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Synthesis of new β-trifluoromethyl containing GABA and β-fluoromethyl containing *N*-benzylpyrrolidinones

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ABSTRACT

A whole series of 3-(mono-, di-, trifluoro)methyl-substituted *N*-benzylpyrrolidinones **5a–c** was synthesized by deoxyfluorination of corresponding 3-functionalized *N*-benzylpyrrolidinones. New β-trifluoromethyl containing GABA **4a** was obtained in two alternative ways: by successive hydrolysis and hydrogenolysis of 3-trifluoromethyl *N*-benzylpyrrolidinone **5a** and from trifluoroacetone as starting compound.

1. Introduction

Fluorinated analogs of natural substances play an important role in the design of new biologically active compounds [1]. Although a large number of various fluorine-containing amino acids have been synthesized during the past 50 years, they still are of particular interest due to their widespread bioorganic applications, e.g. as biological tracers, mechanistic probes and enzyme inhibitors. Every described pathway to a new fluorinated amino acid is paid considerable attention [2].

GABA (4-aminobutanoic acid, γ-aminobutyric acid) is the key central nervous system (CNS) inhibitory neurotransmitter [3]. Activators or inhibitors of GABA-metabolic enzymes (such as GABA-aminotransferase, GABA-AT or glutamate decarboxylase, GAD) as well as agonists/antagonists of GABA-receptors are active in therapy of Alzheimer's disease, Parkinson disorder, Huntington's chorea and epilepsy [4].

One of the most effective methodologies to develop new regulators of active concentration of GABA in the neuronal tissues is a structural modification of γ-aminobutyric acid. Various GABA derivatives and analogs are widely known as medicines, for example: vigabatrin [5], baclofen (Lioresal® and Baclon®) [6], gabapentin (GBP, Neurontin®) [7], pregabalin (Lyrica®) [8] (Fig. 1); and it is easy to see that the introduction of bulky lipophilic substituents in β-position of GABA's core is an essential condition to get new effective CNS regulators. It has been confirmed [9] that the steric parameters of the trifluoromethyl group are between *i*-Pr and *t*-Bu substituents (e.g. Taft steric values E_s for *i*-Pr < *i*-Bu < CF_3 < *t*-Bu are −1.76, −2.17, −2.40 and −2.78, respectively). On the other hand, it is noteworthy that only few examples of GABAs bearing fluoro-substituents at β-position have been synthesized, including some of 3-(fluoroaryl)- [10] and 3-fluoro-GABAs [11].

Recently we published the synthesis of β-hydroxy-β-(tri-, difluoro)methyl GABAs **2a**,**b** based on addition reaction of trimethylsililcyanide to readily available β-ethoxyvinyl (tri-, difluoro)methyl ketones **1a**,**b** (Scheme 1) [12]. Also β-trifluoromethyl carnitine **3** was synthesized from β-hydroxy-β-trifluoromethyl GABA **2a** and some biological tests of the amino acids **2a**,**b** and **3** *in vitro* and *in vivo* were performed [13].

Continuing our research on synthesis of polyfluoroalkyl containing GABAs, we report here about effective synthesis of 3-(mono-, di-, trifluoro)methyl containing *N*-benzylpyrrolidinones **5a–c** (as intermediates towards β-fluoromethyl-GABAs) by deoxyfluorination reactions from corresponding readily available 3-functionalized *N*-benzylpyrrolidinones bearing carboxylic,

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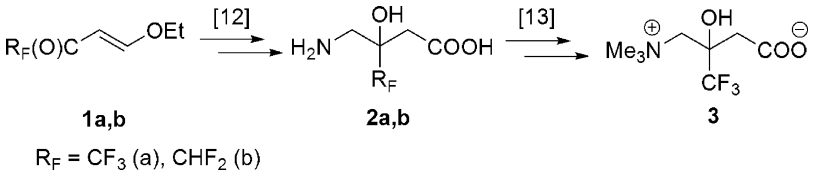


Scheme 1. Reported synthetic way to β-polyfluoromethyl containing GABAs **2** and carnitine **3**.

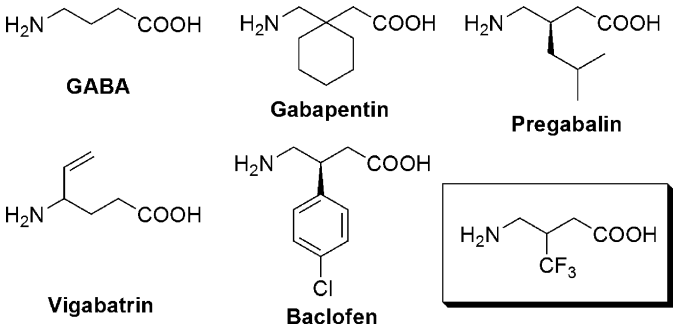


Fig. 1. GABA and its derivatives and analogues.

