Organic & Biomolecular Chemistry

Accepted Manuscript

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/obc

Development of an efficient route to CF_3-substituted pyrrolopyrimidines through understanding the competition between Michael and nitro-Mannich reactions

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Abstract

Regioselective base-catalyzed addition of nitromethane to 2-oxo-4-trifluoromethyl-1,2-dihydropyrimidine-5-carboxylates is reported. It was found that Michael-like pathway is highly reversible and substantially dominating under conditions of kinetic control (0–5 °C, 10 h) whereas aza-Henry reaction leads to thermodynamically stable adducts after 8–24 h exposure at room temperature. The adjacent nitro and alkoxycarbonyl groups were exploited to demonstrate the synthetic potential of the obtained products by converting to the isomeric trifluoromethylated pyrrolo[3,4-*d*]pyrimidine-2,5-diones. For this aim an efficient protocol for selective reduction of nitro-derivatives to corresponding 4- or 6-aminomethyl-2-oxo-4-trifluoromethyl-1,2,3,4-tetrahydropyrimidine-5-carboxylates and their subsequent thermal cyclocondensations was applied.

1. Introduction

Nucleophilic addition of nitroalkanes to imines (the nitro-Mannich or aza-Henry reaction) serves as a powerful synthetic toolkit for a C-C bond creation. Thus produced β-nitroamine derivatives are widely employed as efficient building blocks for fine organic synthesis.[1] Both racemic and asymmetric versions of the aza-Henry reaction are known in the literature.[2] Acyclic aldimines have been explored most thoroughly in syntheses of this kind. In contrast, aza-Henry reaction of compounds containing endocyclic C=N bond was studied considerably less.[3] Introduction of new nitrogen-containing cyclic systems into the aza-Henry reaction is a very interesting synthetic task due to high synthetic utility of nitro group in subsequent transformations and possibility to prepare heterocycles with pronounced biological activity.[4] It should be noted that the aza-Henry reaction with ketimines was much less studied due to their lower electrophilicity. Nevertheless, recently this field attracted considerable attention and important progress has appeared. For example, various versions of asymmetric aza-Henry reaction were published. To the best of our knowledge only 3 publications are connected with CF_3-substituted imines in spite of

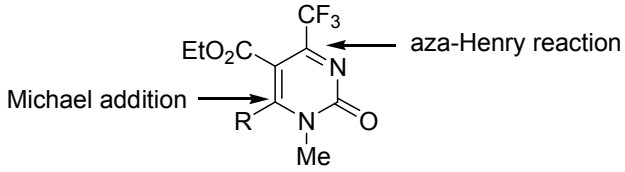
great attractiveness of trifluoromethylated aza-Henry adducts.[3f,5] The organocatalytic enantioselective addition of β-cyclopropylnitroethane to 4-trifluoromethyl-2(1*H*)-quinazolinones is of particular interest as an efficient approach to the promising anti-HIV drug DPC083.[3f]

4-(Trifluoromethyl)-1,2-dihydropyrimidin-2-ones recently prepared by us[6] are an interesting object for aza-Henry reaction. Moreover, pyrimidine unit is a privilege building block for drug discovery and some fluorinated pyrimidines have found important application in this field. 4-(Trifluoromethyl)-1,2-dihydropyrimidin-2-ones have an intriguing distinction from structurally similar 4-trifluoromethyl-2(1*H*)-quinazolinones.[3] Two conjugated double bonds (C=N and C=C) in the structure of these heterocycles are both activated by electron-withdrawing trifluoromethyl and alkoxycarbonyl groups. As a result a competing nucleophilic addition of nitromethane to the imino fragment (the aza-Henry reaction) or the double C=C bond (Michael reaction) is possible. Therefore, the control of chemoselectivity of the reaction with nitromethane is a very interesting and challenging task for this system.[7] Accordingly 4-trifluoromethylated dihydropyrimidin-2-ones substituted with nitromethyl fragment at 4- or 6-position can be prepared.

