Modification of biologically active amides and amines with fluorine-containing heterocycles

4.* Trifluoromethyl-containing heterocyclic pyracetam derivatives

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A one-pot method for the synthesis of trifluoromethyl-containing heterocyclic pyracetam derivatives has been suggested by the reaction of pyracetam, hexafluoroacetone, and 1,3-binucleophiles, *viz.*, 3-aminocrotononitrile, 6-aminouracyls, 6-aminothiouracyl, *N*-benzyl-3-aminocyclohexenone, and 2-aminothiazoline.

Key words: pyracetam, hexafluoroacetone, 3-aminocrotononitrile, 6-aminouracyls, 6-amino-1-phenylthiouracyl, *N*-benzyl-3-aminocyclohexenone, 2-aminothiazoline, fluorine-containing compounds, 1,4-dihydropyrimidine, dihydropyrimido[4,5-*d*]pyrimidines, tetrahydro-1*H*-quinazoline, thiazolo[3,2-*a*][1,3,5]triazine, cyclocondensation.

Pyracetam is a nootropic drug of metabolite action and is widely used for treatment of various diseases of the nervous system.[1] A distinguishing feature of the pyracetam structure, as well as of other cyclic derivatives of γ-aminobutyric acid (oxyracetam, anyracetam, phenontropyl, *etc.*), is the presence of the 2-(2-oxopyrrolidin-1-yl)acetamide fragment on the molecule. It should be noted that the last generation of nootrops is represented by different versions of the basic structure (pyracetam) modifications by introduction of various substituents onto the 2-oxopyrrolidin-1-yl fragment and the amide nitrogen atom.[2] The purpose of our study was modification of pyracetam (2-(2-oxopyrrolidin-1-yl)acetamide (**1**)) by incorporation of its structural fragment into a fluorine-containing heterocyclic system. The present work was prompted by the data obtained during the study of behavior of hexafluoroacetone *N*-acylimines (**2**) in the cyclocondensation reactions with 1,3-N,N- and 1,3-C,N-binucleophiles, which lead to the formation of six-membered trifluoromethyl-containing heterocycles.[3—5]

We failed to obtain the starting bielectrophilic reagent, hexafluoroacetone 2-(2-oxopyrrolidin-1-yl)acetylimine (**3**), in the individual state using known[3] methods for the synthesis of hexafluoroacetone *N*-substituted imines. Therefore, imine **3** was generated *in situ* by sequential addition of pyridine, hexafluoroacetone **2**, and thionyl chloride to a solution of compound **1** in DMF with subsequent involvement of imine **3**, without isolation in the individual state, into the cyclocondensation with 1,3-C,N- and N,N-binucleophiles (Scheme 1). The formation of imine **3** was confirmed by the ^{19}F NMR spectra of the reaction mixtures, which exhibited a signal for the trifluoromethyl group in the region δ 4.1 characteristic of the hexafluoroacetone imines[6], as well as by subsequent chemical transformations.

Such 1,3-binucleophiles as 3-aminocrotononitrile **4**, 6-aminouracyls **6a—c**, 6-amino-1-phenylthiouracyl **8**, *N*-benzyl-3-aminocyclohexenone **10**, and 2-aminothiazoline **12** were used in the cyclocondensation with imine **3**. The reaction of imine **3** with 1,3-binucleophiles was performed upon heating a mixture of reagents in DMF at 90—100 °C for 2 h in the presence of Et_3N in catalytic amount. Cyclocondensation of imine **3** with compounds **4**, **6a—c**, **8**, **10**, and **12** leads to the corresponding heterocyclic pyracetam derivatives **5**, **7a—c**, **9**, **11**, and **13** in 70—76% yields.

Their structures were confirmed by the NMR spectroscopic and elemental analysis data. The ^{19}F NMR spectra of compounds **5**, **7a—c**, **9**, and **11** exhibit characteristic singlet signals for the trifluoromethyl group in the region δ 2—6, for **13** at δ 1.14.