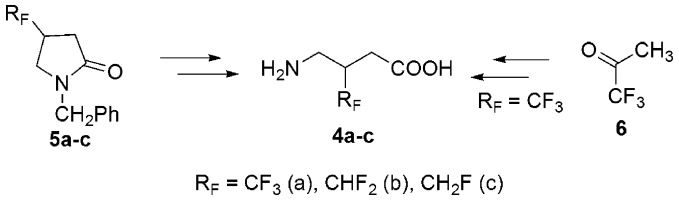
aldehyde and carbinol groups with sulfur tetrafluoride, DAST and Ishikawa's reagent, respectively. It is worth to mention that a lot of pyrrolidinone derivatives are of interest as CNS regulators, for example Piracetam and Levetiracetam [14]. Also racemic β-trifluoromethyl-γ-aminobutyric acid **4a** was synthesized both from *N*-benzyl-3-trifluoromethylpyrrolidinone **5a** by successive hydrolysis and hydrogenolysis and from trifluoroacetone **6** via 3-trifluoromethylcrotonic acid derivatives (Scheme 2).

2. Results and discussion

Some *N*-substituted or unsubstituted pyrrolidinones bearing mono- and trifluoromethyl groups at the position 3 were published previously [15]. 3-Trifluoromethyl containing pyrrolidinone was obtained from methyl 3-trifluoromethylacrylate as starting compound and 3-monofluoromethyl-analog of piracetam was synthesized by nucleophilic substitution of a mesyl group by fluorine using CsF.

The synthesis of a series of desired fluoro-containing pyrrolidinones **5a–c** by deoxyfluorination reactions demands the availability of corresponding heterocycles with carboxylic, aldehyde and carbinol functional groups (Scheme 3). The starting 1-benzyl-5-oxopyrrolidine-3-carboxylic acid **7** has been prepared readily from itaconic acid and benzylamine in 86% yield [16]. The acid **7** was transformed to the corresponding alcohol **8** and aldehyde **9** by common reactions. The alcohol **8** was synthesized in 93.5% overall yield by successive esterification and borohydride reduction. The aldehyde **9** was obtained in 37% yield by Swern oxidation of alcohol **8**.

Deoxyfluorination of acid **7** with SF_4 by heating in a stainless autoclave afforded pyrrolidinone **5a** in 64% yield. Monofluoromethyl pyrrolidinone **5c** was obtained in 80% yield. Both

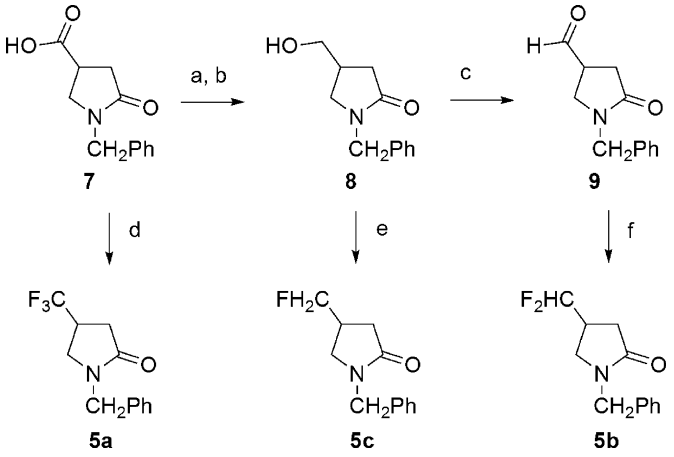


Scheme 2. Synthetic ways to β-polyfluoromethyl containing GABAs **4**.

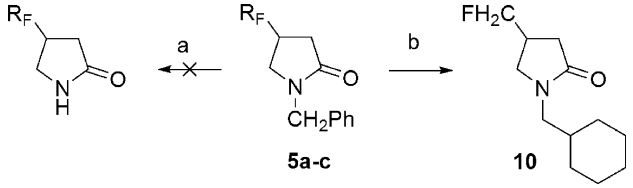
pyrrolidinones **5a**,**c** were conveniently purified by vacuum distillation. The aldehyde **9** was involved in the reaction with DAST immediately after regeneration from bisulfite adduct owing to its instability. Therefore, the yield of difluoromethyl pyrrolidinone **5b** did not exceed 30% after column chromatography. The pyrrolidinones **5a–c** are colorless oils and they are fully characterized by ^1H, ^{13}C and ^{19}F NMR spectra.