An important feature of this type of heterocycles is a unique bioactivity endowed by trifluoromethyl functionality, which is known to significantly improve drug pharmacokinetics due to its strong electron-withdrawing character, lipophilicity, and metabolic stability.[8] Moreover, a variety of effective herbicides,[9] insecticides and acaricides[10] as well as anticancer,[11] antimycobacterial,[12] and antiviral agents[13] were found among trifluoromethylated pyrimidin-2-ones(thiones). The CF_3-substituted pyrimidin-2-one moiety is also contained in antagonists of metabotropic glutamate,[14] dopamine D3,[15] and gonadotropin-releasing hormone receptors[16] as well as in inhibitors of the viral polymerase NS5B.[17]

The present work is focused on peculiarities of nitromethane addition to 4-trifluoromethyl-1,2-dihydropyrimidin-2-ones catalyzed by organic and inorganic bases; scope of the reaction and synthetic application of prepared products are explored as well. Due to polyfunctional nature of these heterocycles, they are a very interesting model to study selectivity of reactions with nucleophiles. Having two electrophilic sites (positions 4 and 6) both aza-Henry reaction and Michael addition are possible for these pyrimidines (fig. 1).

Figure 1. Two pathways for nucleophilic addition of nitromethane to **1**.



2. Results and discussion

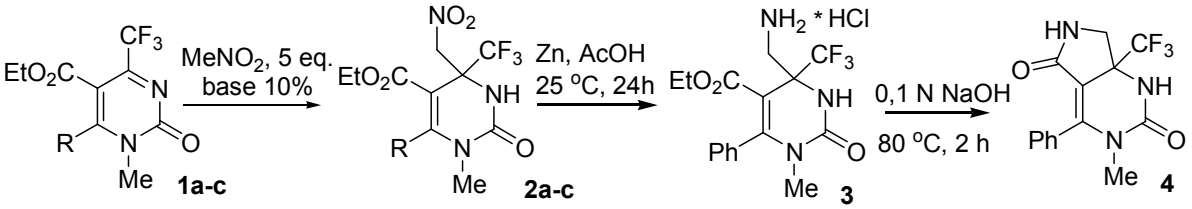
First we studied the reaction of nitromethane with 6-substituted 2-oxo-4-trifluoromethyl-1,2-dihydropyrimidine-5-carboxylates **1a-c**. It was found that a substituent in 6-position of these pyrimidines favored the aza-Henry pathway solely, i.e., the completely regioselective addition of nitromethane to the endocyclic C=N bond taken place to give 1,2,3,4-tetrahydropyrimidin-2-ones **2a-c**. The reaction with excess of nitromethane was found to proceed only in the presence of catalytic amounts (10%) of organic bases [e.g. quinine, triethylamine and diazabicycloundecene (DBU)] or sodium hydrocarbonate. However, organic bases were found to be ineffective to catalyze the process. Up to 36% conversion was observed within 72 h at room temperature or on heating in dichloromethane in the presence of organic bases (see Scheme 1 and Table 1). Notably, the reaction catalyzed by 10% sodium hydrocarbonate in DMSO provided adduct **2a** quantitatively (^{19}F NMR monitoring) which can be isolated in 82% yield. The course of the reaction can be monitored easily by the ^{19}F NMR, CF_3 resonated at –67.3 ppm for **1a** and at –81.0 ppm for **2a**.

The endocyclic C=N bond of 6-aryl substituted compounds **1b,c** exhibited increased electrophilicity, more rapid addition of nitromethane was observed. For example, compound **1b** demonstrated 76, 80, and 83% conversion to **2b** at room temperature during 48 h in the presence of 10% quinine, triethylamine, and DBU respectively. Heating the reaction mixture for 8 h at 40 °C resulted in almost total conversion of **1b**. The reaction can be brought up to 100% completion under catalysis with sodium hydrocarbonate in DMSO. ^{19}F NMR monitoring demonstrated that the reaction has equilibrium nature and in the presence of base, the retro nitro-Mannich reaction takes place. For example, C–C bond cleavage was observed for pure adduct **2b** in dichloromethane under reflux with a catalytic amounts of triethylamine. The most electrophilic substrate, 6-(4-nitrophenyl) substituted pyrimidine **1c,** reacted with nitromethane quantitatively within 24 h (rt/CH_2Cl_2/triethylamine), the reaction was also favored by the low solubility of product **2c**. An attempt to substitute nitromethane by nitroethane led to the formation of only negligible amounts of products.

