** were identified by ^{1}H-NMR and ^{13}C-NMR techniques, liquid chromatography–mass spectrometry (LC-MS) [electrospray ionization (ESI) mode], gas chromatography–mass spectrometry [chemical ionization (CI) mode], and high resolution mass spectrometry analysis. The gas chromatography–mass spectrometry spectra registered in CI mode did not show the molecular ion, but instead showed a positive fragment originated from the loss of the 2-amino group. The LC-MS registered in ESI mode furnished the expected (M + H) ion and a main positive fragment assigned to the loss of the 2-amino group. The resonance signal of the N–H was not assigned because it is probably underneath to other hydrogens.

The structures of the tetrahydropyridines **6** were examined by ^{1}H-NMR spectroscopy. The interpretation of the coupling constants in the ^{1}H-NMR spectra showed that the structures of compounds **6** are consistent with a half-chair conformation for the tetrahydropyrimidine ring with the 2-amino group located at the axial position [23]. The position of the 2-amino group at the axial position was assigned by the coupling constant between H-2 and the vicinal H-3 and H-3′, in which both coupling constants are very small and usually only a broad peak was observed for H-2. All compounds obtained showed the same structural trend.

In conclusion, we have developed a simple, fast, and efficient ABB′ three-component protocol based on ANRORC-type mechanism for the preparation of a new series of 1-arylethyl-2-arylethylamino-5-trifluoroacetyl-1,2,3,4-tetra-hydropyridines and related compounds. The convenience of the reactions presented in this paper, in terms of: (i) requiring short reaction time (5 min.), (ii) mild reaction conditions (RT), (iii) easy isolation and purification, (iv) rendering high yields, and (v) wide scope of ethanamines that can be used in this reaction, call the attention for the potential of this chemistry for future developments of library of compounds through combinatorial chemistry.

EXPERIMENTAL

The 2-alkoxy-5-trifluoroacetyl-3,4-dihydro-2*H*-pyrans (**3** and **4**) were prepared according to the literature [23,30]. All melting points were determined using a Kofler Reichert Thermovar or on an MQAPF-301 apparatus and are uncorrected. LC mass spectra were registered on an LC-MS/MS Agilent 6460 in ESI mode. GC mass spectra were registered in CI mode, using methane as the ionizing gas, on an Agilent 5975B GC-MSD spectrometer. The GC was equipped with a split-splitless injector, auto-sampler, cross-linked HP-5 capillary column (30 m, 0.32 mm of internal diameter), and helium was used as the carrier gas. High resolution mass spectra were recorded using a Bruker Q-TOF spectrometer in ESI mode. ^{1}H-NMR and ^{13}C-NMR spectra were acquired using a Bruker DPX 200 spectrometer (^{1}H at 200.13 MHz and ^{13}C at 50.32 MHz) or a Bruker DPX 400 (^{1}H at 400.13 MHz and ^{13}C at 100.62 MHz) in $CDCl_3$ or DMSO-d_6 and using tetramethylslane as the internal reference.

General procedure for the synthesis of 1-arylethyl-2-arylethylamino-5-trifluoroacetyl-1,2,3,4-tetrahydropyridi-nes and related compounds. Ethanamines **5a–m** (2.0 mmol) were added to a solution of either enone **3** (1.0 mmol, 0.210 g) in methanol (3 mL) or enone **4** (1.0 mmol, 0.224 g) in ethanol (3 mL), and the solution was stirred at room temperature for 5 min. The solvent was evaporated, the solid products were purified by recrystallization from a mixture of chloroform and methanol (5:1), 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. A mixture of chloroform and methanol 5:1 was used as the eluent. The solvent was evaporated, and the product was stored in a desiccator, under vacuum, for the complete removal of solvent. Compounds **6a–m** were obtained in 90–98% yields. Compounds **6a–m** are hygroscopic, and they require storage under refrigeration to prevent decomposition.