In order to transform the pyrrolidinones **5a–c** into the fluorinated GABAs **4a–c** a two-step procedure can be used: hydrogenolysis and hydrolysis in any sequence. However, our attempts to perform catalytic debenzylation of pyrrolidinones **5a–c** failed. Reduction of pyrrolidinone **5c** in the presence of 20% $Pd(OH)_2/C$, 100 °C and 100 bar H_2 led to the fully saturated product **10** (Scheme 4).

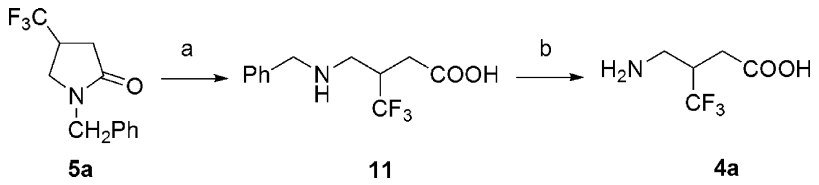
On the other hand, hydrolysis of various pyrrolidinones is a common method to obtain GABAs (for example the synthesis of *N*-Me-GABA from the *N*-Me-pyrrolidinone by refluxing in concentrated hydrochloric acid [17]). We found hydrolysis of pyrrolidinones **5a–c** not a trivial task. Thus, under the usual hydrolytic conditions the pyrrolidinone ring of **5a–c** was totally stable. Moreover, we observed elimination of hydrogen fluoride as a result of degradation of the fluoromethyl groups of pyrrolidinones **5b**,**c** under harder hydrolytic conditions. Only GABA **11** was obtained after heating of pyrrolidinone **5a** with conc. HCl in a sealed tube at 135 °C for 2 days in 22% yield and 74% conversion. Debenzylation of



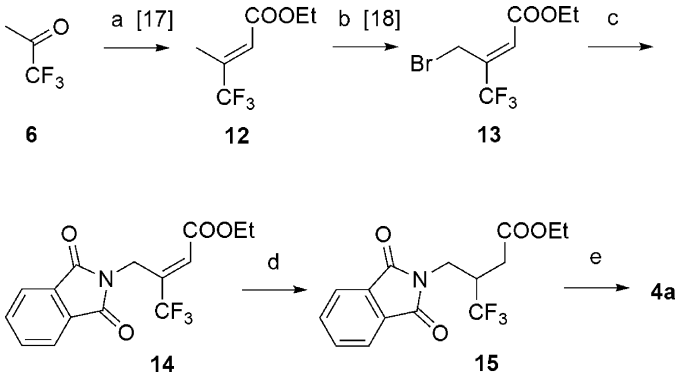
Scheme 3. Reagents and conditions: (a) MeOH, $SOCl_2$, 0–15 °C; (b) $NaBH_4$, *i*-PrOH; (c) Swern's oxidation; (d) SF_4, HF, 80 °C; (e) Ishikawa's reagent, NaF, CH_2Cl_2, RT; (f) DAST, CH_2Cl_2, RT.



Scheme 4. Reagents and conditions: (a) 20–130 °C, H_2 40–150 bar, 5–20% Pd/C; (b) aq. HOAc–H_2SO_4, 100 °C, H_2 100 bar, 20% $Pd(OH)_2/C$.



Scheme 5. Reagents and conditions: (a) conc. HCl, 135 °C, sealed tube; (b) H_2O, H_2 100 bar, 20% $Pd(OH)_2/C$.



Scheme 6. Reagents and conditions: (a) Ph_3P = CHCOOEt, CH_2Cl_2, 0 °C; (b) NBS, CCl_4, 80 °C, $(C_6H_5COO)_2$; (c) PhthNK, DMF, 80 °C; (d) H_2, 10% Pd/C, EtOH, HCOOH; (e) HCl, CH_3COOH, 110 °C.

GABA **11** to the target compound **4a** was performed in water in the presence of 20% $Pd(OH)_2/C$, 20 °C and 100 bar H_2 (Scheme 5).

We have also developed an alternative synthetic route to 3-CF_3-GABA **4a** based on trifluoroacetone **6** via the crotonate **12** as shown on Scheme 6. The crotonates **12** and **13** were readily obtained using procedures published previously: the Wittig reaction of trifluoroacetone afforded crotonate **12** in 70% yield [18], and the following bromination with *N*-bromosuccinimide gave **13** in 80% [19] yield. We found optimal reaction conditions (freshly prepared potassium phthalimide in dry DMF at 80 °C) to obtain pure phthalimide derivative **14**. Enhancement of reaction temperature or using a mixture of K_2CO_3 and phthalimide gave a large quantity of admixtures. Catalytic reduction of **14** in the presence of 10% Pd/C afforded **15** in 85% yield. Further acidic hydrolysis led to deprotection of both amine and carboxylic acid groups resulting in the 3-CF_3-GABA **4a** in good overall yield.