Reduction of adduct **2b** to 4-aminomethylpyrimidone **3** and its further intramolecular cyclization to pyrrolo[3,4-*d*]pyrimidine-2,5-dione **4** exemplify synthetic utility of adducts **2** (see Scheme 1). It should be noted that none of the common methods for the reduction of nitro group to aliphatic amine fragment were suitable to obtain amine **3** from **2b**. For instance, in accordance with GC-MS data catalytic hydrogenation with gaseous hydrogen in the presence of Pd/C leads to a mixture of amine **3**, cyclocondensation product **4**, and small amounts of products having the endocyclic C=C bond hydrogenated (not shown in Scheme 1). Such systems as $NaBH_4/CoCl_2$ and Fe/NH_4Cl were found to be not efficient and selective enough. We have found that the most productive and facile access to amine **3** is the reduction of nitromethyl derivative **2b** with zinc powder in glacial acetic acid at room temperature. The procedure yields 74% of

aminomethylpyrimidone **3** in the form of hydrochloride after treatment with HCl in dioxane. This amine can be further cyclized into **4** by heating in 0.1N aqueous NaOH at 80 °C for 2h.

Scheme 1. Addition of nitromethane to **1a-c**.



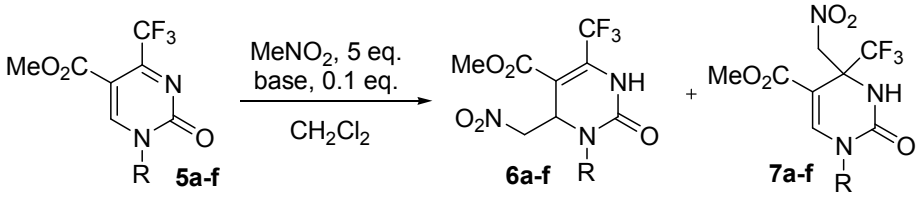
R=Me (**a**), Ph (**b**), 4-$NO_2C_6H_4$ (**c**)

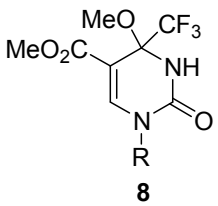
Table 1. Screening of reaction conditions for addition of nitromethane to **1a-c**.

Compd. **1**	Solvent	Base	Temp., °C	Time, h.	Conversion (yield of **2**), %
a	CH_2Cl_2	Et_3N	25	72	25
a	CH_2Cl_2	quinine	25	72	32
a	CH_2Cl_2	DBU	25	72	36
a	CH_2Cl_2	DBU	40	8	29
a	DMSO	$NaHCO_3$	25	24	100 (82)
b	CH_2Cl_2	Et_3N	25	48	80
b	CH_2Cl_2	quinine	25	48	76
b	CH_2Cl_2	DBU	25	48	83
b	CH_2Cl_2	Et_3N	40	8	85
b	DMSO	$NaHCO_3$	25	16	100 (77)
c	CH_2Cl_2	Et_3N	25	24	100 (87)

The knowledge of the peculiarities of the nitromethane addition to pyrimidones **1a-c** in the presence of basic catalysts was essential to understand analogous reactions with unsubstituted 2-oxo-4-trifluoromethyl-1,2-dihydropyrimidine-5-carboxylates **5a-f**. The structure of the latter substrates implies the possibility for two regioisomeric products (Michael type adducts **6** and aza-Henry type adducts **7)** to be formed (see Scheme 2).

Scheme 2. Two pathways of nucleophilic addition of nitromethane to **5a-f**.





Compounds **5-7**:
R = Ph (**a**)
4-ClC_6H_4 (**b**)
4-BrC_6H_4 (**c**)
4-$MeOC_6H_4$ (**d**)
4-$MeOC_6H_4CH_2$ (**e**)
4-$MeOC_6H_4CH_2CH_2$ (**f**)

Compound **8**: R = 4-$MeOC_6H_4CH_2$,

Table 2. Screening of reaction conditions for addition of nitromethane to **5a-f**.

Compd. **5**	Solvent	Base	Temp., °C	Time, h	Conversion, %	**6**:**7** ratio	Yield, % (compd.)
a	CH_2Cl_2	Et_3N	25	24	100	0:100	85 (**7**)
a	CH_2Cl_2	Et_3N	0–5	10	87	98:2	68 (**6**)
a	CH_2Cl_2	quinine	25	24	100	0:100	76 (**7**)
a	CH_2Cl_2	quinine	0–5	10	90	79:21	-[a]
a	CH_2Cl_2	DBU	0–5	10	100	45:55	-[a]
b	CH_2Cl_2	Et_3N	25	24	100	0:100	82 (**7**)
b	CH_2Cl_2	Et_3N	0–5	10	91	94:6	67 (**6**)
c	CH_2Cl_2	Et_3N	25	24	100	0:100	79 (**7**)
c	CH_2Cl_2	Et_3N	0–5	10	91	95:5	70 (**6**)
d	CH_2Cl_2	Et_3N	25	24	100	0:100	85 (**7**)
d	CH_2Cl_2	Et_3N	0–5	10	88	90:10	55 (**6**)
e	CH_2Cl_2	Et_3N	25	24	100	0:100	86 (**7**)
e	CH_2Cl_2	Et_3N	0-5	10	51	54:46	-[a]
e	MeOH	Et_3N	0–5	10	MeOH adduct	-	92 (**8**)
e	DMSO	$NaHCO_3$	10–12	10	100	0:100	90 (7)
f	CH_2Cl_2	Et_3N	25	24	100	0:100	87 (**7**)
f	CH_2Cl_2	Et_3N	0-5	10	45	49:51	-[a]