In conclusion, a one-pot method for the synthesis of trifluoromethyl-containing six-membered heterocyclic pyracetam derivatives suggested by us and consisting in the reaction of pyracetam, hexafluoroacetone, and 1,3-binucleophiles, allows one to accomplish modification of this nootropic drug by incorporation of its struc-

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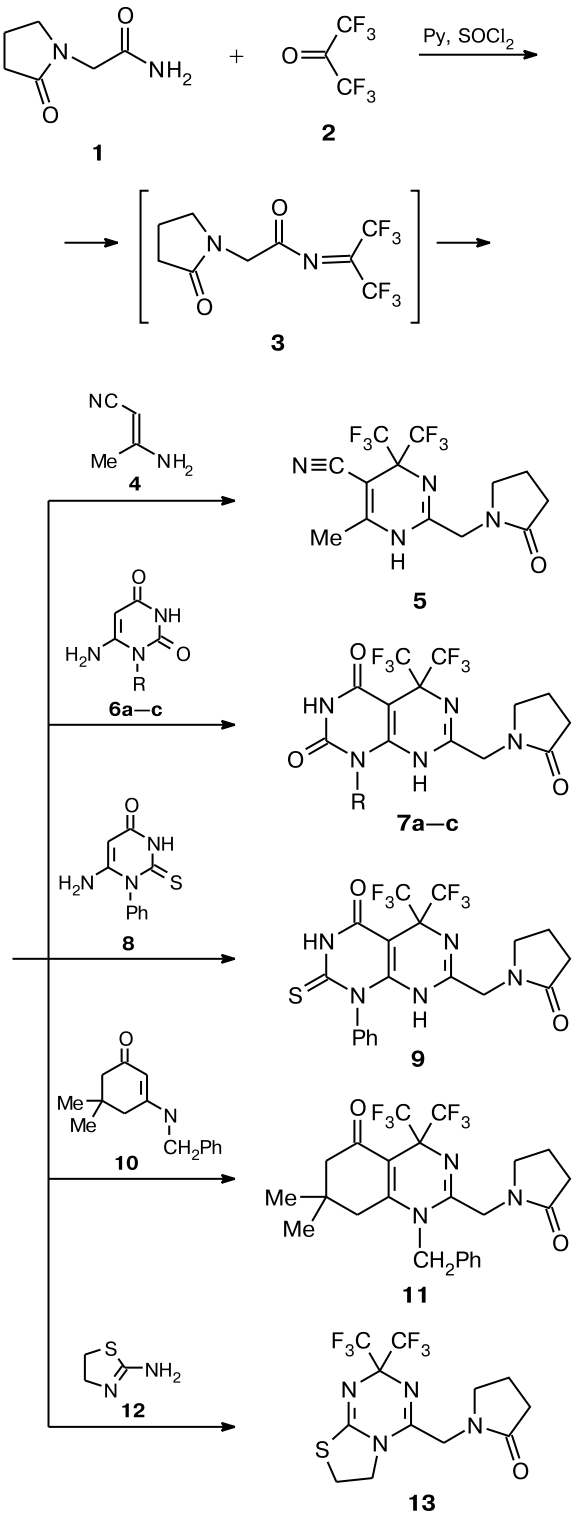
Scheme 1



6, **7:** R = Ph (**a**), $PhCH_2$ (**b**), $PhCH_2CH_2$ (**c**)

tural fragment into the trifluoromethyl-containing heterocyclic system.

Experimental

^1H and ^{19}F NMR spectra were recorded on a Bruker DPX 200 spectrometer (200.13 and 188.29 MHz, respectively) relative to Me_4Si (internal standard) and CF_3COOH (external standard), respectively. Melting points were determined in a glass capillary tube. The starting 6-aminouracyls **6a—c** and **8**,[7] *N*-benzyl-3-aminocyclohexenone **10** (see Ref. 8) were obtained according to the procedures described earlier. 2-(2-Oxopyrrolidin-1-yl)acetamide **1**, hexafluoroacetone **2**, 2-aminocrotononitrile **4**, and 2-aminothiazoline **12** (Aldrich) were used as purchased.