3. Conclusions

In summary, we have developed a new synthetic route to 3-polyfluoromethyl containing *N*-benzylpyrrolidinones **5a–c** based on deoxyfluorination reactions. Owing to high stability of *N*-benzylpyrrolidinone ring to acid hydrolysis and catalytic hydrogenolysis, we succeeded only in the synthesis of 3-CF_3-GABA **4a**. Another effective synthetic route was also proposed to synthesis of the amino acid **4a**. The latter is a new isosteric analog (see Section 1) of the widespread drug pregabalin (Pfizer).

4. Experimental

4.1. General

The ^1H, ^{13}C and ^{19}F NMR spectra were recorded on a Bruker DRX-500 instrument at 500, 125 and 470 MHz respectively. Chemical shifts (δ) are given in ppm relative to TMS (^1H, ^{13}C) and $CFCl_3$ (^{19}F). Compounds **7**, **13** and **14** were prepared according literature procedures [14,17,18]. Palladium catalysts were commercially available from "Aldrich Chemical Company, Inc.". Column chromatography was performed on silica gel 60 (Merck).

4.2. 1-Benzyl-4-(hydroxymethyl)pyrrolidin-2-one (8)

(a) In a 250 ml three-necked flask fitted with thermometer, a reflux condenser connected to a calcium chloride tube and a dropping funnel, was placed a solution of acid **7** (17.52 g, 80 mmol) in dry methanol (170 ml). The mixture was cooled to 0 °C and $SOCl_2$ (6.2 ml, 10.12 g, 85 mmol) was added at a rate that did not cause the temperature to rise above 15 °C. Then the bath was removed and the mixture was allowed to stay at rt for 12 h. The methanol was distilled off under reduced pressure, and the viscous liquid obtained was dissolved in chloroform (200 ml). After washing with water (3 × 40 ml), drying over anhydrous $MgSO_4$ and filtering, chloroform was removed under reduced pressure to give a light yellow oil which solidifies on standing. The yield of methyl 1-benzyl-5-oxopyrrolidine-3-carboxylate was 18.59 g (99.7%). The crude product was used in the next step without purification. ^1H NMR (500 MHz, $CDCl_3$): δ 2.70–2.83 (2H, m, $CH_2C{=}O$), 2.23 (1H, m, CH), 3.46–3.52 (2H, m, CH_2N), 3.73 (3H, s, $COOCH_3$), 4.45 (1H, d, H_a of CH_2Ph, J = 14.7 Hz), 4.52 (1H, d, H_b of CH_2Ph, J = 14.7 Hz), 7.24–7.38 (5H, m, Ph).

(b) To a cooled, vigorously stirred solution of methyl 1-benzyl-5-oxopyrrolidine-3-carboxylate (10.9 g, 47 mmol) of in dry *i*-propanol (100 ml) $NaBH_4$ (5.4 g, 143 mmol) was poured portionwise over 30 min, keeping the temperature between 0 and 5 °C. After 2 h the cooling bath was removed and the reaction mixture was stirred overnight. Then saturated NH_4Cl solution (20 ml) was added carefully (foaming occurs), followed by acetone (10 ml). The mixture was left over 1 h at rt. The solvent was removed completely on a rotary evaporator, the residue was treated with CH_2Cl_2 (200 ml) and filtered. Filter cake was washed with additional portions of CH_2Cl_2 (2 × 50 ml). Combined organic phase was washed with brine (50 ml), dried over $MgSO_4$, filtered and evaporated to give 9 g (93.8%) of pure carbinol **8** as a colorless viscous liquid; ^1H NMR (500 MHz, $CDCl_3$): δ 2.25–2.34 (2H, m, $CH_2C{=}O$), 2.50–2.62 (2H, m, CH + OH), 3.13 (1H, dd, H_a of CH_2N, J = 10.0, 4.7 Hz), 3.38 (1H, dd, H_b of CH_2N, J = 10.0, 8.2 Hz), 3.54–3.64 (2H, m, CH_2OH), 4.43 (1H, d, H_a of CH_2Ph, J = 14.7 Hz), 4.48 (1H, d, H_b of CH_2Ph, J = 14.7 Hz), 7.22–7.37 (5H, m, Ph); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 33.41, 34.60, 49.82, 50.27, 64.68, 127.62, 128.14, 128.71, 136.86, 135.49, 173.89; Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.17; H, 7.52; N, 6.75.