[a] products could not be separated

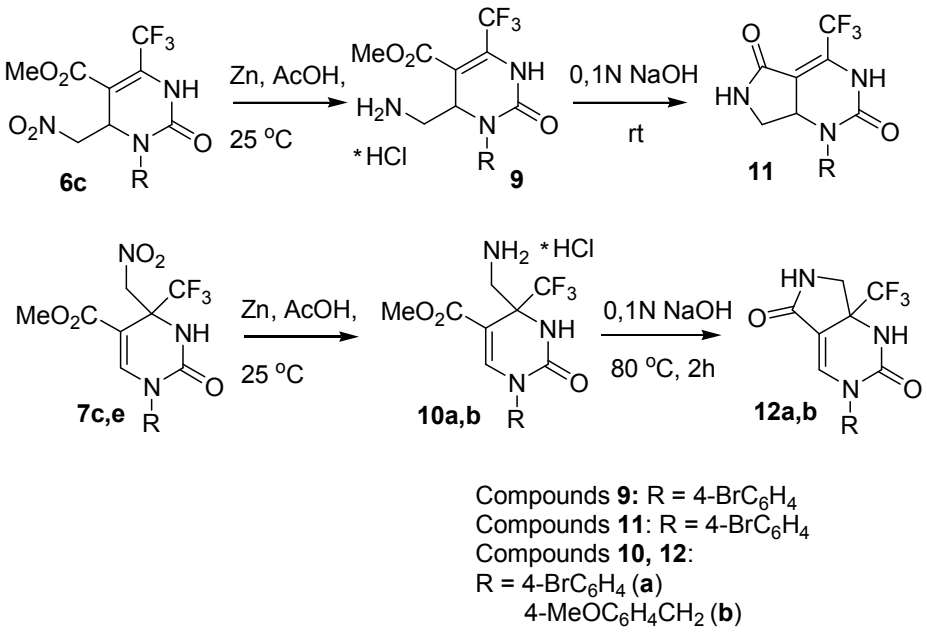
We have succeeded to find the conditions for the regioselective synthesis of each isomer. N(1)-Aryl substituted compounds **5a-d** exhibited enhanced electrophilicity (comparable to reactivity of compounds **1b,c**) and readily yielded adducts **7a-d** in dichloromethane at room temperature in the presence of 10 mol% of organic bases (see Table 2). The formation of minor regioisomeric adducts **6a-d** was also detected by ^{19}F NMR spectroscopy of the reaction mixture. It was demonstrated that the reaction of nitromethane with **5a** carried out at low temperature (0–5 °C) for 10 h (kinetic control conditions) affords predominantly product **6a**. However, the ^{19}F resonance of its CF_3 group vanishes at increased reaction temperature (25 °C) and prolonged time (24 h) thus suggesting nearly complete conversion of compound **6a** to **7a** under conditions of thermodynamic control. These data confirmed the equilibrium nature of the reaction. The nature of the basic catalyst used has a significant effect on the reaction course. As found, the maximum selectivity (**6** to **7** product ratio) was achieved with triethylamine. In the presence of DBU, practically nonselective addition was observed to yield nearly equal amounts of both isomers. This reaction is a classical example of kinetic and thermodynamic control: the formation of the Michael adduct is a kinetically controlled process, whereas the energetically favored aza-Henry adduct results from the reaction under conditions of thermodynamic control. To confirm this proposal we calculated the relative energies for **6a** and **7a (**B3LYP def2-TZVP). It was found that **7a** is energetically more favorable compared to **6a** (2.42 kcal/mol difference in energies).

