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α-Trifluoromethyl-β-aryl enamines in the synthesis of trifluoromethylated heterocycles by the Fischer and the Pictet–Spengler reactions

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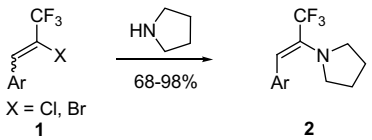
ABSTRACT

α-Trifluoromethyl-β-aryl enamines were successfully used as synthetic equivalents of benzyltrifluoromethyl ketones in both the Fischer indole synthesis and the Pictet–Spengler reaction. Accordingly, 2-trifluoromethyl indoles and a variety of trifluoromethylated 4,5,6,7-terahydro-1*H*-pyridines including carbolines were synthesized in moderate to good yields.

1. Introduction

Fluorine-containing compounds have been object of intensive research in recent decades[1] due to the unique complex of physical and biological properties provided by fluorine substituents.[2] As a result, an enormous progress in this field has been achieved.[3]

Previously, we successfully applied nucleophilic vinylic substitution of halogen in β-chloro-[4] and β-bromo-β-(trifluoromethyl)-styrenes[5] **1** for the synthesis of α-trifluoromethyl-β-aryl enamines.[6] The latter compounds do attract a special interest due to the obvious possibility to react as ketone equivalents (Scheme 1).



Scheme 1. Synthesis of α-trifluoromethyl-β-aryl enamines **2**.

The tendency of trifluoromethylated carbonyl compounds to form stable semiaminals is well known resulting in some difficulties of their further transformation. On the other hand, secondary amino groups such as the pyrrolidino moiety are good leaving groups in acidic media. Consequently, α-trifluoromethyl-β-aryl enamines are expected to be convenient synthetic equivalents of the parent carbonyl compounds and we became attracted to use this strategy for the synthesis of trifluoromethylated indoles, tetrahydroisoquinolines and β-carbolines by Fischer[7] and Pictet–Spengler[8] reactions, respectively. Elaboration of new indole syntheses[9] as well as syntheses of heterocycles with an annulated tetrahydropyridine ring raised great interest due to the manyfold biological activity of their derivatives. Numerous natural alkaloids and drugs do contain these basic skeletons.[10–12] On the other hand, the introduction of fluorine into organic compounds is a well-known strategy to enhance their physiological activity.[2,3c,13] Not surprising, trifluoromethylated indoles have been involved as core structures for the design of pharmaceutically important molecules,[14] and a number of pathways for their synthesis was elaborated in recent decades. These include direct perfluoroalkylations by perfluoroalkylhalides[15–17] and perfluoroalkanoyl peroxides,[18,19] thermolysis of 2-(*N*-trifluoroacetylamino)benzylphosphonium salts,[20] intramolecular cyclization of *N*-trifluoroacetyl-*p*-benzoquinones,[21] palladium-catalyzed annulation of fluorine-containing internal alkynes with various substituted 2-iodoanilines,[22]

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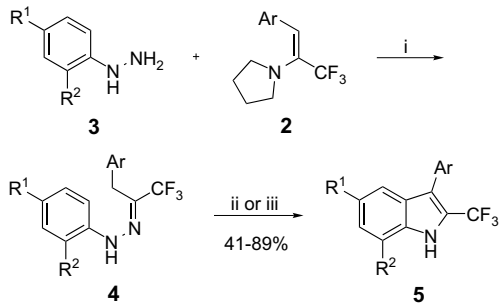
titanium-catalyzed carbonyl coupling of 2-acyl-trifluoroacetanilides,[23] the Grignard cyclization reaction of fluorinated *N*-arylimidoyl chlorides[24] and the reaction of the *N*-trimethylsilyltoluidine dianion with ethyl trifluoroacetate.[25] Furthermore, several Cu catalyzed reactions such as Cu (I) catalyzed nucleophilic substitution of vinyl and aryl halogen atoms of β-halo-β-trifluoromethylstyrenes bearing *ortho*-bromine by primary amines,[26] and the CuI/L-proline-catalyzed coupling-condensation-deacylation cascade reactions of 2-halotrifluoroacetanilides with β-keto esters were developed.[27] Though this variety, most of these approaches suffer from the limited availability of the starting materials, poor yields or low regioselectivity. Therefore, the development of new methods for the preparation of trifluoromethylated heterocycles is still desirable.

2. Results

2.1. Application of α-trifluoromethyl-β-aryl enamines for the synthesis of 3-aryl-2-trifluoromethyl indoles

We assumed that the reaction of enamines **2** with arylhydrazines **3** in acidic media would led to the corresponding hydrazones. Accordingly, refluxing the enamine **2a** with phenylhydrazine in acetic acid for 15–20 min gave the desired hydrazone **4a** in almost quantitative yield. Although some variations of the Fischer reaction exploit heating of the intermediate hydrazones in acetic acid to give indoles, this protocol did not work in case of the α-CF_3-hydrazone **4a** even after several hours of reflux. Probably the acidity of acetic acid is not sufficient to run the rearrangement in the presence of the CF_3-group. Addition of two equivalents of methanesulfonic acid overcame this problem and the formation of the target indole **5a** was completed after few hours. Thus, the reaction of arylhydrazines with 2-aryl-1-trifluoromethyl enamine can be stopped on the stage of the arylhydrazone and can be completed to the corresponding indole by heating in the presence of a strong acid. In order to find milder conditions for the rearrangement and to increase the yields in case of more acid sensitive substrates, the reaction was performed in EtOH using $SOCl_2$ as a catalyst, in acetic acid/TFA and toluene/TFA mixtures. In all cases the formation of hydrazones was observed at room temperature, but, as well as in case of CH_3SO_3H, heating was needed for the rearrangement to the indole. Less acidic catalysts led to significant increase of the reaction time. Moreover, the yield of the indole **5a** dropped to 16–23% under the latter conditions. Thus, quite strong acids are necessary to facilitate the Fischer reaction of α-CF_3-hydrazones. Having found optimal conditions, we performed a series of reactions of enamines **2** with arylhydrazines **3**, varying both the arylhydrazines and the enamine components (Scheme 2, Table 1).



Scheme 2. Reactions of α-trifluoromethyl-β-aryl enamines **2** with arylhydrazines **3**. *Conditions*: (i) AcOH, reflux; (ii) 2 equiv CH_3SO_3H, reflux (**5a**–**5j**, **5m**); (iii) 2 equiv CH_3SO_3H, 90 °C, argon atmosphere (**5k**, **5l**, **5n**).

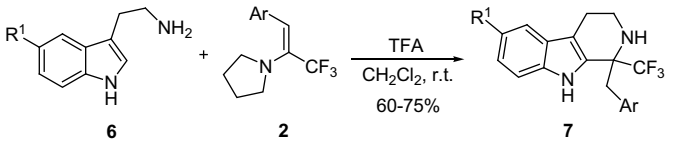
As a result, a variety of 3-aryl-2-trifluoromethyl indoles **5** was synthesized in moderate to high yields without isolation of the intermediate hydrazones **4**. Trifluoromethylated indoles bearing different combinations of electron-donating and electron-withdrawing substituents in the aryl or indole rings can be obtained by this method. The Fischer reaction proceeded regioselectively resulting in the formation of only one regioisomer. The highest yields were obtained with compounds bearing electron-withdrawing groups (**5a**, **5h**). This can be explained by their higher stability in acidic media under air comparing with substrates carrying electron-donating substituents. Performing the reactions under argon atmosphere at 90 °C led to significantly higher yields in case of electron donating substituents. In this way the yields of the indoles **5k**, **5l** and **5n** were increased from 29% to 76% (**5k**), 21% to 41% (**5l**) and 23% to 68% (**5n**). To the best of our knowledge, these are the first examples of the synthesis of trifluoromethyl indoles by the Fischer synthesis starting from enamines **2**. The parent trifluoromethylbenzyl ketones have not been used in the Fischer indole synthesis so far.[28]

Table 1
Synthesis of 3-aryl-2-trifluoromethyl indoles **5**

Indole **5**	Ar	R_1	R_2	Yield (%)	Indole **5**	Ar	R_1	R_2	Yield (%)
a	4-$NO_2C_6H_4$	H	H	88	**h**	4-ClC_6H_4	Cl	H	89
b	4-ClC_6H_4	H	H	68	**i**	4-ClC_6H_4	F	H	69
c	Ph	H	H	45	**j**	4-ClC_6H_4	CN	H	50
d	4-$MeCO_2C_6H_4$	H	H	43	**k**	4-ClC_6H_4	Me	H	76
e	2-BrC_6H_4	H	H	70	**l**	4-ClC_6H_4	MeO	H	41
f	2-$NO_2C_6H_4$	H	H	45	**m**	4-ClC_6H_4	Cl	Cl	52
g	3-$NO_2C_6H_4$	H	H	70	**n**	4-ClC_6H_4	Me	Me	68

2.2. Application of α-trifluoromethyl-β-aryl enamines in the Pictet–Spengler reaction

Succeeded in the application of α-trifluoromethyl-β-aryl enamines **2** in the Fischer indole synthesis, we decided to also use these enamines in the Pictet–Spengler reaction. However, heating of the enamines **2** with the tryptamines **6** in an ethanol-water mixture using HCl as catalyst (classical Pictet–Spengler's conditions[8]) gave only tar, perhaps due to acid catalyzed polymerization of the indole moiety. Carrying out this reaction under milder conditions in CH_2Cl_2 using TFA as acid overcame this problem and the corresponding 2,3,4,9-tetrahydro-1*H*-β-carbolines **7** were obtained in satisfactory yields after a week at room temperature. This reaction is quite general and permitted the preparation of a wide variety of carbolines, bearing both electron-donating and electron-withdrawing substituents in the aromatic ring of enamines **2** (Scheme 3, Table 2).