4.3. 1-Benzyl-5-oxopyrrolidine-3-carbaldehyde (9)

To stirred solution of dimethylsulfoxide (2.85 ml, 2.59 g, 33.2 mmol) in dry dichloromethane (20 ml) the solution of trifluoroacetic anhydride (4.50 ml, 6.71 g, 31.9 mmol) in dichloromethane (10 ml) was slowly added at −70 °C. After the 15 min the solution of hydroxymethyl compound **8** (4.35 g, 21.2 mmol) in dichloromethane (25 ml) was added dropwise. Stirring was continued for 1.5 h at −65 °C, and triethylamine (8.40 ml, 6.10 g, 50.4 mmol) was added in such a rate to maintain the temperature near −55 °C. The mixture was allowed to stand at −60 °C for 30 min and water (35 ml) was added. The phases were separated and the water was extracted with dichloromethane (2 × 30 ml).

Combined organic phase was washed with water (15 ml), dried over the $MgSO_4$, filtered and evaporated to give oily crude aldehyde **9**. The letter was dissolved in methanol (40 ml) and mixed with a solution of $NaHSO_3$ (2.8 g, 26.9 mmol) in water (5 ml) and heated at 60 °C for 5 min. After the cooling the precipitated solid was filtered, washed with ether twice, dried under reduced pressure and 2.4 g (36.8%) of bisufite adduct of **9** was obtained. ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.36 (2H, m, CH_2C=O), 2.74 (1H, m, CH_2CHCH_2), 3.17 (1H, dd, H_a of CH_2N, J = 9.8, 8.8 Hz), 3.89 (1H, dd, H_b of CH_2N, J = 9.8, 5.0 Hz), 4.31 (1H, d, H_a of CH_2Ph, J = 15.4 Hz), 4.39 (1H, d, H_b of CH_2Ph, J = 15.4 Hz), 5.67 (1H, d, J = 5.3 Hz, CH(OH)SO_2ONa), 7.18–7.37 (5H, m, Ph); Anal. Calcd for $C_{12}H_{14}NNaO_5S$: S, 10.43. Found: S, 10.06.

4.4. 1-Benzyl-4-(trifluoromethyl)pyrrolidin-2-one (5a)

A mixture of acid **7** (6.5 g, 30 mmol) and 15 ml of anhydrous HF was placed in a 50 ml high-pressure stainless still autoclave. Gaseous SF_4 (11.0 g, 0.1 mol) was placed in the autoclave under cooling with a liquid nitrogen. The reaction mixture was stirred at 85 °C for 4 h, then cooled to the rt and gaseous products were vented off. The residue was poured carefully into 100 g of ice and the bomb was rinsed three times with water. Combined water phase was extracted with ethyl acetate (3 × 100 ml). The organic phase was washed with 5% sodium carbonate solution, saturated NaCl solution, and dried over anhydrous $MgSO_4$. After the filtration and evaporation of EtOAc the dark brown oily residue was distilled under reduced pressure. The yield of the desired lactame was 4.6 g (63.8%) as colorless liquid, bp 81 °C/1 mmHg; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.65 (1H, dd, H_a CH_2C=O, J = 17.5; 6.9 Hz), 2.74 (1H, dd, H_b CH_2C=O, J = 17.5, 9.8 Hz), 3.06 (1H, m, CHCF_3), 3.37 (1H, dd, H_a of CH_2N, J = 10.0, 5.6 Hz), 3.46 (1H, dd, H_b of CH_2N, J = 10.0, 10.4 Hz), 4.46 (1H, d, H_a of CH_2Ph, J = 15.0 Hz), 4.52 (1H, d, H_a of CH_2Ph, J = 15.0 Hz), 7.27–7.39 (5H, m, Ph); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 30.86, 35.18 (q, J = 29.0 Hz), 45.47, 46.62, 126.59 (q, J = 277.2 Hz), 127.97, 128.13, 128.90, 135.49, 171.24; ^{19}F NMR (470 MHz, $CDCl_3$) δ: −73.62 (d, CF_3, J = 9.0 Hz); Anal. Calcd for $C_{12}H_{12}F_3NO$: C, 59.26; H, 4.97; N, 5.76. Found: C, 59.17; H, 5.22; N, 5.55.