N(1)-alkyl substituted pyrimidones **5e,f** are somewhat less reactive than their N(1)-aryl counterparts **5a-d** and add nitromethane under analogous conditions of kinetic control (0–5 °C, 10

h, CH_2Cl_2) with a conversion of up to 51% within 10 hours and low regioselectivity. As expected, prolonged exposure of the reaction mixture at room temperature or using $NaHCO_3$ as catalyst in DMSO leads to the formation of thermodynamically controlled products **7e,f** in high yields. Interestingly, the reaction of substrate **5e** conducted in methanol furnishes 4-methoxy-1,2,3,4-tetrahydropyrimidin-2-one **8** rather than a nitromethane adduct, which is indicative of a high affinity of the C=N bond in pyrimidones **5** for O-nucleophiles.

Prepared nitromethane adducts are very interesting building blocks for subsequent transformations (Scheme 3). We studied the reduction of nitromethyl fragment and the possibility to prepare bicyclic heterocycles having trifluoromethyl moiety. The procedure elaborated for reduction of nitro compound **2b** (zinc powder in acetic acid) worked well for adducts **6** and **7**. The corresponding amines **9, 10** were prepared using this method in good yield and isolated in a stable form as hydrochlorides after treatment with HCl in dioxane. Due to the presence of ester fragment in their structure, amine derivatives **9** and **10** can be cyclized to the corresponding lactams **11** and **12** under basic conditions. We succeeded to find conditions for such intramolecular cyclization, however distinct difference in the reaction rate was observed. Under the action of alkali (addition of 0.1N NaOH to an aqueous solution of salt **9),** spontaneous cyclization was observed. Contrary, isomeric salts **10a,b** can be converted to much more stable free bases. Heating in 0.1N NaOH at 80°C for 2h was necessary to prepare the corresponding pyrrolopyrimidines. These data can be easily explained in terms of different nucleophilicity of amino fragment in **6** and **7**. Due to both electron-withdrawing and steric impact of CF_3 moiety, the nucleophilicity of amino group in **7** is much lower. For example, it is known that pK_a are decreased significantly for non-fluorinated amines and for γ-trifluoromethylated amines such difference in pK_a is approximately 1 (10.7 for non-fluorinated primary amine and 9.7 for trifluoromethylated in γ-position).[18]

Scheme 3. Synthesis of trifluoromethylated pyrrolo[3,4-*d*]pyrimidine-2,5-diones **11** and **12**



Compounds **9:** R = 4-BrC_6H_4
Compounds **11**: R = 4-BrC_6H_4
Compounds **10, 12**:
R = 4-BrC_6H_4 (**a**)
4-$MeOC_6H_4CH_2$ (**b**)

4. Conclusions

We have studied the base-catalyzed addition of nitromethane to 2-oxo-4-trifluoromethyl-1,2-dihydropyrimidine-5-carboxylates with and without the 6-methyl(aryl) substituent. In the latter case, the nucleophilic addition was shown to proceed through the competing aza-Henry and Michael pathways. Correlation was established between the ratio of the resulting regioisomeric products, on the one hand, and the heterocyclic substrate structure, the catalyst nature, and the reaction conditions, on the other; this knowledge makes it possible to control the regioselectivity of the process, i.e. to purposefully prepare either of the isomers. The presence of the nitro and alkoxycarbonyl groups adds to the synthetic potential of the adducts obtained which can be converted to 4- or 6-aminomethyl-2-oxo-4-trifluoromethyl-1,2,3,4-tetrahydropyrimidine-5-carboxylates and further to the corresponding isomeric trifluoromethylated pyrrolo[3,4-*d*]pyrimidine-2,5-diones.

3. Experimental

All chemicals were obtained from commercially available sources (Sigma-Aldrich, Enamine Ltd.) and used without further purification. All solvents were purified by standard methods. Melting points are uncorrected. IR spectra were measured with a UR-20 spectrometer in KBr. The n_{max} (cm^{-1}) values of the IR spectra are given for the main absorption bands. ^{19}F NMR spectra were recorded on a Varian VXR-300 spectrometer with $CFCl_3$ as an internal standard; ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian VXR-300, Varian Mercury-400 or Bruker Avance DRX-500 spectrometers with TMS as an internal standard. Multiplets were assigned as s (singlet), d (doublet), t (triplet), dd (doublet of doublet), m (multiplet) and br s (broad singlet). LC-MS spectra were

recorded using a chromatography/mass spectrometric system that consists of high-performance liquid chromatograph "Agilent 1100 Series" equipped with diode-matrix and mass-selective detector "Aligent LC/MSD SL". Microanalyses were performed in the Microanalytical Laboratory of the Institute of Organic Chemistry, National Academy of Sciences of Ukraine.