6-Methyl-2-(2-oxopyrrolidin-1-ylmethyl)-4,4-bis(trifluoromethyl)-1,4-dihydropyrimidine-5-carbonitrile (5). Pyridine (1.56 g, 0.01 mol) was added to a solution of compound **1** (1.42 g, 0.01 mol) in DMF (20 mL) with stirring, followed by bubbling hexafluoroacetone **2** (1.66 g, 0.01 mol), then the following reagents were sequentially added: after stirring for 30 min, $SOCl_2$ (1.19 g, 0.01 mol); after stirring for 1 h, nitrile **4** (0.82 g, 0.01 mol); after stirring for 1 h at 20 °C, Et_3N (0.1 g). The reaction mixture was heated for 2 h at 90—100 °C and cooled, poured into 10% aqueous sodium chloride (50 mL), a precipitate formed was filtered off and recrystallized from 50% aq. EtOH. The yield was 2.7 g (76%). M.p. 168—170 °C. Found (%): C, 44.27; H, 3.22; N, 25.59. $C_{13}H_{12}F_6N_4O$. Calculated (%): C, 44.08; H, 3.41; N, 25.82. ^1H NMR, δ: 2.00 (m, 2 H, CH_2); 2.19 (s, 3 H, Me); 2.29 (t, 2 H, CH_2, J = 8.3 Hz); 3.39 (t, 2 H, CH_2, J = 6.7 Hz); 4.05 (s, 2 H, CH_2); 10.98 (s, 1 H, NH). ^{19}F NMR, δ: 2.49 (s).

7-(2-Oxopyrrolidin-1-ylmethyl)-1-phenyl-5,5-bis(trifluoromethyl)-5,8-dihydro-1*H*-pyrimido[4,5-*d*]pyrimidine-2,4-dione (7a) was obtained similarly to compound **5**. The yield was 3.5 g (74%). M.p. 261—262 °C. Found (%): C, 48.25; H, 3.37; N, 14.94. $C_{19}H_{15}F_6N_5O_3$. Calculated (%): C, 48.01; H, 3.18; N, 14.73. ^1H NMR, δ: 1.63 (m, 2 H, CH_2); 1.89 (t, 2 H, CH_2, J = 8.3 Hz); 3.04 (t, 2 H, CH_2, J = 6.7 Hz); 4.13 (s, 2 H, CH_2); 7.31 (d, 2 H, CH_{Ar}, J = 6.7 Hz); 7.57 (m, 3 H, CH_{Ar}, J = 7.1 Hz); 10.07, 11.46 (both s, 1 H, NH). ^{19}F NMR, δ: 4.73 (s).

1-Benzyl-7-(2-oxopyrrolidin-1-ylmethyl)-5,5-bis(trifluoromethyl)-5,8-dihydro-1*H*-pyrimido[4,5-*d*]pyrimidine-2,4-dione (7b) was obtained similarly to compound **5**. The yield was 3.4 g (70%). M.p. 204—206 °C. Found (%): C, 49.31; H, 3.68; N, 14.49. $C_{20}H_{17}F_6N_5O_3$. Calculated (%): C, 49.09; H, 3.50; N, 14.31. ^1H NMR, δ: 1.83 (m, 2 H, CH_2); 2.16 (t, 2 H, CH_2, J = 8.3 Hz); 3.28 (t, 2 H, CH_2, J = 6.7 Hz); 4.33, 5.29 (both s, 2 H, CH_2); 7.28 (d, 2 H, CH_{Ar}, J = 6.7 Hz); 7.40 (t, 3 H, CH_{Ar}, J = 6.7 Hz); 10.37, 11.55 (both s, 2 H, NH). ^{19}F NMR, δ: 4.99 (s).