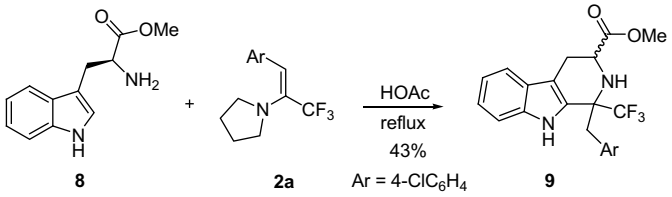


Scheme 3. Reactions of α-trifluoromethyl-β-aryl enamines **2** with tryptamines **6**.

Table 2
Synthesis of 2,3,4,9-tetrahydro-1*H*-β-carbolines **7**

Comp **7**	Ar	R_1	Yield (%)
a	4-$NO_2C_6H_4$	H	70
b	4-ClC_6H_4	H	63
c	Ph	H	60
d	4-$MeCO_2C_6H_4$	H	70
e	2-BrC_6H_4	H	61
f	2-$NO_2C_6H_4$	H	66
g	3-$NO_2C_6H_4$	H	68
h	4-$MeOC_6H_4$	H	67
i	4-ClC_6H_4	n-C_4H_9	75

In case of L-tryptophane methyl ester (**8**), the formation of the cyclization product proceeded very slowly and in low yield under the mentioned conditions. This might be explained by lower steric accessibility and lower nucleophilicity of the nitrogen atom. Refluxing the reaction mixture did not lead to a remarkable increase of the reaction rate. However, replacement of CH_2Cl_2 with the higher-boiling acetic acid gave the corresponding cyclic derivative **9** in moderate yield as a 67:33 mixture of diastereomers, which were not assigned (Scheme 4).



Scheme 4. Synthesis of cyclic derivative **9**.

The synthesized compounds **7** and **9** are analogs of the natural alkaloid Harman (arabine, 1-methyl-*S*-carboline), which has been found in plants[29] and revealed as enzyme inhibitor, mutagen and antagonist of the benzodiazepine receptors.[30] On the other hand, due to the presence of two well known pharmacophores (the 2-arylethylamine moiety and the CF_3-group) in compounds **7**, one can expect particular biological activity, which makes them promising objects for bioorganic chemistry. However, preliminary tests of their activity as σ-receptor antagonists did not show significant effects (Fig. 1).[31]

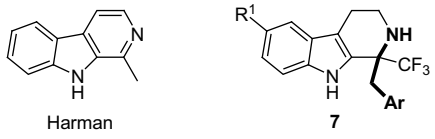
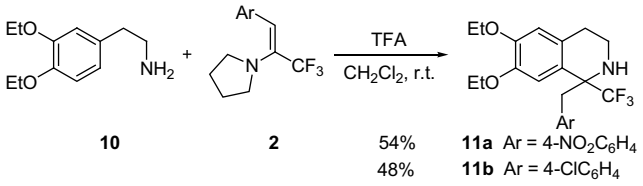


Figure 1. Structures of Harman and compounds **7**.

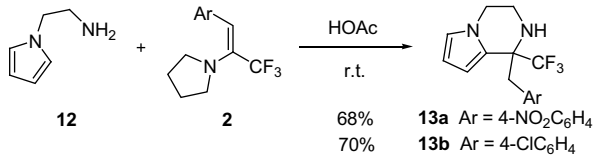
In order to plumb the synthetic scope of the method we performed a series of reactions of enamines **2** with several other ethylamines, containing both aryl- and hetaryl substituents, activated for electrophilic attack. For example, the reaction of **2** with 2-(3,4-diethoxyphenyl)ethylamine (**10**) in CH_2Cl_2 in the presence of TFA at rt gave the 1,2,3,4-tetrahydroisoquinoline derivatives **11a** and **11b** in moderate yields (Scheme 5).



Scheme 5. Synthesis of 1,2,3,4-tetrahydroisoquinolines **11a** and **11b**.

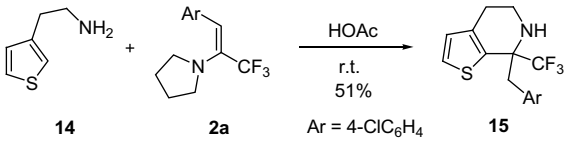
Next we focused on the preparation of 1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazines, which are of considerable interest because of their antiamnesic, antihypoxic,[32] psychotropic,[33] antihypersensitive,[34] and aldose reductase inhibitor activities.[35] Furthermore, pyrrolopyrazines do also selectively bind to $GABA_a$ receptors[36] and are useful starting materials for the synthesis of octahydropyrrolo-[1,2-*a*]pyrazine-based coronary-dilators and neuroleptics.[37]

Because of the well known easy polymerization of pyrroles in acidic media, the reactions of enamines **2a** and **2b** with 2-(1-pyrrolyl)ethylamine (**12**) were performed in acetic acid, which is four orders of magnitude weaker comparing to trifluoroacetic acid used before. The desired 1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine derivatives **13a** and **13b** were isolated in good yields as bright crystals after several days of standing at room temperature (Scheme 6).



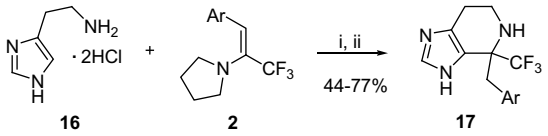
Scheme 6. Synthesis of 1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazines **13a** and **13b**.

Furthermore, the reaction of 2-(3-thienyl)ethylamine (**14**) with enamine **2** in acetic acid gave the 4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine **15** in moderate yield (Scheme 7).



Scheme 7. Synthesis of 4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine **15**.

In case of histamine dihydrochloride (**16**), the reaction was carried out in two steps. At first a mixture of histamine dihydrochloride and enamine **2** was heated under reflux in ethanol until the enamine was completely consumed to give an intermediate iminium salt. Subsequently, two equivalents of KOH were added for neutralization of the acid. Thus, cyclization to form **17** occurred under basic conditions In acidic medium, the imidazole ring is not active enough to be attacked electrophilically (Scheme 8, Table 3).



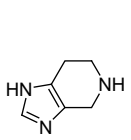
Scheme 8. Reactions of enamines **2** with histamine dihydrochloride (**16**). *Conditions*: (i) EtOH, reflux; (ii) 2 equiv KOH, reflux.

Table 3
Synthesis of 4,5,6,7-tetrahydro-3*H*-imidazo[4,5-*c*]pyridines (**17**)

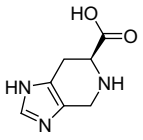
Compound **17**	Ar	Yield (%)
a	4-$NO_2C_6H_4$	66
b	4-ClC_6H_4	54
c	Ph	77
d	4-$MeCO_2C_6H_4$	44
h	4-$MeOC_6H_4$	45

In summary, a number of substituted 4,5,6,7-tetrahydro-3*H*-imidazo[4,5-*c*]pyridines **17**, bearing either electron-withdrawing or electron-donating substituents in the aryl ring, was obtained from enamines **2** in moderate to good yields. The parent trifluoromethylbenzyl ketones of **2** have not been used in the Pictet–Spengler reaction yet.[28] The heterocyclic core of the synthesized compounds **17** is the alkaloid spinaceamine (4,5,6,7-tetrahydroimidazo[4,5-*c*]pyridine) and a constituent of spinacine (4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridine-6-carboxylic acid),

which both play an important biological role in flora and fauna.[38]



Spinaceamine



Spinacine

3. Conclusions

α-Trifluorometyl-β-aryl enamines **2** have been shown to be synthetic equivalents of corresponding benzyltrifluoromethyl ketones in both the Fischer and the Pictet–Spengler reactions, although the latter compounds have not been used in these reactions so far. The enamines **2** reacted smoothly with arylhydrazines in acetic acid to give α-CF_3-hydrazones **4**. The Fischer rearrangement of trifluoromethylated hydrazones needs stronger acids to occur but was successful in refluxing methanesulfonic acid and a series of 3-aryl-2-trifluoromethyl indoles **5** were prepared in moderate to high yields. The one-pot transformation of **2** to **5** was also elaborated. Moreover, a new versatile approach to polycyclic trifluoromethylated 4,5,6,7-tetrahydro-1*H*-pyridines including carbolines was developed using the Pictet–Spengler reaction of α-trifluorometyl-β-aryl enamines **2** with aryl- and hetarylamines. The thus synthesized heterocyclic compounds contain three pharmacophore fragments simultaneously, which might be interesting for biomedical investigations.

4. Experimental

4.1. General

^1H, ^{13}C and ^{19}F NMR spectra were recorded on Bruker ARX 300 and Bruker AMX 400 spectrometers in $CDCl_3$ with TMS, and CCl_3F as internal standards. IR spectra were obtained as films. Column and TLC chromatography were performed using silica gel Merck 60 or Merck $60F_{254}$ plates, respectively. Mass spectra were measured on a MicroTof Bruker Daltonics (ESI-MS). Column and TLC chromatography were performed on silica gel Merck 60 and Merck $60F_{254}$ plates, respectively. The α-trifluoromethyl-β-aryl enamines were synthesized according to our previously reported procedure.[6]

4.2. 1,1,1-Trifluoro-3-(4-nitrophenyl)acetone phenylhydrazone (4a)

Phenylhydrazine (120 mg, 1.05 mmol), enamine **2a** and acetic acid (5 mL) were mixed in a 25 mL round bottomed flask and refluxed for 1 h. Acetic acid was removed in vacuo, the residue was dissolved in CH_2Cl_2 (30 mL), washed with saturated solution of K_2CO_3 (10 mL) and dried over Na_2SO_4. CH_2Cl_2 was evaporated in vacuum, and the residue was filtered through a short silica gel pad using CH_2Cl_2. Yield: 284 mg (88%); yellow crystals; mp 155–157 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 3.97 (s, 2H, CH_2), 7.00 (t, J=7.6 Hz, 1H, Ph), 7.09 (d, J=7.6 Hz, 2H, Ph), 7.26–7.34 (m, 2H, Ph), 7.43 (d, J=8.5 Hz, 2H, 4-$NO_2C_6H_4$–), 7.71 (d, J=8.5 Hz, 2H, 4-$NO_2C_6H_4$–), 8.18 (br s, 1H, N*H*); ^{19}F NMR (282 MHz, $CDCl_3$): δ −68.40; ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.8 (CH_2), 121.9 (q, J=272.2 Hz, CF_3), 128.5 (q, J=34.4 Hz, *C*–CF_3), 113.9, 122.4, 128.9, 141.3 (Ph), 124.4, 129.4, 142.9, 147.1 (4-$NO_2C_6H_4$–). ESI-MS (m/z): calcd for $C_{15}H_{12}F_3N_3O_2Na$ [M^+] 346.0779, found 346.0774.