General procedure for the synthesis of compounds 2a-c, 7a-f, 8.

To the solution of compound **1a-c** or **5a-f** (0.7 mmol) and base (0.07 mmol) in the corresponding solvent (see table 1 or 2) (4 mL) nitromethane (0.19 mL, 3.5 mmol) was added at 20–25 °C. The reaction was monitored by ^{19}F NMR spectroscopy. After completion of the addition the reaction mixture was poured in 0.1M HCl solution (10 mL), organic layer was separated, washed with brine, dried over Na_2SO_4 and evaporated. If DMSO was used as a solvent the mixture after addition of HCl solution was extracted with CH_2Cl_2 (2×15 mL), the organic layer was washed with brine, dried over Na_2SO_4 and evaporated. The obtained residue was crystallized from hexane/isopropanol mixture, 3:1.

Ethyl 1,6-dimethyl-4-(nitromethyl)-2-oxo-4-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (2a). White solid, yield: 0.19 g (82%), mp 120–122 °C. IR (KBr, cm^{-1}): ν 1555 (NO_2), 1715 (C=O), 1720 (C=O), 3215 (N–H). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30 (t, 3H, $^3J_{HH}$ = 7.2 Hz, CH_3), 2.33 (s, 3H, CH_3), 3.21 (s, 3H, CH_3), 4.23 (q, 2H, $^3J_{HH}$ = 7.2 Hz, CH_2), 4.56 (d, 1H, $^2J_{HH}$ = 14.0 Hz, CH_2), 5.47 (d, 1H, $^2J_{HH}$ = 14.0 Hz, CH_2), 7.25–7.50 (bs, 1H, N-H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.6, 18.1, 30.1, 61.0, 61.5 (q, $^2J_{CF}$ = 30.0 Hz, C-4), 74.5, 95.4, 123.4 (q, $^1J_{CF}$ = 288.8 Hz, CF_3), 150.6, 151.8, 165.2. ^{19}F NMR (188 MHz, DMSO-d_6): –81.1 (s, CF_3). $C_{11}H_{14}F_3N_3O_5$ (325.2): calcd. C 40.62, H 4.34, N 12.92; found C 40.52, H 4.36, N 12.96. LCMS: MH^+, 326.

Ethyl 1-methyl-4-(nitromethyl)-2-oxo-6-phenyl-4-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (2b). White solid, yield: 0.21 g (77%), mp 158–160 °C. IR (KBr, cm^{-1}): ν 1560 (NO_2), 1670 (C=O), 1695 (C=O), 3190 (N–H). ^{1}H NMR (400 MHz, $CDCl_3$): 0.64 (t, 3H, $^3J_{HH}$ = 8.0 Hz, CH_3), 2.79 (s, 3H, CH_3), 3.70 (q, 2H, $^3J_{HH}$ = 8.0 Hz, CH_2), 4.66 (d, 1H, $^2J_{HH}$ = 14.4 Hz, CH_2), 5.65 (d, 1H, $^2J_{HH}$ = 14.4 Hz, CH_2), 7.25 (bs, 2H, NH, CH), 7.35–7.50 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): 13.1, 32.7, 60.8, 62.3 (q, $^2J_{CF}$ = 30.0 Hz, C-4), 75.1, 97.2, 123.7 (q, $^1J_{CF}$ = 287.5 Hz, CF_3), 127.3, 127.8, 128.4, 128.7, 129.5, 134.3, 152.3, 152.7, 165.3. ^{19}F NMR (188 MHz, $CDCl_3$): –79.7 (s, CF_3). $C_{16}H_{16}F_3N_3O_5$ (387.3): calcd. C 49.62, H 4.16, N 10.85; found C 49.75, H 4.15, N 10.87. LCMS: MH^+, 388.