4.5. 1-Benzyl-4-(difluoromethyl)pyrrolidin-2-one (5b)

To the solution of aldehyde **9** (0.390 g, 1.9 mmol) (freshly regenerated from its bisulfite adduct, Section 4.3) in dry dichloromethane (5 ml) the cooled solution of morpholinosulfur trifluoride (0.4 g, 2.5 mmol) in the CH_2Cl_2 (5 ml) was slowly added at 0 °C and stirring. The mixture was slowly warmed to rt and after the 5 h the reaction mixture was poured in dichloromethane (30 ml), concentrated aqueous sodium bicarbonate (5 ml) was added and the mixture was carefully shaken. Dichloromethane phase was separated, dried over anhydrous $MgSO_4$ and concentrated on a rotary evaporator. The product **5b** was purified by column chromatography on silica gel, R_f = 0.55, eluent EtOAc/Hexane (3/2). The yield of difluoromethyl compound **5b** was 128 mg (29.6%) as colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.52 (1H, dd, H_a CH_2C=O, J = 17.2; 6.3 Hz), 2.65 (dd, 1H, H_b CH_2C=O, J = 17.2; 9.9 Hz), 3.06 (m, 1H, CHCHF_2), 3.37 (dd, 1H, H_a of CH_2N, J = 10.3; 5.3 Hz), 3.46 (dd, 1H, H_b of CH_2N, J = 10.3; 9.3 Hz), 4.46 (d, 1H, H_a of CH_2Ph, J = 14.9 Hz), 4.49 (d, 1H, H_b of CH_2Ph, J = 14.9 Hz), 5.76 (td, 1H, CHF_2, J = 56.4, 4.3 Hz), 7.27–7.39 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 30.18, 34.20 (t, J = 22 Hz), 45.96 (t, J = 66.5 Hz), 52.83, 115.70 (t, J = 243.2 Hz), 127.21, 127.57, 128.25, 135.22, 171.46; ^{19}F NMR (470 MHz, CDCl3) δ: −122.89 (ddd, F_a of CHF_2, J = 284.1, 56.1, 12.8 Hz), −124.27 (ddd, F_b of CHF_2, J = 284.1, 56.1, 15.3 Hz); Anal. Calcd for $C_{12}H_{13}F_2NO$: C, 63.99; H, 5.82; N, 6.22. Found: C, 64.17; H, 5.92; N, 6.25.

4.6. 1-Benzyl-4-(fluoromethyl)pyrrolidin-2-one (5c)

To the mixture of carbinol **8** (3.6 g, 17.6 mmol) and dry NaF (1.0 g, 23.8 mmol) in dichloromethane (50 ml) Ishikawa reagent was added (4.7 g, 21.1 mmol) under stirring at 0–5 °C. The reaction mixture was slowly warmed to rt and stirred for 3 days (reaction was controlled by TLC, eluent CH_2Cl_2/MeOH, 40/1, R_f = 0.72). After completing the reaction the mixture was poured into ice-cold saturated aqueous sodium bicarbonate (50 ml), organic phase was separated and aqueous layer was extracted with dichloromethane (2 × 30 ml). Combined organic phase was washed sequentially with 10% aqueous sodium bisulfate and dried over anhydrous $MgSO_4$. Then dichloromethane and main part of tetrafluoropropionyl diethylamide (hydrolysate of Ishikawa reagent) was removed under reduced pressure. The rest was distilled and 2.9 g (79.8%) of product **5c** was obtained as a colorless oil; bp 142–144 °C/0.1 mmHg; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.29 (1H, dd, H_a of CH_2C=O, J = 16.2, 6.0 Hz), 2.60 (1H, dd, H_b of CH_2C=O, J = 16.2, 9.3 Hz), 2.97 (1H, m, CH), 3.17 (1H, m, H_a of CH_2N), 3.34 (1H, m, H_b of CH_2N), 4.23–4.49 (4H, m, CH_2F and CH_2Ph), 7.27–7.39 (5H, m, Ph); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 31.52 (d, J = 20.3 Hz), 32.80 (d, J = 7.0 Hz), 46.61, 48.30 (d, J = 6.1 Hz), 84.30 (d, J = 170.0 Hz), 127.74, 128.16, 128.80, 136.16, 173.12; ^{19}F NMR (470 MHz, $CDCl_3$) δ: −211.99 (m, CH_2F); Anal. Calcd for $C_{12}H_{14}FNO$: C, 69.55; H, 6.81; N, 6.76. Found: C, 69.47; H, 6.97; N, 6.45.