4.3. Synthesis of 3-aryl-2-trifluoromethyl indoles 5 (general procedure)

Arylhydrazine **4** (1 mmol), the corresponding enamine **2** (1 mmol) and acetic acid (5 mL) were mixed in a 25 mL round bottomed flask and refluxed for 1 h. CH_3SO_3H (202 mg, 2.1 mmol) was added and the reaction mixture was refluxed for another 10–15 h until the hydrazone disappeared (TLC control). In the case of indoles **5k**, **5l**, **5n** the reactions were carried out under argon atmosphere at 90 °C. Acetic acid was evaporated in vacuo, the residue was dissolved in CH_2Cl_2 (30 mL), washed with saturated solution of K_2CO_3 (10 mL) and dried over Na_2SO_4. CH_2Cl_2 was removed in vacuo and the residue was purified by column chromatography on silica gel using mixtures of CH_2Cl_2 and hexane as eluents.

*4.3.1. 3-(4-Nitrophenyl)-2-trifluoromethyl-1H-indole (**5a**)*

Obtained from enamine **2a** (286 mg, 1 mmol) and phenylhydrazine (108 mg, 1 mmol). Yield: 270 mg (88%); yellow crystals; mp 184–185 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 (td, J=7.9, 0.8 Hz, 1H, Ind), 7.44 (t, J=7.9 Hz, 1H, Ind), 7.54 (d, J=7.9 Hz, 1H, Ind), 7.64 (d, J=7.9 Hz, 1H, Ind), 7.73 (d, J=8.7 Hz, 2H, Ar), 8.37 (d, J=8.7 Hz, 2H, Ar), 8.79 (br s, 1H, N*H*, Ind); ^{13}C NMR (100 MHz, $CDCl_3$) δ 112.1, 117.3 (q, J=2.3 Hz, *C*=C–CF_3), 120.4, 122.0 (q, J=36.6 Hz, *C*–CF_3), 122.1, 125.7, 126.6, 130.9, 134.9 (Ind), 121.1 (q, CF_3, J=268.6 Hz), 123.8, 130.7, 139.3, 147.1 (Ar). ^1H NMR and ^{13}C NMR spectra are in agreement with the literature data.[22]

*4.3.2. 3-(4-Chlorophenyl)-2-trifluoromethyl-1H-indole (**5b**)*

Obtained from enamine **2b** (276 mg, 1 mmol) and phenylhydrazine (108 mg, 1 mmol). Yield: 201 mg (68%); yellow powder; mp 81–82 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (t, J=7.5 Hz, 1H, Ind), 7.43 (d, J=7.9 Hz, 1H, Ind), 7.45–7.50 (m, 5H, Ind, Ar), 7.65 (d, J=7.5 Hz, 1H, Ind), 8.54 (br s, 1H, N*H*, Ind); ^{13}C NMR (100 MHz, $CDCl_3$) δ 111.9, 118.5 (q, J=2.9 Hz, *C*=C–CF_3), 120.6, 121.3 (q, J=36.9 Hz, *C*–CF_3), 121.5, 125.3, 130.6, 134.9 (Ind), 121.5 (q, J=268.6 Hz, CF_3), 127.1, 128.7, 131.3, 133.5 (Ar). ^1H NMR and ^{13}C NMR spectra are in agreement with the literature data.[22]

*4.3.3. 3-Phenyl-2-trifluoromethyl-1H-indole (**5c**)*

Obtained from enamine **2c** (241 mg, 1 mmol) and phenylhydrazine (108 mg, 1 mmol). Yield: 118 mg (45%); pale brown crystals; mp 66–67 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.24 (td, J=7.8, 0.8 Hz, 1H, Ind), 7.38–7.47 (m, 2H, Ind, Ar), 7.48–7.54 (m, 3H, Ar), 7.55–7.59 (m, 2H, Ar), 7.69 (d, J=7.8 Hz, 1H, Ind), 8.53 (br s, 1H, N*H*, Ind); ^{19}F NMR (282 MHz, $CDCl_3$) δ −57.32; ^{13}C NMR (100 MHz, $CDCl_3$) δ 117.7, 119.9 (q, J=3.6 Hz, *C*=C–CF_3), 121.1, 121.2 (q, J=37.3 Hz, *C*–CF_3), 121.3, 125.2, 132.1, 135.0 (Ind), 121.7 (q, CF_3, J=268.6 Hz), 127.3, 127.6, 128.4, 129.9 (Ar). ESI-MS (m/z): calcd for $C_{15}H_{10}F_3NNa$ [M^+] 284.0663, found 284.0658. Anal. Calcd for $C_{15}H_{10}F_3N$: C, 68.96; H, 3.86. Found: C, 68.95; H, 3.85.

*4.3.4. Methyl 4-(2-trifluoromethyl-1H-indole-3-yl)benzoate (**5d**)*

Obtained from enamine **2d** (299 mg, 1 mmol) and phenylhydrazine (108 mg, 1 mmol). Yield: 137 mg (43%); pale brown powder; mp 144–146 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 4.02 (s, 3H, CO_2CH_3), 7.26 (t, J=7.8 Hz, 1H, Ind), 7.42 (t, J=7.8 Hz, 1H, Ind), 7.53 (d, J=7.8 Hz, 1H, Ind), 7.65–7.70 (m, 3H, Ind, Ar), 8.21 (d, J=8.3 Hz, 2H, Ar), 9.15 (br s, 1H, N*H*, Ind); ^{19}F NMR (282 MHz, $CDCl_3$) δ −56.82; ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.3 (CO_2CH_3), 112.0, 118.5 (q, J=2.8 Hz, *C*=C–CF_3), 120.7, 121.6, 121.8 (q, J=30.7 Hz, *C*–CF_3), 125.3, 126.9, 135.1 (Ind), 121.6 (q, J=270.1 Hz, CF_3), 129.1, 129.7, 130.0, 137.4 (Ar), 167.3 (CO_2CH_3). ESI-MS (m/z): calcd for $C_{17}H_{12}F_3NO_2Na$ [M^+] 342.0718, found 342.0712. Anal. Calcd for $C_{17}H_{12}F_3NO_2$: C, 63.95; H, 3.79. Found: C, 63.84; H, 3.72.

*4.3.5. 3-(2-Bromophenyl)-2-trifluoromethyl-1H-indole (**5e**)*

Obtained from enamine **2e** (320 mg, 1 mmol) and phenylhydrazine (108 mg, 1 mmol). Yield: 238 mg (70%); yellow viscous oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29 (td, J=7.5, 1.0 Hz, 1H, Ind), 7.34–7.40 (m, 1H, Ind, Ar), 7.43–7.53 (m, 5H, Ind, Ar), 7.55–7.59 (m, 2H, Ar), 7.82 (d, J=7.8 Hz, 1H, Ind), 8.54 (br s, 1H, N*H*, Ind); ^{19}F NMR

(282 MHz, $CDCl_3$) δ −58.56; ^{13}C NMR (100 MHz, $CDCl_3$) δ 111.9, 119.0 (q, J=2.9 Hz, C=C–CF_3), 121.4 (q, J=269.3 Hz, CF_3), 121.4, 121.5, 122.2 (q, J=37.3 Hz, C–CF_3), 125.1, 125.3, 127.1, 127.2, 129.8, 132.7, 132.8, 133.4, 134.9. ESI-MS (m/z): calcd for $C_{15}H_9BrF_3NNa$ [M^+] 361.9768, found 361.9763. Anal. Calcd for $C_{15}H_9ClF_3N$: C, 52.97; H, 2.67. Found: C, 53.04; H, 2.65.

4.3.6. 3-(2-Nitrophenyl)-2-trifluoromethyl-1H-indole (**5f**)

Obtained from enamine **2f** (286 mg, 1 mmol) and phenylhydrazine (108 mg, 1 mmol). Yield: 138 mg (45%); yellow viscous oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (td, J=7.7, 0.9 Hz, 1H, Ar), 7.30–7.40 (m, 2H, Ind), 7.43 (d, J=8.1 Hz, 1H, Ind), 7.54 (dd, J=7.7, 1.3 Hz, 1H, Ar), 7.62 (dd, J=8.1, 1.5 Hz, 1H, Ind), 7.71 (td, J=7.7, 1.3 Hz, 1H, Ar), 8.12 (dd, J=7.7, 0.9 Hz, 1H, Ar), 8.72 (br s, 1H, NH, Ind); ^{19}F NMR (282 MHz, $CDCl_3$) δ −58.24; ^{13}C NMR (100 MHz, $CDCl_3$) δ 112.1, 114.7 (q, J=2.9 Hz, C=C–CF_3), 120.1, 121.7, 121.8 (q, J=38.1 Hz, C–CF_3), 125.4, 127.0, 134.9 (Ind), 121.3 (q, J=269.3 Hz, CF_3), 124.6, 127.2, 129.2, 132.7, 133.6, 149.8 (Ar). ESI-MS (m/z): calcd for $C_{15}H_9F_3N_2O_2Na$ [M^+] 329.0514, found 329.0514. Anal. Calcd for $C_{15}H_9F_3N_2O_2$: C, 58.83; H, 2.96. Found: C, 58.77; H, 3.02.