5-Trifluoroacetyl-2-N-(2-methoxyphenethylamino)-1-(2-methoxyphenethyl)-1,2,3,4-tetrahydropyridine (6a). This compound was obtained as a yellow oil in 90% yield from **3** and 92% from **4**. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 7.24–7.10 (m, 3H, H-6, Ar), 7.01–6.82 (m, 6H, Ar), 4.01 (t, 1H, *J* = 2.6 Hz, H-2), 3.76–3.78 (s, 6H, OMe), 3.72–3.68 (m, 1H, H-7), 3.48–3.41 (m, 1H, H-7), 2.87–2.78 (m, 8H, H-7′, H-8, H-8′), 2.49–2.45 (m, 1H, H-4), 2.03–2.01 (m, 1H, H-3), 1.92–1.83 (m, 1H, H-4), 1.45–1.41 (m, 1H, H-3). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 174.4 (q, $^2J_{C–F}$ = 31.4, C=O), 157.3, 157.2, 130.6, 130.1, 128.3, 127.6, 125.3, 120.5, 120.4, 110.2 (12C, Ar), 150.4 (C-6), 119.5 (q, $^1J_{C–F}$ = 292.0, CF_3), 102.0 (C-5), 69.6 (C-2), 55.0 (2C, OMe), 54.5 (C-7) 45.9 (C-7′), 31.4 (C-8), 31.1 (C-8′), 25.3 (C-3), 14.1 (C-4). MS (ESI): *m/z*: 463 $[M + H]^+$. HRMS (ESI): *m/z* calcd for $C_{25}H_{30}F_3N_2O_3$ [M + H]: 463.2208; found: 463.2205.

5-Trifluoroacetyl-2-N-(4-methoxyphenethylamino)-1-(4-methoxyphenethyl)-1,2,3,4-tetrahydropyridine (6b). This compound was obtained as a yellow solid in 97% yield from **3** and 98% from **4**, mp 72–75°C. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 7.27 (s, 1H, H-6), 7.07 (d, 2H, *J* = 7.6, Ar), 6.98 (d, 2H, *J* = 7.6, Ar), 6.81 (d, 4H, *J* = 8.0, Ar), 3.90 (t, 1H, *J* = 3.2, H-2), 3.75 (s, 6H, OMe), 3.64–3.59 (m, 1H, H-7), 3.42–3.7 (m, 1H, H-7), 2.90–2.82 (m, 2H, H-7′), 2.78–2.73 (m, 2H, H-8), 2.68 (t, 2H, *J* = 6.8, H-8′), 2.49–2.45 (m, 1H, H-4), 2.07–1.99 (m, 1H, H-3), 1.90–1.86 (m, 1H, H-4), 1.54–1.45 (m, 1H, H-3). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 174.7 (q, $^2J_{C–F}$ = 31.2, C=O), 158.6, 158.2, 131.3, 129.5, 129.3, 114.2, 113.9 (12C, Ar), 150.1 (C-6), 118.0 (q, $^1J_{C–F}$ = 296.2, CF_3), 102.0 (C-5), 69.6 (C-2), 55.9 (C-7), 55.1, 55.0 (2C, OMe), 47.2 (C-7′), 35.6 (C-8), 35.2 (C-8′), 25.3 (C-3), 14.8 (C-4). MS (ESI): *m/z*: 463 $[M + H]^+$. HRMS (ESI): *m/z* calcd for $C_{25}H_{30}F_3N_2O_3$ [M + H]: 463.2208; found: 463.2205.

5-Trifluoroacetyl-2-N-(3,4-dimethoxyphenethylamino)-1-(3,4-dimethoxyphenethyl)-1,2,3,4-tetrahydropyridine (6c). This compound was obtained as a yellow oil in 91% yield from **3** and 92% from **4**. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 7.28 (s, 1H, H-6), 6.80–6.63 (m, 6H, Ar), 3.95 (t, 1H, *J* = 2.8, H-2), 3.84 (brs, 12H, OMe), 3.81–3.76 (m, 1H, H-7), 3.50–3.43 (m, 1H, H-7), 2.93–2.86 (m, 2H, H-7′), 2.79 (t, *J* = 6.8, 2H, H-8), 2.73 (t, 2H, *J* = 7.2, H-8′), 2.52–2.48 (m, 1H, H-4), 2.08–2.01 (m, 1H, H-3), 1.97–1.93 (m, 1H, H-4), 1.55–1.46 (m, 1H, H-3). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 174.9 (q, $^2J_{C–F}$ = 32.2, C=O), 150.0 (C-6), 149.1, 148.9, 148.0, 147.5, 131.6, 129.7, 122.2, 120.8, 120.3, 111.9, 111.5, 111.2 (12C, Ar), 119.3 (q, $^1J_{C–F}$ = 289.8, CF_3), 102.1 (C-5), 69.5 (C-2), 56.0 (C-7), 55.7 (4C, OMe), 47.3 (C-7′), 35.9 (C-8), 35.7 (C-8′), 25.1 (C-3), 14.6 (C-4). MS (ESI): *m/z*: 523 $[M+H]^+$. HRMS (ESI): *m/z* calcd for $C_{27}H_{34}F_3N_2O_5$ $[M+H]^+$: 523.2420; found: 523.2418.