4.7. 1-(Cyclohexylmethyl)-4-(fluoromethyl)pyrrolidin-2-one (10)

A mixture of pyrrolidinone **5c** (190 mg, 0.92 mmol), water (0.2 ml), HOAc (0.2 ml), conc. H_2SO_4 (180 mg) and 20% $Pd(OH)_2$/C (100 mg) was hydrogenated at 100 °C under the 100 bar pressure overnight. Then water (1.5 ml) was added, the mixture was filtered through silica gel which was washed with water (2 ml). The filtered catalyst on silica gel was washed with dichloromethane (30 ml), after drying over $MgSO_4$ dichloromethane was evaporated and 186 mg (95.1%) of the product **10** was obtained as colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.87–1.75 (11H, m, C_6H_{11}), 2.20 (1H, dd, H_a CH_2C=O, J = 17.0, 6.1 Hz), 2.53 (1H, dd, H_b CH_2C=O, J = 17.0, 9.3 Hz), 2.72 (1H, m, CHCH_2F), 3.08 (2H, m, C$H_2C_6H_{11}$), 3.24 (1H, dd, H_a CH_2N, J = 10.0, 5.1 Hz), 3.48 (1H, dd, H_b CH_2N, J = 10.0, 8.3 Hz), 4.26–4.45 (2H, m, CH_2F); Anal. Calcd for $C_{12}H_{20}FNO$: C, 67.57; H, 9.45; N, 6.57. Found: C, 67.38; H, 5.66; N, 6.35.

4.8. 3-((Benzylamino)methyl)-4,4,4-trifluorobutanoic acid (11) hydrochloride

A mixture of pirrolidinone **5c** (1.79 g, 7.37 mmol) and 20 ml of conc. hydrochloric acid was heated in a sealed tube at 130 °C for 48 h. The excess of hydrochloric acid was evaporated under reduced pressure to dryness and the residue was triturated with ether (15 ml). The white crystals formed was filtered and washed with ether (2 × 2 ml) giving 480 mg (21.9%) of the product. Evaporation of mother liquors gave 1.26 g of starting pyrrolidinone **11** (conversion 74.0%); ^{1}H NMR (500 MHz, D_2O) δ: 2.57 (1H, dd, H_a CH_2C=O, J = 17.5, 8.4 Hz), 2.53 (1H, dd, H_b CH_2C=O, J = 17.6, 4.4 Hz), 3.16 (1H, m, CHCF_3), 3.22 (1H, dd, H_a CH_2N, J = 13.6, 5.3 Hz), 3.39 (1H, dd, H_b CH_2N, J = 13.6, 6.4 Hz), 4.22 (1H, d, H_a CH_2Ph, J = 13.3 Hz), 4.25 (1H, d, H_b CH_2Ph, J = 13.3 Hz), 7.41 (5H, s, Ph); ^{19}F NMR (470 MHz, D_2O) δ: −71.48 (d, J = 9.9 Hz); Anal. Calcd for $C_{12}H_{16}F_3NO_2$·HCl: C, 48.09; H, 5.72; N, 4.67. Found: C, 47.91; H, 5.94; N, 4.55.

4.9. 3-(Aminomethyl)-4,4,4-trifluorobutanoic acid (4a) hydrochloride

A mixture of *N*-benzylaminoacid hydrochloride **11** (240 mg, 0.81 mmol) and 20% $Pd(OH)_2$/C (100 mg) in distilled water (2 ml)

was hydrogenated at room temperature and a pressure of 100 bar for 24 h. The solution was then filtered through silica gel and washed with water (10 ml). Evaporation of the filtrate under reduced pressure yielded desired amino acid hydrochloride **4a** as a thick white powder (130 mg, yield 77.6%); ^{1}H NMR (500 MHz, D_2O) δ: 2.53 (1H, dd, H_a CH_2C=O, J = 17.2, 8.0 Hz), 2.74 (1H, dd, H_b CH_2C=O, J = 17.2, 3.3 Hz), 3.01 (1H, m, CHCF$_3$), 3.18 (1H, dd, H_a CH_2N, J = 13.4, 4.0 Hz), 3.30 (1H, dd, H_b CH_2N, J = 13.4, 7.1 Hz); ^{13}C NMR (125 MHz, D_2O) δ: 32.02, 37.82, 38.41 (q, J = 27.4 Hz), 126.46 (q, J = 279.9 Hz), 174.94; ^{19}F NMR (470 MHz, D_2O) δ: −69.52 (d, J = 9.1 Hz); Anal. Calcd for $C_{15}H_{10}F_3NO_2$·HCl: C, 28.65; H, 5.29; N, 6.68. Found: C, 28.83; H, 5.42; N, 6.27.