4.3.7. 3-(3-Nitrophenyl)-2-trifluoromethyl-1H-indole (**5g**)

Obtained from enamine **2g** (286 mg, 1 mmol) and phenylhydrazine (108 mg, 1 mmol). Yield: 214 mg (70%); yellow crystals; mp 126–127 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (td, J=8.0, 0.8 Hz, 1H, Ind), 7.45 (t, J=8.0 Hz, 1H, Ind), 7.54 (d, J=8.0 Hz, 1H, Ind), 7.63 (d, J=8.0 Hz, 1H, Ind), 7.69 (t, J=7.9 Hz, 1H, Ar), 7.89 (d, J=7.9 Hz, 1H, Ar), 8.31 (ddd, J=7.9, 1.9, 1.0 Hz, 1H, Ar), 8.46 (t, J=1.9 Hz, 1H, Ar), 8.86 (br s, 1H, NH, Ind); ^{19}F NMR (282 MHz, $CDCl_3$) δ −56.85; ^{13}C NMR (100 MHz, $CDCl_3$) δ 112.1, 117.0 (q, J=2.9 Hz, C=C–CF_3), 120.3, 122.0 (q, J=37.3 Hz, C–CF_3), 122.5, 126.7, 129.5, 135.0 (Ind), 121.4 (q, J=268.6 Hz, CF_3), 122.0, 124.7, 125.7, 134.1, 136.1, 148.4 (Ar). ESI-MS (m/z): calcd for $C_{15}H_9F_3N_2O_2Na$ [M^+] 329.0514, found 329.0508. Anal. Calcd for $C_{15}H_9F_3N_2O_2$: C, 58.83; H, 2.96. Found: C, 58.84; H, 2.93.

4.3.8. 5-Chloro-3-(4-chlorophenyl)-2-trifluoromethyl-1H-indole (**5h**)

Obtained from enamine **2b** (276 mg, 1 mmol) and (4-chlorophenyl)hydrazine (143 mg, 1 mmol). Yield: 294 mg (89%); white crystals; mp 110–111 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.41 (m, 2H, Ind), 7.62 (d, J=0.8 Hz, 1H, Ind), 7.46 (d, J=8.6 Hz, 2H, Ar), 7.50 (d, J=8.6 Hz, 2H, Ar), 8.60 (br s, 1H, NH, Ind); ^{13}C NMR (100 MHz, $CDCl_3$) δ 113.1, 118.2 (q, J=2.9 Hz, C=C–CF_3), 120.2, 121.3 (q, J=270.1 Hz, CF_3), 122.6 (q, J=37.5 Hz, C–CF_3), 125.9, 127.4, 128.1, 128.9, 129.9, 131.1, 133.2, 134.0. ^{1}H NMR and ^{13}C NMR spectra are in agreement with the literature data.[22]

4.3.9. 5-Fluoro-3-(4-chlorphenyl)-2-trifluoromethyl-1H-indole (**5i**)

Obtained from enamine **2b** (276 mg, 1 mmol) and (4-fluorophenyl)hydrazine (126 mg, 1 mmol). Yield: 217 mg (69%); white crystals; mp 62–63 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (td, J=9.0, 2.1 Hz, 1H, Ind), 7.27 (dd, J=9.4, 2.1 Hz, 1H, Ind), 7.41–7.45 (m, 1H, Ind), 7.45 (d, J=8.6 Hz, 2H, Ar), 7.49 (d, J=8.6 Hz, 2H, Ar), 8.64 (br s, 1H, NH, Ind); ^{19}F NMR (282 MHz, $CDCl_3$) δ −121.47 (td, J=9.1, 4.3 Hz, F), −57.14 (CF_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 105.5 (d, J=23.4 Hz), 112.9 (d, J=10.3 Hz), 114.4 (d, J=26.3 Hz), 118.6 (q, J=2.9 Hz, C=C–CF_3), 121.3 (q, J=269.3 Hz, CF_3), 123.0 (q, J=36.6 Hz, C–CF_3), 127.6 (d, J=10.3), 133.9, 158.8 (d, J=237.1 Hz) (Ind), 128.9, 130.2, 131.0, 131.5 (Ar). Anal. Calcd for $C_{15}H_8F_4N$: C, 57.43; H, 2.57. Found: C, 57.38; H, 2.58.

4.3.10. 5-Cyano-3-(4-chlorophenyl)-2-trifluoromethyl-1H-indole (**5j**)

Obtained from enamine **2b** (276 mg, 1 mmol) and (4-cyanophenyl)hydrazine (133 mg, 1 mmol). Yield: 161 mg (50%); brown crystals; mp 198–200 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, J=8.8 Hz, 2H, Ar), 7.51 (d, J=8.8 Hz, 2H, Ar), 7.59–7.65 (m, 2H, Ind), 7.99 (s, 1H, Ind), 9.24 (br s, 1H, NH, Ind); ^{19}F NMR (282 MHz, $CDCl_3$) δ −57.33; ^{13}C NMR (100 MHz, $CDCl_3$) δ 104.9 (CN), 113.1, 119.1 (q, J=2.9 Hz, C=C–CF_3), 119.7, 123.6 (q, J=37.3 Hz, C–CF_3), 126.9, 127.0, 134.5, 136.5 (Ind), 121.0 (q, J=269.3 Hz, CF_3), 127.7, 129.1, 130.3, 131.1 (Ar). ESI-MS (m/z): calcd for $C_{16}H_8ClF_3N_2Na$ [M^+] 343.0226, found 343.0220. Anal. Calcd for $C_{16}H_8ClF_3N_2$: C, 59.92; H, 2.51. Found: C, 60.04; H, 2.62.

4.3.11. 5-Methyl-3-(4-chlorophenyl)-2-trifluoromethyl-1H-indole (**5k**)

Obtained from enamine **2b** (276 mg, 1 mmol) and (4-methylphenyl)hydrazine (122 mg, 1 mmol). Yield: 236 mg (76%); green-yellow crystals; mp 98–99 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.48 (s, 3H, CH_3), 7.25 (d, J=8.3 Hz, 1H, Ind), 7.38 (d, J=8.3 Hz, 1H, Ind), 7.42 (s, 1H, Ind), 7.50 (s, 4H, Ar), 8.44 (br s, 1H, NH, Ind); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4 (CH_3), 111.5, 118.1 (q, J=2.9 Hz, C=C–CF_3), 120.1, 121.4 (q, J=36.6 Hz, C–CF_3), 121.6 (q, J=269.3 Hz, CF_3), 127.2, 127.4, 128.7, 130.9, 131.1, 131.2, 133.3, 133.6. ^{1}H NMR and ^{13}C NMR spectra are in agreement with the literature data.[22]

4.3.12. 5-Methoxy-3-(4-chlorophenyl)-2-trifluoromethyl-1H-indole (**5l**)

Obtained from enamine **2b** (276 mg, 1 mmol) and (4-methoxyphenyl)hydrazine (138 mg, 1 mmol). Yield: 134 mg (41%); white crystals; mp 72–73 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.83 (s, 3H, OCH_3), 7.00 (d, J=2.1 Hz, 1H, Ind), 7.06 (dd, J=8.9, 2.1 Hz, 1H, Ind), 7.38 (d, J=8.9 Hz, 1H, Ind), 7.48 (s, 4H, Ar), 8.47 (br s, 1H, NH, Ind); ^{19}F NMR (282 MHz, $CDCl_3$) δ −56.84; ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.8 (OCH_3), 101.3, 112.7, 116.5, 118.1 (q, J=2.9 Hz, C=C–CF_3), 121.9 (q, J=37.3 Hz, C–CF_3), 130.8, 133.6, 155.5 (Ind), 121.5 (q, J=269.3 Hz, CF_3), 127.6, 128.8, 130.0, 131.1 (Ar). Anal. Calcd for $C_{16}H_{11}ClF_3NO$: C, 59.00; H, 3.40. Found: C, 58.78; H, 3.42.

4.3.13. 5,7-Dichloro-3-(4-chlorophenyl)-2-trifluoromethyl-1H-indole (**5m**)

Obtained from enamine **2b** (276 mg, 1 mmol) and (2,4-dichlorophenyl)hydrazine (177 mg, 1 mmol). Yield: 190 mg (52%); white crystals; mp 101–103 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.45 (m, 3H, Ind, Ar), 7.47–7.52 (m, 3H, Ind, Ar), 8.72 (br s, 1H, NH, Ind); ^{13}C NMR (100 MHz, $CDCl_3$) δ 117.9, 119.2 (q, J=2.9 Hz, C=C–CF_3), 119.1, 119.4 (q, J=38.1 Hz, C–CF_3), 120.9 (q, J=270.1 Hz, CF_3), 124.9, 127.5, 128.7, 129.0, 129.3, 131.0, 134.4. Anal. Calcd for $C_{15}H_7Cl_3F_3N$: C, 49.42; H, 1.94. Found: C, 49.32; H, 1.82.

4.3.14. 5,7-Dimethyl-3-(4-chlorophenyl)-2-trifluoromethyl-1H-indole (**5n**)

Obtained from enamine **2b** (276 mg, 1 mmol) and (2,4-dimethylphenyl)hydrazine (136 mg, 1 mmol). Yield: 220 mg (68%); yellow-green powder; mp 99–101 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.45 (s, 3H, CH_3), 2.48 (s, 3H, CH_3), 7.07 (s, 1H, Ind), 7.27 (s, 1H, Ind), 7.50 (s, 4H, Ar), 8.34 (br s, 1H, NH, Ind); ^{19}F NMR (282 MHz, $CDCl_3$) δ −56.90; ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.4 (CH_3), 21.4 (CH_3), 117.7, 118.6 (q, J=2.9 Hz, C=C–CF_3), 120.8, 121.2 (q, J=36.6 Hz, C–CF_3), 121.8 (q, J=269.3 Hz, CF_3), 127.1, 127.6, 128.7, 131.1, 131.2, 131.4, 133.1, 133.5. Anal. Calcd for $C_{17}H_{13}F_3N$: C, 63.07; H, 4.05. Found: C, 63.02; H, 4.08.