5-Trifluoroacetyl-2-N-(4-fluorophenethylamino)-1-(4-fluorophenethyl)-1,2,3,4-tetrahydropyridine (6d). This compound was obtained as a light yellow oil in 90% yield from **3** and 91% from **4**. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 7.26 (s, 1H, H-6), 7.14–6.93 (m, 8H, Ar), 3.90 (t, 1H, *J* = 3.6, H-2), 3.68–3,51 (m, 1H, H-7), 3.45–3.38 (m, 1H, H-7), 2.93–2.91 (m, 2H, H-7′), 2.84–2.79 (m, 2H, H-8), 2.73 (t, 2H, *J* = 6.8, H-8′), 2.51–2.46 (m, 1H, H-4), 2.08–2.01 (m, 1H, H-3), 1.94–1.88 (m, 1H, H-4), 1.55–1.48 (m, 1H, H-3). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 175.1 (q, $^2J_{C–F}$ = 30.0, C=O), 161.9 (d, $^1J_{C–F}$ = 246.0 , Ar), 161.6 (d, $^1J_{C–F}$ = 247.0, Ar), 149.9 (C-6), 135.2, 133.3, 130.2–129.9, (6C, Ar), 116.0–113.0 (4C, Ar) 119.4 (q, $^1J_{C–F}$ = 290.1, CF_3), 102.4 (C-5), 69.8 (C-2), 55.7 (C-7), 47.3 (C-7′), 35.9 (C-8), 35.3 (C-8′), 25.4 (C-3), 14.9 (C-4). MS (ESI): *m/z*: 439 $[M+H]^+$. HRMS (ESI): *m/z* calcd for $C_{23}H_{24}F_5N_2O$: $[M+H]^+$: 439.1809; found: 439.1808.

5-Trifluoroacetyl-2-N-(2-chlorophenethylamino)-1-(2-chlorophenethyl)-1,2,3,4-tetrahydropyridine (6e). This compound was obtained as a light yellow oil in 98% yield from **3** and 92% from **4**. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ = 7.25–6.95 (m, 9H, H-6, Ar), 3.90 (t, 1H, *J* = 3.6, H-2), 3.73–3.59 (m, 1H, H-7), 3.49–3.36 (m, 1H, H-7), 2.97–2.91 (m, 2H, H-7′), 2.85–2.69 (m, 4H, H-8, H-8′), 2.56–2.45 (m, 1H, H-4), 2.10–2.02 (m, 1H, H-3), 1.90–1.88 (m, 1H, H-4), 1.59–1.51 (m, 1H, H-3). ^{13}C-NMR ($CDCl_3$, 50 MHz): δ = 175.7 (q, $^2J_{C–F}$ = 31.4, C=O), 150.1 (C-6), 141.4, 139.4, 134.4, 134.1, 129.9, 129.6, 128.7, 128.6, 127.0, 126.8, 126.7, 126.4 (12C, Ar), 120.7 (q, $^1J_{C–F}$ = 292.0, CF_3), 102.1 (C-5), 69.6 (C-2), 55.4 (C-7), 46,8 (C-7′), 36.2 (C-8), 35.7 (C-8′), 25.0 (C-3), 14.7 (C-4). MS (ESI): *m/z*: 471 $[M+H]^+$, 473 $[M+H+2]^+$, 475 $[M+H+4]^+$. HRMS (ESI): *m/z* calcd for $C_{23}H_{24}Cl_2F_3N_2O$ $[M+H]^+$: 471.1218; found: 471.1209.