Ethyl 1-methyl-4-(nitromethyl)-6-(4-nitrophenyl)-2-oxo-4-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (2c). White solid, yield: 0.25 g (87%), mp 196–198 °C. IR (KBr, cm^{-1}): ν 1560 (NO_2), 1710 (C=O), 1715 (C=O), 3215 (N–H). ^{1}H NMR (400 MHz, $CDCl_3$): δ

0.73 (t, 3H, $^3J_{HH}$ = 6.8 Hz, CH_3), 2.78 (s, 3H, CH_3), 3.77 (q, 2H, $^3J_{HH}$ = 6.8 Hz, CH_2), 4.64 (d, 1H, $^2J_{HH}$ = 13.6 Hz, CH_2), 5.71 (d, 1H, $^2J_{HH}$ = 13.6 Hz, CH_2), 7.15 (bs, 1H, N–H), 7.46 (m, 2H), 8.32 (d, 2H, $^3J_{HH}$ = 9.2 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 12.9, 32.4, 60.9, 62.0 (q, $^2J_{CF}$ = 30.0 Hz, C-4), 74.1, 97.6, 123.3 (q, $^1J_{CF}$ = 287.5 Hz, CF_3), 123.4, 123.7, 128.6, 129.3, 140.2, 148.0, 150.7, 151.5, 163.7. ^{19}F NMR (188 MHz, $CDCl_3$): –79.7 (s, CF_3). $C_{15}H_{13}F_3N_4O_7$ (418.3): calcd. C 43.07, H 3.13, N 13.39; found C 42.98, H 3.12, N 13.36. LCMS: MH^+, 419.

Methyl 4-(nitromethyl)-2-oxo-1-phenyl-4-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (7a). White solid, yield: 0.21 g (85%), mp 198–200 °C. IR (KBr, cm^{-1}): ν 1550 (NO_2), 1690 (C=O), 1725 (C=O), 3230 (N–H). ^{1}H NMR (500 MHz, $CDCl_3$): 3.79 (s, 3H, CH_3), 4.58 (d, 1H, $^2J_{HH}$ = 14.0 Hz, CH_2), 5.84 (d, 1H, $^2J_{HH}$ = 14.0 Hz, CH_2), 7.26 (s, 1H, NH), 7.31 (d, 2H, $^3J_{HH}$ = 7.5 Hz), 7.40–7.55 (m, 3H), 7.80 (s, 1H, CH). ^{13}C NMR (125 MHz, $CDCl_3$): 52.1, 62.7 (q, $^2J_{CF}$ = 31.6 Hz), 73.1, 96.7, 123.8 (q, $^1J_{CF}$ = 273.6 Hz, CF_3), 126.6, 128.7, 129.5, 138.4, 145.4, 150.6, 163.9. ^{19}F NMR (188 MHz, $CDCl_3$): –79.9 (s, CF_3). $C_{14}H_{12}F_3N_3O_5$ (359.3): calcd. C 46.80, H 3.37, N 11.70; found C 46.95; H 3.36; N 11.65. LCMS: MH^+, 360.

Methyl 1-(4-chlorophenyl)-4-(nitromethyl)-2-oxo-4-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (7b). White solid, yield: 0.23 g (82%), mp 192–194 °C. IR (KBr, cm^{-1}): ν 1555 (NO_2), 1710 (C=O), 1730 (C=O), 3120 (N–H). ^{1}H NMR (500 MHz, $CDCl_3$): 3.80 (s, 3H, CH_3), 4.63 (d, 1H, $^2J_{HH}$ = 13.5 Hz, CH_2), 5.92 (d, 1H, $^2J_{HH}$ = 13.5 Hz, CH_2), 7.26 (d, 2H, $^3J_{HH}$ = 8.0 Hz), 7.29 (s, 1H, NH), 7.45 (d, 2H, $^3J_{HH}$ = 8.0 Hz), 7.76 (s, 1H, CH). ^{13}C NMR (125 MHz, $CDCl_3$): 51.9, 62.4 (q, $^2J_{CF}$ = 31.3 Hz, C-4), 73.4, 96.7, 123.2 (q, $^1J_{CF}$ = 287.5 Hz, CF_3), 127.5, 129.3, 134.4, 136.3, 144.3, 149.6, 163.3. ^{19}F NMR (188 MHz, $CDCl_3$): –79.6 (s, CF_3). $C_{14}H_{11}ClF_3N_3O_5$ (393.7): calcd. C 42.71, H 2.82, N 10.67; found C 42.65, H 2.83, N 10.71. LCMS: MH^+, 395.