4.10. (E)-Ethyl 3-((1,3-dioxoisoindolin-2-yl)methyl)-4,4,4-trifluorobut-2-enoate (14)

A mixture of crotonate **13** (3.0 g, 11.5 mmol) and potassium phthalimide (2.13 g, 11.5 mmol) in 15 ml of dry DMF was heated at 80–90 °C and stirring for 3–4 h (reaction was controlled by TLC). After completing the reaction the mixture was cooled and concentrated in vacuum. The rest was treated with EtOAc (30 ml), washed with water (2 × 25 ml) and organic phase was dried over the $MgSO_4$. After evaporation of the solvent in vacuum the product **14** was purified by column chromatography, the yield was 3.1 g (82.4%) as white crystals, R_f = 0.56, eluent EtOAc/Hexane (1/4); mp 57 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.37 (3H, t, J = 7.1 Hz, CH_3), 4.34 (2H, q, J = 7.1 Hz, OCH_2), 5.11 (1H, s, CH_2N), 6.60 (1H, s, =CH), 7.72 (2H, m, arom.), 7.85 (2H, m, arom.); ^{19}F NMR (470 MHz, $CDCl_3$) δ: −67.7 (s, CF_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.08, 32.43, 61.67, 122.47 (q, J_{CF} = 279.0 Hz), 123.49, 127.08 (q, J_{CF} = 5.8 Hz), 131.87, 134.17, 136.96 (q, J_{CF} = 29.4 Hz), 164.06, 167.28; Anal. Calcd for $C_{15}H_{12}F_3NO_4$: C, 55.26; H, 3.80; N, 4.14. Found: C, 55.05; H, 3.70; N, 4.28.

4.11. Ethyl 3-((1,3-dioxoisoindolin-2-yl)methyl)-4,4,4-trifluorobutanoate

A mixture of compound **14** (1 g, 3 mmol) and Pd/C (0.1 g) in EtOH (10 ml) and formic acid (2 ml) was stirred in hydrogen atmosphere (1 bar) at rt for 5–8 h (reaction was controlled by TLC). After completing the reaction the catalyst was filtered off, the solvents were evaporated in vacuum, ethyl 3-((1,3-dioxoisoindolin-2-yl)methyl)-4,4,4-trifluorobutanoate was purified by column chromatography, the yield was 0.85 g (84.5%) as white crystals, R_f = 0.48, eluent CH_2Cl_2/Et_2O (1/2); mp 70–72 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.08 (3H, t, J = 7.1 Hz, CH_3), 2.46 (1H, dd, J = 17.0, 7.8 Hz, H_a of CH_2C=O), 2.62 (1H, dd, J = 17.0, 5.0 Hz, H_b of CH_2C=O), 3.26 (1H, m, CH), 3.82 (2H, m, CH_2N), 3.92 (2H, m, CH_2O), 7.67 (2H, m, arom.), 7.80 (2H, m, arom.); ^{19}F NMR (470 MHz, $CDCl_3$) δ: −71.61 (d, J_{HF} = 8.0 Hz); Calcd for $C_{15}H_{14}F_3NO_4$: C, 54.92; H, 4.36; N, 4.10. Found: C, 54.73; H, 4.29; N, 4.25.

4.12. 3-(Aminomethyl)-4,4,4-trifluorobutanoic acid (4a)

A mixture of ethyl 3-((1,3-dioxoisoindolin-2-yl)methyl)-4,4,4-trifluorobutanoate (0.8 g, 2.4 mmol) in HOAc (8.0 ml) and conc. HCl (2 ml) was stirred at 110 °C for 2 days. After completing the reaction the solvents were evaporated in vacuum, the rest was treated by water (20 ml), the solution was extracted by EtOAc (2 × 15 ml) and amino acid **4a** was isolated from water phase by ion exchange resin Amberlite IR-120 with following aq. NH_3 elution and evaporation. The yield of GABA **4a** was 0.31 g (74.5%); ^{1}H NMR (500 MHz, D_2O) δ: 2.33 (1H, dd, H_a of CH_2C=O, J = 16.2, 8.0 Hz), 2.56 (1H, dd, 1H, H_b of CH_2C=O, J = 16.2, 5.2 Hz), 2.98 (1H, m, CH), 3.11 (1H, dd, H_a of CH_2N, J = 13.6, 5.6 Hz), 3.26 (1H, dd, H_b of CH_2N, J = 13.6, 6.7 Hz); ^{19}F NMR (470 MHz, D_2O) δ: −71.63 (d, J = 6.4 Hz); ^{13}C NMR (125 MHz, D_2O) δ: 34.75, 38.31, 39.32 (q, J = 26.7 Hz), 124.69 (q, J = 280.0 Hz), 177.72. Anal. Calcd for $C_5H_8F_3NO_2$: C, 35.29; H, 4.90; N, 7.81. Found: C, 35.10; H, 4.71; N, 8.19.

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