5-Trifluoroacetyl-2-N-(3-chlorophenethylamino)-1-(3-chlorophenethyl)-1,2,3,4-tetrahydropyridine (6f). This compound was obtained as a light yellow oil in 93% yield from both **3** and **4**. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ = 7.24–6.95 (m, 9H, H-6, Ar), 3.89 (t, 1H, *J* = 3.4, H-2), 3.73-3.49 (m, 1H, H-7) 3.50-3.36 (m, 1H, H-7), 2.99–2.89 (m, 2H, H-7′), 2.84–2.72 (m, 4H, H-8, H-8′), 2.58–2.44 (m, 1H, H-4), 2.11–1.89 (m, 2H, H-3, H-4), 1.65–1.44 (m, 1H, H-3). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 174.3 (q, $^2J_{C–F}$ = 32.7, C=O), 158.8 (C-6), 137.7, 135.6, 135.3, 134.7, 133.1, 132.8, 131.0, 129.9, 129.6, 129.3, 127.4, 126.9 (12C, Ar), 119.4 (q, $^1J_{C–F}$ = 290.2, CF_3), 101.9 (C-5), 68.6 (C-2), 54.5 (C-7), 44.4 (C-7′), 33.9 (C-8), 33.5 (C-8′), 25.4 (C-3), 14.6 (C-4). MS (ESI): *m/z*: 471 $[M+H]^+$, 473 $[M+H+2]^+$, 475 $[M+H+4]^+$. HRMS (ESI): *m/z* calcd for $C_{23}H_{24}Cl_2F_3N_2O$ $[M+H]^+$: 471.1218; found: 471.1211.

5-Trifluoroacetyl-2-N-(4-chlorophenethylamino)-1-(4-chlorophenethyl)-1,2,3,4-tetrahydropyridine (6g). This compound was obtained as a light yellow oil in 92% yield from **3** and 97% from **4**. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ = 7.38–7.02 (m, 9H, H-6, Ar), 3.95 (t, 1H, *J* = 3.2 Hz, H-2), 3.78–3.64 (m, 1H, H-7), 3.51–3.37 (m, 1H, H-7), 2.98–2.85 (m, 6H, H-7′, H-8, H-8′), 2.58–2.48 (m, 1H, H-4), 2.17–2.05 (m, 1H, H-3), 2.01–1.89 (m, 1H, H-4), 1.65–1.49 (m, 1H, H-3). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 175.7 (q, $^2J_{C–F}$ = 31.4, C=O), 159.4 (C-6), 135.2, 134.8, 134.6, 133.9, 133.6, 132.2, 130.8, 130.5, 129.6, 129.3, 127.2, 127.0 (12C, Ar), 119.8 (q, $^1J_{C–F}$ = 289.2, CF_3), 101.5 (C-5), 69.7 (C-2), 53.3 (C-7), 45.4 (C-7′), 34.1 (C-8), 33.6 (C-8′), 25.2 (C-3), 14.6 (C-4). MS (ESI): *m/z*: 471 $[M+H]^+$, 473 $[M+H+2]^+$, 475 $[M+H+4]^+$. HRMS (ESI): *m/z* calcd for $C_{23}H_{24}Cl_2F_3N_2O$ $[M+H]^+$: 471.1218; found: 471.1215.

5-Trifluoroacetyl-2-N-(2,4-dichlorophenethylamino)-1-(2,4-dichlorophenethyl)-1,2,3,4-tetrahydropyridine (6h). This compound was obtained as a light yellow oil in 95% yield from **3** and 94% from **4**. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ = 7.37–7.09, (m, 7H, H-6, Ar), 3.98 (t, 1H, *J* = 3.4, H-2), 3.87–3.68 (m, 1H, H-7), 3.53–3.39 (m, 1H, H-7), 3.00–2.87 (m, 6H, H-7′, H-8, H-8′), 2.57–2.45 (m, 1H, H-4), 2.15–2.06 (m, 1H, H-3), 1.98–1.87 (m, 1H, H-4), 1.62–1.51 (m, 1H, H-3). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 175.3 (q, $^2J_{C–F}$ = 32.9, C=O), 159.8 (C-6), 135.7, 134.6, 134.5, 133.7, 133.5, 132.8, 131.7, 131.5, 129.6, 129.3, 127.4, 127.0 (12C, Ar), 119.4 (q, $^1J_{C–F}$ = 291.2, CF_3), 102.5 (C-5), 69.6 (C-2), 53.5 (C-7), 45.4 (C-7′), 34.0 (C-8), 33.7 (C-8′), 25.4 (C-3), 14.8 (C-4). MS (ESI): *m/z*: 541 $[M+H]^+$, 543 $[M+H+2]^+$, 545 $[M+H+4]^+$, 547 $[M+H+6]^+$, 549 $[M+H+8]^+$. HRMS (ESI): *m/z* calcd for $C_{23}H_{22}Cl_4F_3N_2O$ $[M+H]^+$: 541.2403; found: 541.0417.