4.4. Synthesis of 1-benzyl-1-(trifluoromethyl)-2,3,4,9-tetrahydro-1*H*-β-carbolines 7 and 1-benzyl-6,7-diethoxy-1-(trifluoromethyl)-1,2,3,4-tetrahydroisoquinolines 11 (general procedure)

In a 25 mL round bottomed flask the corresponding β-substituted ethylamine (1.05 mmol) and the enamine **2** (1 mmol) were dissolved in CH_2Cl_2 (3 mL) and CF_3COOH was added (0.16 mL, 2 mmol). The reaction mixture remained at room temperature for 5–7 days (TLC monitoring), diluted with CH_2Cl_2 (20–30 mL) and washed with

saturated K_2CO_3 solution in a separating funnel. After drying over Na_2SO_4, the volatiles were removed in vacuo and the residue was purified by column chromatography on silica gel using CH_2Cl_2 as eluent.

4.4.1. 1-(4-Nitrobenzyl)-1-trifluoromethyl-2,3,4,9-tetrahydro-1H-β-carboline (**7a**)

Obtained from enamine **2a** (286 mg, 1 mmol) and tryptamine (168 mg, 1.05 mmol). Yield: 263 mg (70%); yellow crystals; mp 181–183 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.71 (br s, 1H, CH_2CH_2NH), 2.18–2.31, 2.60–2.69, 2.98–3.07, 3.12–3.22, (all m, 1H, CH_2CH_2NH), 3.26, 3.48 (both d, *J*=13.5 Hz, 1H, CH_2Ar), 6.99 (d, *J*=8.5 Hz, 2H, Ar), 7.17 (t, *J*=7.2 Hz, 1H, Ind), 7.29 (t, *J*=7.2 Hz, 1H, Ind), 7.44–7.53 (m, 2H, Ind), 7.97 (d, *J*=8.5 Hz, 2H, Ar), 8.15 (br s, 1H, NH, Ind); ^{19}F NMR (282 MHz, $CDCl_3$) δ −75.61; ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8 (CH_2CH_2NH), 40.3, 40.6 (CH_2CH_2NH, CH_2Ar), 60.2 (q, *J*=25.6 Hz, *C*–CF_3), 126.9 (q, *J*=288.3 Hz, CF_3), 111.3, 115.8, 119.0, 120.1, 123.3, 126.4, 126.5, 136.2 (Ind), 123.1, 131.2, 141.8, 147.2 (Ar). ESI-MS (*m*/*z*): calcd for $C_{19}H_{17}F_3N_3O_2$ [M^+] 376.1273, found 376.1272. Anal. Calcd for $C_{19}H_{16}F_3N_3O_2$: C, 60.80; H, 4.30. Found: C, 60.81; H, 4.24.

4.4.2. 1-(4-Chlorobenzyl)-1-trifluoromethyl-2,3,4,9-tetrahydro-1H-β-carboline (**7b**)

Obtained from enamine **2b** (276 mg, 1 mmol) and tryptamine (168 mg, 1.05 mmol). Yield: 230 mg (63%); yellow powder; mp 169–172 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.21–2.31, 2.63–2.70, 3.04–3.09, 3.11–3.16, (all m, 1H, CH_2CH_2NH), 3.16, 3.41 (both d, *J*=13.9 Hz, 1H, CH_2Ar), 6.71 (d, *J*=8.3 Hz, 2H, Ar), 7.10 (d, *J*=8.3 Hz, 2H, Ar), 7.20 (t, *J*=7.6 Hz, 1H, Ind), 7.31 (t, *J*=7.6 Hz, 1H, Ind), 7.44–7.50 (m, 2H, Ind), 8.43 (br s, 1H, NH, Ind); ^{19}F NMR (282 MHz, $CDCl_3$) δ −75.45; ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.0 (CH_2CH_2NH), 39.6, 40.4 (CH_2CH_2NH, CH_2Ar), 59.9 (q, *J*=26.4 Hz, *C*–CF_3), 127.0 (q, *J*=287.6 Hz, CF_3), 111.4, 115.6, 119.0, 119.8, 123.1, 126.6, 127.0, 136.2 (Ind), 128.5, 131.6, 132.0, 133.4 (Ar). ESI-MS (*m*/*z*): calcd for $C_{19}H_{17}ClF_3N_2$ [M^+] 365.1032, found 365.1027. Anal. Calcd for $C_{19}H_{16}ClF_3N_2$: C, 62.56; H, 4.42. Found: C, 63.81; H, 4.24.

4.4.3. 1-Benzyl-1-trifluoromethyl-2,3,4,9-tetrahydro-1H-β-carboline (**7c**)

Obtained from enamine **2c** (241 mg, 1 mmol) and tryptamine (168 mg, 1.05 mmol). Yield: 198 mg (60%); grey powder; mp 117–118 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.75 (br s, 1H, CH_2CH_2NH), 2.18–2.29, 3.03–3.11, 3.13–3.20 (all m, 1H, CH_2CH_2NH), 2.78 (dt, *J*=15.2, 3.7 Hz, 1H, CH_2CH_2NH), 3.23, 3.48 (both d, *J*=13.6 Hz, 1H, CH_2Ar), 6.82 (d, *J*=7.1 Hz, 2H, Ar), 7.15–7.28 (m, 4H, Ind, Ar), 7.35 (td, *J*=7.9, 1.0 Hz, 1H, Ind), 7.50 (d, *J*=7.9 Hz, 1H, Ind), 7.58 (d, *J*=7.9 Hz, 1H, Ind), 8.20 (br s, 1H, NH, Ind); ^{19}F NMR (282 MHz, $CDCl_3$) δ −75.61; ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.0 (CH_2CH_2NH), 40.4, 40.5 (CH_2CH_2NH, CH_2Ar), 60.0 (q, *J*=26.3 Hz, *C*–CF_3), 127.1 (q, *J*=286.9 Hz, CF_3), 111.4, 115.6, 118.9, 119.8, 123.0, 126.7, 136.2 (Ind), 127.5, 128.5, 130.3, 133.4 (Ar). ESI-MS (*m*/*z*): calcd for $C_{19}H_{18}F_3N_2$ [M^+] 331.1422, found 331.1417. Anal. Calcd for $C_{19}H_{17}F_3N_2$: C, 69.08; H, 5.19. Found: C, 68.98; H, 5.13.

4.4.4. Methyl 4-([1-trifluoromethyl-2,3,4,9-tetrahydro-1H-β-carboline-1-yl]methyl)benzoate (**7d**)

Obtained from enamine **2d** (299 mg, 1 mmol) and tryptamine (168 mg, 1.05 mmol). Yield: 272 mg (70%); white powder; mp 87–89 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.83 (br s, 1H, CH_2CH_2NH), 2.18–2.27, 2.95–3.05, 3.10–3.19 (all m, 1H, CH_2CH_2NH), 2.65 (dt, *J*=15.2, 3.4 Hz, 1H, CH_2CH_2NH), 3.22, 3.49 (both d, *J*=13.5 Hz, 1H, CH_2Ar), 3.89 (s, 3H, CO_2CH_3), 6.88 (d, *J*=8.1 Hz, 2H, Ar), 7.19 (t, *J*=7.7 Hz, 1H, Ind), 7.30 (t, *J*=7.7 Hz, 1H, Ind), 7.47 (d, *J*=7.7 Hz, 1H, Ind), 7.52 (d, *J*=7.7 Hz, 1H, Ind), 7.82 (d, *J*=8.1 Hz, 2H, Ar), 8.58 (br s, 1H, NH, Ind); ^{19}F NMR (282 MHz, $CDCl_3$) δ −75.38; ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.9 (CH_2CH_2NH), 40.4 (CH_2CH_2NH, CH_2Ar), 52.1 (CO_2CH_3), 60.0 (q, *J*=26.3 Hz, *C*–CF_3), 126.9 (q, *J*=287.6 Hz, CF_3), 111.3, 115.6, 118.9, 119.8, 123.1, 126.5, 126.9, 136.2 (Ind), 129.2, 129.5, 130.4, 139.1 (Ar), 166.9 (CO_2CH_3). ESI-MS (*m*/*z*): calcd for $C_{21}H_{20}F_3N_2O_2$ [M^+] 389.1477, found 389.1474. Anal. Calcd for $C_{21}H_{19}F_3N_2O_2$: C, 64.94; H, 4.93. Found: C, 65.07; H, 4.69.

4.4.5. 1-(2-Bromobenzyl)-1-trifluoromethyl-2,3,4,9-tetrahydro-1H-β-carboline (**7e**)

Obtained from enamine **2e** (320 mg, 1 mmol) and tryptamine (168 mg, 1.05 mmol). Yield: 249 mg (61%); white powder; mp 142–144 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.07 (br s, 1H, CH_2CH_2NH), 2.23–2.33, 2.85–2.94, 3.08–3.18 (all m, 1H, CH_2CH_2NH), 2.66 (dt, *J*=15.4, 4.3 Hz, 1H, CH_2CH_2NH), 3.42, 3.81 (both d, *J*=13.9 Hz, 1H, CH_2Ar), 6.48 (dd, *J*=7.8, 1.1 Hz, 1H, Ar), 6.92 (td, *J*=7.8, 1.1 Hz, 1H, Ar), 7.04 (td, *J*=7.8, 1.1 Hz, 1H, Ar), 7.19 (td, *J*=7.6, 0.8 Hz, 1H, Ind), 7.30 (td, *J*=7.6, 1.1 Hz, 1H, Ind), 7.47 (d, *J*=7.8 Hz, 1H, Ar), 7.52–7.56 (m, 2H, Ind), 8.15 (br s, 1H, NH, Ind); ^{19}F NMR (282 MHz, $CDCl_3$) δ −75.48; ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8 (CH_2CH_2NH), 39.3, 40.3 (CH_2CH_2NH, CH_2Ar), 61.0 (q, *J*=26.4 Hz, *C*–CF_3), 127.0 (q, *J*=286.9 Hz, CF_3), 111.3, 115.9, 118.9, 119.8, 123.0, 126.4, 126.6, 136.2 (Ind), 126.9, 127.3, 128.8, 131.6, 132.8, 133.9 (Ar). ESI-MS (*m*/*z*): calcd for $C_{19}H_{17}BrF_3N_2$ [M^+] 409.0527, found 409.0522. Anal. Calcd for $C_{19}H_{16}BrF_3N_2$: C, 55.76; H, 3.94. Found: C, 55.59; H, 3.84.