7-(2-Oxopyrrolidin-1-ylmethyl)-1-phenethyl-5,5-bis(trifluoromethyl)-5,8-dihydro-1*H*-pyrimido[4,5-*d*]pyrimidine-2,4-dione (7c) was obtained similarly to compound **5**. The yield was 3.4 g (70%). M.p. 238—240 °C. Found (%): C, 50.29; H, 3.62; N, 13.63. $C_{21}H_{19}F_6N_5O_3$. Calculated (%): C, 50.11; H, 3.80; N, 13.91. ^1H NMR, δ: 1.96 (m, 2 H, CH_2); 2.23 (t, 2 H, CH_2, J = 7.2 Hz); 2.88 (t, 2 H, CH_2, J = 8.0 Hz); 3.48 (t, 2 H, CH_2, J = 7.2 Hz); 4.21 (t, 2 H, CH_2, J = 7.2 Hz); 4.29 (s, 2 H, CH_2); 7.26 (m, 5 H, CH_{Ar}); 10.04, 11.22 (both s, 1 H, NH). ^{19}F NMR, δ: 4.42 (s).

7-(2-Oxopyrrolidin-1-ylmethyl)-1-phenyl-2-thioxo-5,5-bis(trifluoromethyl)-2,3,5,8-tetrahydro-1*H*-pyrimido[4,5-*d*]pyrimidin-4-one (9) was obtained similarly to compound **5**. The yield was 3.7 g (75%). M.p. 271—273 °C. Found (%): C, 46.63; H, 3.22; N, 14.01. $C_{19}H_{15}F_6N_5O_2S$. Calculated (%): C, 46.44; H, 3.08; N, 14.25. ^1H NMR, δ: 1.45 (m, 2 H, CH_2); 1.74 (t, 2 H, CH_2, J = 8.3 Hz); 2.78 (t, 2 H, CH_2, J = 6.7 Hz); 4.04 (s, 2 H, CH_2);

7.13 (d, 2 H, CH_{Ar}, J =6.7 Hz); 7.44 (m, 3 H, CH_{Ar}, J = 7.5 Hz); 10.31, 12.75 (both s, 1 H, NH). ^{19}F NMR, δ: 5.25 (s).

1-Benzyl-7,7-dimethyl-2-(2-oxopyrrolidin-1-ylmethyl)-4,4-bis(trifluoromethyl)-4,6,7,8-tetrahydro-1*H*-quinazolin-5-one (11) was obtained similarly to compound **5**. The yield was 3.9 g (74%). M.p. 235—237 °C. Found (%): C, 57.52; H, 4.81; N, 8.19. $C_{24}H_{25}F_6N_3O_2$. Calculated (%): C, 57.28; H, 5.03; N, 8.38. ^{1}H NMR, δ: 0.98 (s, 6 H, Me); 1.78 (m, 2 H, CH_2); 2.03 (t, 2 H, CH_2, J = 7.2 Hz); 2.26, 2.52 (both s, 2 H, CH_2); 3.31 (t, 2 H, CH_2, J = 6.7 Hz); 4.25, 5.05 (both s, 2 H, CH_2); 7.13 (d, 2 H, CH_{Ar}, J = 7.7 Hz); 7.37 (m, 3 H, CH_{Ar}). ^{19}F NMR, δ: 6.21 (s).

1-{2,2-Bis(trifluoromethyl)-6,7-dihydro-2*H*-thiazolo[3,2-*a*]-[1,3,5]triazin-4-ylmethyl}pyrrolidin-2-one (13) was obtained similarly to compound **5**. The yield was 2.6 g (70%). M.p. 208—210 °C. Found (%): C, 38.32; H, 3.44; N, 15.16. $C_{12}H_{12}F_6N_4OS$. Calculated (%): C, 38.51; H, 3.23; N, 14.97. ^{1}H NMR, δ: 2.06 (m, 2 H, CH_2); 2.32 (t, 2 H, CH_2, J = 8.3 Hz); 3.34 (t, 2 H, CH_2, J = 7.0 Hz); 3.43 (t, 2 H, CH_2, J = 7.0 Hz); 4.17 (t, 2 H, CH_2, J = 6.5 Hz); 4.25 (s, 2 H, CH_2). ^{19}F NMR, δ: −1.14 (s).

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