5-Trifluoroacetyl-2-N-(4-hydroxyphenethylamino)-1-(4-hydroxyphenethyl)-1,2,3,4-tetrahydropyridine (6i). This compound was obtained as a light yellow solid, hygroscopic, in 94% yield: from **3** and 90% from **4**. ^{1}H-NMR (DMSO-d_6, 400 MHz): δ = 7.32 (s, 1H, H-6), 7.01–6.96 (m, 4H, Ar), 6.69 (d, 4H, Ar) 4.09 (t, 1H, *J* = 3.2, H-2), 3.69–3.63 (m, 1H, H-7) 3.56–3.49 (m, 1H, H-7), 3.19 (s, 2H, OH), 2.79–2.70 (m, 4H, H-7′, H-8), 2.60 (t, 2H, *J* = 7.2, H-8′), 2.31–2.27 (m, 1H, H-4), 2.10–2.03 (m, 1H, H-3), 1.88–1.84 (m, 1H, H-4), 1.48–1.40 (m, 1H, H-3). ^{13}C-NMR (DMSO-d_6, 100 MHz): δ = 172.5 (q, $^2J_{C–F}$ = 30.0, C=O), 155.7, 155.3, 130.0, 129.5, 129.1, 127.0, 115.0, 114.9 (12C, Ar), 150.7 (C-6), 119.3 (q, $^1J_{C–F}$ = 292.7, CF_3), 100.6 (C-5), 68.5 (C-2), 55.2 (C-7), 47.2 (C-7′), 35.1 (C-8), 34.1 (C-8′), 24.9 (C-3), 14.7 (C-4). MS (ESI): *m/z*: 435 $[M+H]^+$. HRMS (ESI): *m/z* calcd for $C_{23}H_{26}F_3N_2O_3$ $[M+H]^+$: 435.1895; found: 435.1893.

5-Trifluoroacetyl-2-N-(2-cyclohexenylethylamino)-1-(2-cyclohexenylethyl)-1,2,3,4-tetrahydropyridine (6j). This compound was obtained as an orange oil in 95% yield from **3** and 93% from **4**. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 7.44 (s, 1H, H-6), 5.43 (s, 2H, =CH cyclohexenyl), 4.06 (t, 1H, *J* = 3.2, H-2), 3.59–3,54 (m, 1H, H-7), 3.36–3.29 (m, 1H, H-7), 2.73–2.69 (m, 2H, H-7′), 2.58–2.53 (m, 1H, H-4), 2.20 (t, 2H, *J* = 6.8, H-8), 2.11 (t, 2H, *J* = 6.4, H-8′), 2.05–1.88 (m, 9H, H-4, cyclohexenyl), 1.64–1.22 (m, 9H, H-3, cyclohexenyl). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 174.7 (q, $^2J_{C–F}$ = 30.02, C=O), 150.4 (C-6), 134.0, 133.0 (2C, =C cyclohexenyl), 125.2, 123.3 (2C, =CH cyclohexenyl), 119.5 (q, $^1J_{C–F}$ = 298.5, CF_3), 101.8 (C-5), 69.0 (C-2), 53.1 (C-7), 43.4 (C-7′), 38.2 (C-8), 37.9 (C-8′), 27.9, 27.8, 25.0, 22.7, 22.4, 22.2, 21.9 (7C, CH_2 cyclohexenyl), 25.0 (C-3), 14.7, (C-4). MS (ESI): *m/z*: 411 $[M+H]^+$. HRMS (ESI): *m/z* calcd for $C_{23}H_{34}F_3N_2O$ $[M+H]^+$: 411.2623; found: 411.2630.