4.4.6. 1-(2-Nitrobenzyl)-1-trifluoromethyl-2,3,4,9-tetrahydro-1H-β-carboline (**7f**)

Obtained from enamine **2f** (286 mg, 1 mmol) and tryptamine (168 mg, 1.05 mmol). Yield: 248 mg (66%); yellow powder; mp 116–118 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.17–2.26, 2.89–2.97, 3.10–3.18 (all m, 1H, CH_2CH_2NH), 2.56 (dt, *J*=14.9, 3.4 Hz, 1H, CH_2CH_2NH), 3.48, 3.97 (both d, *J*=13.6 Hz, 1H, CH_2Ar), 6.81 (dd, *J*=7.8, 1.0 Hz, 1H, Ar), 7.10–7.16 (m, 2H, Ind), 7.22–7.29 (m, 2H, Ar), 7.44 (d, *J*=8.6 Hz, 2H, Ind), 7.76 (dd, *J*=8.1, 1.3 Hz, 1H, Ar), 8.16 (br s, 1H, NH, Ind); ^{19}F NMR (282 MHz, $CDCl_3$) δ −75.90; ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3 (CH_2CH_2NH), 36.3, 40.0 (CH_2CH_2NH, CH_2Ar), 61.2 (q, *J*=25.6 Hz, *C*–CF_3), 127.3 (q, *J*=287.1 Hz, CF_3), 111.3, 115.7, 118.7, 119.8, 122.9, 126.0, 126.4, 136.3 (Ind), 124.2, 127.8, 129.3, 131.9, 132.7, 151.3 (Ar). ESI-MS (*m*/*z*): calcd for $C_{19}H_{17}F_3N_3O_2$ [M^+] 376.1273, found 376.1267. Anal. Calcd for $C_{19}H_{16}F_3N_3O_2$: C, 60.80; H, 4.30. Found: C, 60.91; H, 4.14.

4.4.7. 1-(3-Nitrobenzyl)-1-trifluoromethyl-2,3,4,9-tetrahydro-1H-β-carboline (**7g**)

Obtained from enamine **2g** (286 mg, 1 mmol) and tryptamine (168 mg, 1.05 mmol). Yield: 255 mg (68%); yellow powder; mp 167–168 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.80 (br s, 1H, CH_2CH_2NH), 2.20–2.30, 3.03–3.11, 3.15–3.22 (all m, 1H, CH_2CH_2NH), 2.65 (dt, *J*=15.2, 3.5 Hz, 1H, CH_2CH_2NH), 3.25, 3.47 (both d, *J*=13.9 Hz, 1H, CH_2Ar), 7.05 (d, *J*=8.0 Hz, 1H, Ar), 7.16 (t, *J*=7.8 Hz, 1H, Ind), 7.24 (t, *J*=8.0 Hz, 1H, Ar), 7.28 (t, *J*=7.8 Hz, 1H, Ind), 7.47 (t, *J*=7.8 Hz, 2H, Ind), 7.89 (d, *J*=1.4 Hz, 1H, Ar), 8.03 (dd, *J*=8.0, 1.4 Hz, 1H, Ar), 8.22 (br s, 1H, NH, Ind); ^{19}F NMR (282 MHz, $CDCl_3$) δ −75.11; ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8 (CH_2CH_2NH), 40.3, 40.4 (CH_2CH_2NH, CH_2Ar), 60.2 (q, *J*=25.6 Hz, *C*–CF_3), 127.5 (q, *J*=287.3 Hz, CF_3), 111.3, 115.8, 118.8, 120.0, 123.2, 126.3, 126.4, 136.2 (Ind), 122.3, 125.5, 128.9, 136.3, 147.8 (Ar). ESI-MS (*m*/*z*): calcd for $C_{19}H_{17}F_3N_3O_2$ [M^+] 376.1273, found 376.1267. Anal. Calcd for $C_{19}H_{16}F_3N_3O_2$: C, 60.80; H, 4.30. Found: C, 60.71; H, 4.20.

4.4.8. 1-(4-Methoxybenzyl)-1-trifluoromethyl-2,3,4,9-tetrahydro-1H-β-carboline (**7h**)

Obtained from enamine **2h** (271 mg, 1 mmol) and tryptamine (168 mg, 1.05 mmol). Yield: 240 mg (67%); white powder; mp 126–127 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.74 (br s, 1H, CH_2CH_2NH), 2.20–2.31, 3.05–3.13, 3.14–3.22 (all m, 1H, CH_2CH_2NH), 2.69 (dt, *J*=15.2, 3.4 Hz, 1H, CH_2CH_2NH), 3.17, 3.43 (both d, *J*=13.9 Hz, 1H, CH_2Ar), 3.75 (s, 3H, OCH_3), 6.70 (s, 4H, Ar), 7.24 (td, *J*=7.8, 0.8 Hz, 1H,

Ind), 7.35 (td, 1H, Ind, J=7.8, 1.1 Hz), 7.49 (d, 1H, Ind, J=7.8 Hz), 7.59 (d, 1H, Ind, J=7.8 Hz), 8.30 (br s, 1H, N*H*, Ind); ^{19}F NMR (282 MHz, $CDCl_3$) δ −75.53; ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.1 (*C*H_2CH$_2$NH), 39.4, 40.6 (CH$_2$*C*H$_2$NH, *C*H_2Ar), 55.2 (OCH_3), 55.9 (q, J=25.6 Hz, *C*–CF_3), 127.1 (q, J=286.9 Hz, CF_3), 111.4, 115.6, 118.9, 119.8, 122.9, 126.7, 127.7, 136.2 (Ind), 113.9, 125.2, 131.4, 159.0 (Ar). ESI-MS (m/z): calcd for $C_{20}H_{20}F_3N_2O$ [M^+] 361.1528, found 361.1525. Anal. Calcd for $C_{20}H_{19}F_3N_2O$: C, 66.66; H, 5.31. Found: C, 66.90; H, 5.19.

4.4.9. 6-n-Butyl-1-(4-chlorobenzyl)-1-trifluoromethyl-2,3,4,9-tetrahydro-1H-β-carboline (**7i**)

Obtained from enamine **2b** (276 mg, 1 mmol) and 2-(5-butyl-1*H*-indol-3-yl)ethylamine (227 mg, 1.05 mmol). Yield: 316 mg (75%); brown viscous oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02 (t, J=7.3 Hz, 3H, $CH_2CH_2CH_2CH_3$), 1.35 (br s, 1H, CH_2CH_2NH), 1.41–1.53, 1.69–1.78 (both m, 2H, $CH_2CH_2CH_2CH_3$), 2.67 (dt, J=15.4, 3.4 Hz, 1H, CH_2CH_2NH), 2.79 (t, J=7.7 Hz, 2H, $CH_2CH_2CH_2CH_3$), 2.22–2.31, 3.02–3.08, 3.12–3.20, (all m, 1H, CH_2CH_2NH), 3.16, 3.41 (both d, J=13.8 Hz, 1H, CH_2Ar), 6.74 (d, J=8.3 Hz, 2H, Ar), 7.14 (d, J=8.3 Hz, 2H, Ar), 7.17 (d, J=7.6 Hz, 1H, Ind), 7.35 (s, 1H, Ind), 7.39 (d, J=8.3 Hz, 1H, Ind), 8.14 (br s, 1H, N*H*, Ind); ^{19}F NMR (282 MHz, $CDCl_3$) δ −75.73; ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1 ($CH_2CH_2CH_2CH_3$), 22.1 (*C*H_2CH$_2$NH), 22.6 ($CH_2CH_2CH_2CH_3$), 34.5 ($CH_2CH_2CH_2CH_3$), 35.9 (*C*$H_2CH_2CH_2CH_3$), 39.8, 40.5 (CH$_2$*C*H$_2$NH, *C*H_2Ar), 60.0 (q, J=26.4 Hz, *C*–CF_3), 127.0 (q, J=287.6 Hz, CF_3), 111.0, 115.4, 118.0, 124.1, 126.8, 127.2, 134.5, 134.8 (Ind), 128.6, 131.7, 132.2, 133.5 (Ar). ESI-MS (m/z): calcd for $C_{23}H_{25}ClF_3N_2$ [M^+] 421.1658, found 421.1653. Anal. Calcd for $C_{23}H_{24}ClF_3N_2$: C, 65.63; H, 5.75. Found: C, 65.54; H, 5.86.

4.4.10. 6,7-Diethoxy-1-(4-nitrobenzyl)-1-trifluoromethyl-1,2,3,4-tetrahydroisoquinoline (**11a**)

Obtained from enamine **2a** (286 mg, 1 mmol) and 2-(3,4-diethoxyphenyl)ethylamine (220 mg, 1.05 mmol). Yield: 181 mg (54%); viscous yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46, 1.48 (both t, J=7.0 Hz, 3H, OCH_2CH_3), 1.90 (br s, 1H, CH_2CH_2NH), 2.32–2.41, 2.45–2.54, 2.83–2.92, 3.09–3.16 (all m, 1H, CH_2CH_2NH), 3.18, 3.46 (both d, J=13.7 Hz, 1H, CH_2Ar), 4.06, 4.14 (both q, J=7.0 Hz, 2H, OCH_2CH_3), 6.52 (s, 1H, Ar), 7.10 (s, 1H, Ar), 7.16 (d, J=8.7 Hz, 2H, 4-$NO_2C_6H_4$–), 7.99 (d, J=8.7 Hz, 2H, 4-$NO_2C_6H_4$–); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.8, 14.9 (both OCH_2CH_3), 29.7 (*C*H_2CH$_2$NH), 39.4, 42.2 (CH$_2$*C*H$_2$NH, *C*H_2Ar), 61.8 (q, J=24.4 Hz, *C*–CF_3), 64.2, 65.3 (both OCH_2CH_3), 127.5 (q, J=290.6 Hz, CF_3), 122.8, 131.6, 143.1, 146.7 (4-$NO_2C_6H_4$–), 113.3, 113.4, 121.9, 131.1, 146.9, 148.9 (Ar). Anal. Calcd for $C_{21}H_{23}F_3N_2O_4$: C, 59.43; H, 5.46. Found: C, 59.57; H, 5.24.

4.4.11. 6,7-Diethoxy-1-(4-chlorobenzyl)-1-trifluoromethyl-1,2,3,4-tetrahydroisoquinoline (**11b**)

Obtained from enamine **2b** (276 mg, 1 mmol) and 2-(3,4-diethoxyphenyl)ethylamine (220 mg, 1.05 mmol). Yield: 157 mg (48%); viscous colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46–1.52 (m, 6H, 2 °CH_2CH_3), 1.68 (br s, 1H, CH_2CH_2NH), 2.28–2.38, 2.48–2.56, 2.80–2.88, 3.04–3.11 (all m, 1H, CH_2CH_2NH), 3.08, 3.36 (both d, J=13.8 Hz, 1H, CH_2Ar), 4.09, 4.15 (both q, J=7.0 Hz, 2H, OCH_2CH_3), 6.54 (s, 1H, Ar), 6.88 (d, J=8.3 Hz, 2H, 4-ClC_6H_4–), 7.11 (s, 1H, Ar), 7.13 (d, J=8.3 Hz, 2H, 4-ClC_6H_4–), ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.8, 14.9 (both OCH_2CH_3), 29.7 (*C*H_2CH$_2$NH), 39.5, 41.6 (CH$_2$*C*H$_2$NH, *C*H_2Ar), 61.6 (q, J=24.2 Hz, *C*–CF_3), 64.2, 65.2 (both OCH_2CH_3), 127.5 (q, J=288.4 Hz, CF_3), 128.2, 132.0, 133.3, 139.3 (4-ClC_6H_4–), 113.3, 114.1, 122.8, 131.2, 146.6, 148.6 (Ar). Anal. Calcd for $C_{21}H_{23}ClF_3NO_2$: C, 60.94; H, 5.60. Found: C, 60.71; H, 5.74.

4.5. Methyl 1-(4-chlorobenzyl)-1-trifluoromethyl-2,3,4,9-tetrahydro-1*H*-β-carboline-3-carboxylate (9)

In a 25 mL round bottomed flask a mixture of methyl L-tryptophanate hydrochloride (0.28 g, 1.05 mmol), enamine **2b** (276 mg, 1 mmol) and HOAc (3 mL) were stirred until the enamine disappeared (about 1 h, TLC monitoring). The reaction mixture was refluxed for 3 h and HOAc was evaporated in vacuo. The residue was diluted with CH_2Cl_2 (30 mL) and washed with saturated K_2CO_3 solution. After drying over Na_2SO_4, the volatiles were removed in vacuo and the residue was purified by column chromatography on silica gel using CH_2Cl_2 as eluent giving a 67:33 mixture of diastereomers. Yield: 181 mg (43%); colorless solid; IR (Nujol) 1360, 1540 (NO_2), 1670 (C=C) cm^{-1}. Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.73–2.83, 2.97–3.07, 3.08–3.13 (all m, 1H, $CHCH_2NH$), 3.24, 3.45 (both d, J=13.9 Hz, 1H, CH_2Ar), 3.80 (s, 3H, CO_2CH_3), 6.91 (d, J=8.2 Hz, 2H, Ar), 7.16 (d, J=8.2 Hz, 2H, Ar), 7.19 (t, J=7.5 Hz, 1H, Ind), 7.29 (t, J=7.5 Hz, 1H, Ind), 7.42–7.49 (m, 1H, Ind), 7.52–7.58 (m, 1H, Ind), 8.26 (br s, 1H, N*H*, Ind); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.3 (*C*HCH_2NH), 38.7, 40.7 (CH*C*H$_2$NH, *C*H_2Ar), 52.5 (CO_2CH_3), 61.5 (q, J=26.3 Hz, *C*–CF_3), 125.8 (q, J=285.4 Hz, CF_3), 111.4, 113.1, 118.8, 120.1, 123.2, 126.2, 127.2, 136.6 (Ind), 128.7, 131.5, 132.6, 135.5 (Ar), 172.1 (*C*O_2CH_3). Minor diastereomer: ^{1}H NMR ($CDCl_3$) δ 2.05–2.14, 3.95–4.02 (both m, 1H, $CHCH_2NH$), 3.17, 3.37 (both d, J=13.7 Hz, 1H, CH_2Ar), 6.72 (d, J=8.3 Hz, 2H, Ar), 7.16 (d, J=8.3 Hz, 2H, Ar), 8.36 (br s, 1H, N*H*, Ind); ^{13}C NMR ($CDCl_3$) δ 23.7 (*C*HCH_2NH), 38.3, 39.7 (CH*C*H$_2$NH, *C*H_2Ar), 52.3 (CO_2CH_3), 57.9 (q, J=27.1 Hz, *C*–CF_3), 114.2, 118.7, 120.0, 123.3, 126.1, 126.6, 136.4 (Ind), 128.8, 131.6, 132.5, 133.4 (Ar), 172.3 (*C*O_2CH_3), the other signals are identical to those of the major diastereomer. Calcd for $C_{21}H_{18}ClF_3N_2O_2$: C, 59.65; H, 4.29. Found: C, 59.71; H, 4.24.

4.6. Synthesis of 1-trifluoromethyl-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazines 13 (general procedure)

In a 25 mL round bottomed flask 2-(1*H*-pyrrol-1-yl)ethylamine **12** (0.12 g, 1.05 mmol), the corresponding enamine **2** (1 mmol) and HOAc were stirred at room temperature for 5 days (TLC monitoring). HOAc was removed in vacuo, the residue was diluted with CH_2Cl_2 (30 mL) and washed with saturated K_2CO_3 solution. After drying over Na_2SO_4, the volatiles were removed in vacuo and the residue was purified by column chromatography on silica gel using CH_2Cl_2 as eluent.

4.6.1. 1-(4-Nitrobenzyl)-1-trifluoromethyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine (**13a**)

Obtained from enamine **2a** (286 mg, 1 mmol). Yield: 221 mg (68%); red crystals; mp 110.1–111.5 °C; IR (Nujol) 1360, 1540 (NO_2), 1670 (C=C) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.85 (br s, 1H, CH_2CH_2NH), 2.87–2.95, 3.22–3.26, 3.27–3.36, 3.73–3.80 (all m, 1H, CH_2CH_2NH), 3.17, 3.44 (both d, J=13.1 Hz, 1H, CH_2Ar), 6.21–6.25, 6.33–6.37, 6.54–6.57 (all m, 1H, pyrrolyl), 7.14 (d, J=8.7 Hz, 2H, Ar), 8.03 (d, J=8.7 Hz, 2H, Ar); ^{19}F NMR (282 MHz, $CDCl_3$) δ −77.49; ^{13}C NMR (100 MHz, $CDCl_3$) δ 40.2, 42.7, 45.1 (*C*H_2CH$_2$NH, CH$_2$*C*H$_2$Ar), 60.8 (q, J=26.4 Hz, *C*–CF_3), 126.7 (q, J=287.6 Hz, CF_3), 107.2, 108.0, 120.6, 121.7 (pyrrolyl), 122.9, 131.7, 142.9, 147.1 (Ar). ESI-MS (m/z): calcd for $C_{15}H_{15}F_3N_3O_2$ [M^+] 326.1116, found 326.1116. Anal. Calcd for $C_{15}H_{14}F_3N_3O_2$: C, 55.39; H, 4.34. Found: C, 55.37; H, 4.16.

4.6.2. 1-(4-Chlorobenzyl)-1-trifluoromethyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine (**13b**)

Obtained from enamine **2b** (276 mg, 1 mmol). Yield: 220 mg (70%); pink powder; mp 105–107 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.73 (br s, 1H, CH_2CH_2NH), 2.86–2.93, 3.17–3.25, 3.26–3.35, 3.73–3.79 (all m, 1H, CH_2CH_2NH), 3.09, 3.39 (both d, J=13.5 Hz, 1H, CH_2Ar), 6.26–6.30, 6.36–6.40, 6.58–6.61 (all m, 1H, pyrrolyl), 6.87 (d, J=8.4 Hz, 2H, Ar), 7.20 (d, J=8.4 Hz, 2H, Ar); ^{19}F NMR (282 MHz, $CDCl_3$) δ −77.54; ^{13}C NMR (100 MHz, $CDCl_3$) δ 40.4, 42.2, 45.0 (*C*H_2CH$_2$NH, CH$_2$*C*H$_2$Ar), 60.5 (q, J=26.3 Hz, *C*–CF_3), 127.1 (q, J=286.9 Hz, CF_3), 107.2, 108.0, 120.4, 122.3 (pyrrolyl), 128.4, 131.9, 133.1, 133.3 (Ar). ESI-MS (m/z): calcd for $C_{15}H_{14}ClF_3N_2$ [M^+] 315.0876, found

315.0870. Anal. Calcd for $C_{15}H_{13}ClF_3N_2$: C, 57.43; H, 4.18. Found: C, 57.61; H, 4.24.

4.7. 7-(4-Chlorobenzyl)-7-trifluoromethyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine (15)