5-Trifluoroacetyl-2-N-(2-(N-morpholyl)-ethylamino)-1-(2-(N-morpholyl)-ethyl)-1,2,3,4-tetrahydropyridine (6k). This compound was obtained as an orange oil in 95% yield from **3** and 92% from **4**. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 7.61 (s, 1H, H-6), 4.14 (t, 1H, *J* = 3.2, H-2), 3.69–3.65 (m, 8H, CH_2-O morpholyne) 3.59–3.51 (m, 1H, H-7), 3.39–3.36 (m, 1H, H-7), 2.79–2.68 (m, 2H, H-7′), 2.61–2.60 (m, 1H, H-4), 2.56 (t, 2H, *J* = 6.0 Hz H-8), 2.50–2.45 (m, 10H, H-8′, CH_2-N morpholyne), 2.20–2.02 (m, 1H, H-4), 1.69–1.60 (m, 1H, H-3). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 175.0 (q, $^2J_{C–F}$ = 31, C=O), 150.7 (C-6), 119.5 (q, $^1J_{C–F}$ = 288.7, CF_3), 102.2 (C-5), 69.8 (C-2), 66.8, 66.6 (2C, OCH_2 morpholyne), 58.0 (2C, C-7 e C-8), 53.6, 53.4 (2C, CH_2-N morpholyne), 51.2 (C-7′), 41.8 (C-8′), 25.2 (C-3), 14.7 (C-4). MS (ESI): *m/z*: 421 $[M+H]^+$. HRMS (ESI): *m/z* calcd for $C_{19}H_{32}F_3N_4O_3$ $[M+H]^+$: 421.2426; found: 421.2424.

5-Trifluoroacetyl-2-N-(2-(1-N^2,N^2-diethylamino) (ethylamino)-1-(2-(1-N^1,N^1-diethylamino)ethyl)-1,2,3,4-tetrahydropyridine (6l). This compound was obtained as an orange oil in 95% yield from **3** and 96% from **4**. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 7.59 (s, 1H, H-6), 4.16 (s, 1H, *J* = 3.2, H-2), 3.53–3.50 (m, 1H, H-7), 3.32–3.27 (m, 1H, H-7), 2.69–2.67 (m, 2H, H-7′), 2.59–2.46 (m, 16H, H-8, H-8′, H-9, H-9′), 2.18–2.14 (m, 2H, H-4, H-3), 2.06–2.02 (m, 1H, H-4), 1.70–1.61 (m, 1H, H-3), 1.60–1.71 (m, 12H, CH_3). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 174.8 (q, $^2J_{C–F}$ = 31.3, C=O), 150.0 (C-6), 119.6 (q, $^1J_{C–F}$ = 290.4, CF_3), 102.0 (C-5), 70.0 (C-2), 53.1 (C-8), 53.0 (C-7), 52.7 (C-8′), 46.9 (C-9), 46.7 (C-9′), 43.4 (C-7′), 25.9 (C-3), 14.8 (C-4), 11.7, 11.6 (2C, CH_3). MS (ESI): *m/z*: 393 $[M+H]^+$. HRMS (ESI): *m/z* calcd for $C_{27}H_{34}F_3N_2O_5$ $[M+H]^+$: 523.2420; found: 523.2418.

5-Trifluoroacetyl-2-N-(1H-indol-3-yl-ethylamino)-1-(1H-indol-3-yl-ethyl)-1,2,3,4-tetrahydropyridine (6m). This compound was obtained as a brown solid, hygroscopic, in 92% yield from **3** and 90% from **4**. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 8.45, 8.34 (s, 2H, NH indole), 7.56–6.76 (m, 11H, H-6, Ar), 3.89 (t, 1H, *J* = 3.2, H-2), 3.71–3.62 (m, 1H, H-7), 3.44–3.38 (m, 1H, H-7), 2.99–2.87 (m, 6H, H-7′, H-8, H-8′), 2.40–2.40 (m, 1H, H-4), 2.00–1.94 (m, 1H, H-3), 1.82–1,78 (m, 1H, H-4), 1,41–1,35 (m, 1H, H-3). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 174.8 (q, $^2J_{C–F}$ = 30.5, C=O), 150.8 (C-6), 136.3, 127.1, 126.5, 122.6, 122.1, 122.0, 121.9, 119.4, 191.1, 118.5, 117.9, 112.9, 111.5, 111.3, 111.2, 110.9 (16C, Ar), 118.6 (q, $^1J_{C–F}$ = 292.0, CF_3), 102.0 (C-5), 69.6 (C-2), 54.8 (C-7), 45.9 (C-7′), 25.9 (C-8), 25.8 (C-8′), 25.2 (C-3), 14.8 (C-4). MS (ESI): *m/z*: 481 $[M+H]^+$. HRMS (ESI): *m/z* calcd for $C_{27}H_{28}F_3N_4O$ $[M+H]^+$: 481.2215; found: 481.2211.

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