In a 25 mL round bottomed flask 2-thien-3-ylethylamine **14** (0.13 g, 1.05 mmol), enamine **2b** (276 mg, 1 mmol) and HOAc were stirred at room temperature for 2 days (TLC monitoring). HOAc was removed in vacuo, the residue was diluted with CH_2Cl_2 (30 mL) and washed with saturated K_2CO_3 solution. After drying over Na_2SO_4, the volatiles were removed in vacuo and the residue was purified by column chromatography on silica gel using CH_2Cl_2 as eluent. Yield: 179 mg (54%); white powder; mp 72.9–75.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.70 (br s, 1H, CH_2CH_2NH), 2.04–2.15, 2.91–2.98, 3.00–3.10 (all m, 1H, CH_2CH_2NH), 2.51 (dt, J=15.9, 2.9 Hz, 1H, CH_2CH_2NH), 3.14, 3.31 (both d, J=13.6 Hz, 1H, CH_2Ar), 6.78 (d, J=5.1 Hz, 1H, Th), 6.84 (d, J=8.3 Hz, 2H, Ar), 7.17 (d, J=8.3 Hz, 2H, Ar), 7.32 (d, J=5.1 Hz, 1H, Th); ^{19}F NMR (282 MHz, $CDCl_3$) δ −76.07; ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.5 (CH_2CH_2NH), 40.0, 42.5 (CH_2CH_2NH, CH_2Ar), 61.9 (q, J=26.4 Hz, C–CF_3), 126.6 (q, J=286.9 Hz, CF_3), 125.0, 127.3, 129.5, 140.3 (Th), 128.4, 131.7, 132.4, 133.4 (Ar). ESI-MS (m/z): calcd for $C_{15}H_{14}ClF_3NS$ [M^+] 332.0488, found 332.0482. Anal. Calcd for $C_{15}H_{13}ClF_3NS$: C, 54.30; H, 3.95. Found: C, 54.53; H, 4.16.

4.8. Synthesis of 4-trifluoromethyl-4,5,6,7-tetrahydro-3*H*-imidazo[4,5-*c*]pyridines 17 (general procedure)

In a 25 mL round bottomed flask a mixture of histamine dihydrochloride **16** (0.19 g, 1.05 mmol), the corresponding enamine **2** (1 mmol) and EtOH (5 mL) were refluxed until the enamine disappeared (about 3 h, TLC monitoring). A solution of KOH (0.12 g, 2.1 mmol) in EtOH (5 mL) was added in one portion and the reaction mixture was refluxed for another 15–20 h. EtOH was evaporated in vacuo, the residue was diluted with CH_2Cl_2 (30 mL) and washed with saturated K_2CO_3 solution. After drying over Na_2SO_4, the volatiles were removed in vacuo and the residue was purified by column chromatography on silica gel using a mixture CH_2Cl_2/MeOH 30:1 as eluent.

*4.8.1. 4-(4-Nitrobenzyl)-4-trifluoromethyl-4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridine (**17a**)*

Obtained from enamine **2a** (286 mg, 1 mmol). Yield: 215 mg (66%); viscous brown oil; IR (Nujol) 1360, 1540 (NO_2), 1670 (C=C) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.15–2.27, 2.40–2.48, 2.88–2.96, 3.14–3.21 (all m, 1H, CH_2CH_2NH), 3.08, 3.55 (both d, J=13.3 Hz, 1H, CH_2Ar), 7.08 (d, J=8.8 Hz, 2H, Ar), 7.58 (s, 1H, imidazolyl), 7.92 (d, J=8.8 Hz, 2H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.3 (CH_2CH_2NH), 39.6, 39.7 (CH_2CH_2NH, CH_2Ar), 60.7 (q, J=25.6 Hz, C–CF_3), 127.0 (q, J=289.1 Hz, CF_3), 128.2, 129.2, 134.3 (imidazolyl), 122.7, 131.5, 143.2, 146.8 (Ar). Anal. Calcd for $C_{14}H_{13}F_3N_4O_2$: C, 51.54; H, 4.02. Found: C, 51.71; H, 4.14.

*4.8.2. 4-(4-Chlorobenzyl)-4-trifluoromethyl-4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridine (**17b**)*

Obtained from enamine **2b** (276 mg, 1 mmol). Yield: 171 mg (54%); viscous brown oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.72 (br s, 1H, CH_2CH_2NH), 2.01–2.17, 2.61–2.69 (both m, 1H, CH_2CH_2NH), 2.92–3.09 (m, 2H, CH_2CH_2NH), 3.19, 3.55 (both d, J=14.3 Hz, 1H, CH_2Ar), 6.67 (d, J=8.3 Hz, 2H, Ar), 6.78 (s, 1H, imidazolyl), 7.20 (d, J=8.3 Hz, 2H, Ar), 7.84 (br s, 1H, NH, imidazolyl); ^{19}F NMR (282 MHz, $CDCl_3$) δ −75.70; ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7 (CH_2CH_2NH), 37.3, 40.4 (CH_2CH_2NH, CH_2Ar), 73.7 (q, J=29.3 Hz, C–CF_3), 124.6 (q, J=288.4 Hz, CF_3), 128.1, 133.7 (imidazolyl), 129.3, 129.6, 131.6, 134.5 (Ar). ESI-MS (m/z): calcd for $C_{14}H_{14}ClF_3N_3$ [M^+] 316.0828, found 316.0823. Anal. Calcd for $C_{14}H_{13}ClF_3N_3$: C, 53.26; H, 4.15. Found: C, 52.83; H, 4.16.

*4.8.3. 4-Benzyl-4-trifluoromethyl-4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridine (**17c**)*

Obtained from enamine **2c** (241 mg, 1 mmol). Yield: 216 mg (77%); viscous brown oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.81 (br s, 1H, CH_2CH_2NH), 1.95–2.06, 2.56–2.64 (both m, 1H, CH_2CH_2NH), 2.86–3.01 (m, 2H, CH_2CH_2NH), 3.19, 3.56 (both d, J=14.3 Hz, 1H, CH_2Ar), 6.69–6.77 (m, 2H, Ar), 7.17–7.26 (m, 3H, Ar), 7.86 (s, 1H, imidazolyl); ^{19}F NMR (282 MHz, $CDCl_3$) δ −75.78; ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6 (CH_2CH_2NH), 37.3, 40.9 (CH_2CH_2NH, CH_2Ar), 73.8 (q, J=28.6 Hz, C–CF_3), 124.8 (q, J=287.6 Hz, CF_3), 128.3, 131.0, 133.9 (imidazolyl), 127.0, 128.4, 129.1, 130.2 (Ar). ESI-MS (m/z): calcd for $C_{14}H_{15}F_3N_3$ [M^+] 282.1218, found 282.1216. Anal. Calcd for $C_{14}H_{14}F_3N_3$: C, 59.78; H, 5.02. Found: C, 60.01; H, 5.12.

*4.8.4. Methyl 4-[(4-trifluoromethyl-4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridine-4-yl)methyl]benzoate (**17d**)*

Obtained from enamine **2d** (299 mg, 1 mmol). Yield: 149 mg (44%); white powder; mp 153–154 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.72 (br s, 1H, CH_2CH_2NH), 2.11–2.21, 2.38–2.46, 2.83–2.92, 3.05–3.16 (all m, 1H, CH_2CH_2NH), 3.09, 3.57 (both d, J=13.1 Hz, 1H, CH_2Ar), 3.86 (s, 3H, CO_2CH_3), 6.95 (d, J=8.2 Hz, 2H, Ar), 7.62 (s, 1H, imidazolyl), 7.80 (d, J=8.2 Hz, 2H, Ar), ^{19}F NMR (282 MHz, $CDCl_3$) δ −75.75; ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.6 (CH_2CH_2NH), 39.8 (CH_2CH_2NH, CH_2Ar), 52.1 (CO_2CH_3), 60.5 (q, J=25.6 Hz, C–CF_3), 127.0 (q, J=287.6 Hz, CF_3), 128.6, 129.3, 134.3 (imidazolyl), 128.8, 129.1, 130.6, 140.3 (Ar), 167.1 (CO_2CH_3). ESI-MS (m/z): calcd for $C_{16}H_{17}F_3N_3O_2$ [M^+] 340.1273, found 340.1269. Anal. Calcd for $C_{16}H_{16}F_3N_3O_2$: C, 56.64; H, 4.75. Found: C, 56.28; H, 4.56.

*4.8.5. 4-(4-Methoxybenzyl)-4-trifluoromethyl-4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridine (**17h**)*

Obtained from enamine **2h** (271 mg, 1 mmol). Yield: 140 mg (45%); brown-yellow powder; mp 114–117 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.06–2.18, 2.37–2.45, 2.87–2.95, 3.04–3.12 (all m, 1H, CH_2CH_2NH), 2.99, 3.48 (both d, J=13.6 Hz, 1H, CH_2Ar), 3.71 (s, 3H, CH_3O), 6.68 (d, J=8.7 Hz, 2H, Ar), 6.73 (d, J=8.7 Hz, 2H, Ar), 7.63 (s, 1H, imidazolyl); ^{19}F NMR (282 MHz, $CDCl_3$) δ −75.82; ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.8 (CH_2CH_2NH), 38.6, 39.9 (CH_2CH_2NH, CH_2Ar), 55.1 (CH_3O), 60.1 (q, J=26.4 Hz, C–CF_3), 129.9 (q, J=285.4 Hz, CF_3), 127.8, 130.3, 134.2 (imidazolyl), 113.7, 126.0, 131.4, 158.7 (Ar). ESI-MS (m/z): calcd for $C_{15}H_{17}F_3N_3O$ [M^+] 312.1324, found 312.1318. Anal. Calcd for $C_{15}H_{16}F_3N_3O$: C, 57.87; H, 5.18. Found: C, 57.98; H, 5.11.

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