Methyl 1-(4-bromophenyl)-4-(nitromethyl)-2-oxo-4-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (7c). White solid, yield: 0.24 g (79%), mp 214–216 °C. IR (KBr, cm^{-1}): ν 1555 (NO_2), 1695(C=O), 1725 (C=O), 3250 (N–H). ^{1}H NMR (400 MHz, DMSO-d_6): 3.68 (s, 3H, CH_3), 4.89 (d, 1H, $^2J_{HH}$ = 14.0 Hz, CH_2), 5.83 (d, 1H, $^2J_{HH}$ = 14.0 Hz, CH_2), 7.30 (d, 2H, $^3J_{HH}$ = 8.4 Hz), 7.64 (d, 2H, $^3J_{HH}$ = 8.4 Hz), 7.89 (s, 1H, CH), 9.19 (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): 51.9, 61.9 (q, $^2J_{CF}$ = 30.0 Hz, C-4), 73.0, 96.3, 121.0, 124.0 (q, $^1J_{CF}$ = 290.0 Hz, CF_3), 128.9, 132.1, 137.7, 144.7, 149.4, 163.8. ^{19}F NMR (188 MHz, DMSO-d_6): –80.0 (s, CF_3). $C_{14}H_{11}BrF_3N_3O_5$ (438.2): calcd. C 38.38, H 2.53, N 9.59; found C 38.51, H 2.54, N 9.58. LCMS: MH^+, 439.

Methyl 1-(4-methoxyphenyl)-4-(nitromethyl)-2-oxo-4-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (7d). White solid, yield: 0.23 g (85%), mp 184–186 °C. IR (KBr, cm^{-1}): ν 1570 (NO_2), 1685 (C=O), 1725 (C=O), 3230 (N–H). ^{1}H NMR (500 MHz, $CDCl_3$): δ

3.76 (s, 3H, CH_3), 3.84 (s, 3H, CH_3), 4.56 (d, 1H, $^2J_{HH}$ = 12.5 Hz, CH_2), 5.83 (d, 1H, $^2J_{HH}$ = 12.5 Hz, CH_2), 6.95 (d, 2H, $^3J_{HH}$ = 8.5 Hz), 7.20 (d, 2H, $^3J_{HH}$ = 8.5 Hz), 7.28 (s, 1H, N–H), 7.74 (s, 1H, CH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 51.7, 55.2, 62.3 (q, $^2J_{CF}$ = 31.3 Hz, C-4), 73.1, 95.8, 114.3, 123.3 (q, $^1J_{CF}$ = 288.8 Hz, CF_3), 127.6, 130.7, 145.1, 150.6, 159.3, 163.6. ^{19}F NMR (188 MHz, $CDCl_3$): –80.3 (s, CF_3). $C_{15}H_{14}F_3N_3O_6$ (389.3): calcd. C 46.28, H 3.62, N 10.79; found C 46.19, H 3.63, N 10.81. LCMS: MH^+, 390.

Methyl 1-[(4-methoxyphenyl)methyl]-4-(nitromethyl)-2-oxo-4-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (7e). White solid, yield: 0.24 g (86%), mp 134–136 °C. IR (KBr, cm^{-1}): ν 1560 (NO_2), 1700 (C=O), 1730 (C=O), 3305 (N–H). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.75 (s, 3H, CH_3), 3.82 (s, 3H, CH_3), 4.58 (d, 1H, $^2J_{HH}$ = 14.0 Hz, CH_2), 4.64 (d, 1H, $^2J_{HH}$ = 14.4 Hz, CH_2), 4.86 (d, 1H, $^2J_{HH}$ = 14.4 Hz, CH_2), 5.88 (d, 1H, $^2J_{HH}$ = 14.0 Hz, CH_2,), 6.91 (d, 2H, $^3J_{HH}$ = 8.4 Hz), 7.18 (d, 2H, $^3J_{HH}$ = 8.4 Hz), 7.34 (s, 1H, N–H), 7.61 (s, 1H, CH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 50.5, 52.0, 55.3, 62.6 (q, $^2J_{CF}$ = 30.0 Hz, C-4), 73.8, 96.1, 114.5, 123.7 (q, $^1J_{CF}$ = 287.5 Hz, CF_3), 127.5, 128.9, 144.5, 151.5, 159.6, 163.9. ^{19}F NMR (188 MHz, $CDCl_3$): δ –80.0 (s, CF_3). $C_{16}H_{16}F_3N_3O_6$ (403.3): calcd. C 47.65, H 4.00, N 10.42; found C 47.82, H 4.01, N 10.38. LCMS: MH^+, 404.

Methyl 1-[2-(4-methoxyphenyl)ethyl]-4-(nitromethyl)-2-oxo-4-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (7f). White solid, yield: 0.25 g (87%), mp 127–129 °C. IR (KBr, cm^{-1}): ν 1565 (NO_2), 1685 (C=O), 1725 (C=O), 3120 (N–H). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.84 (m, 2H, CH_2), 3.68 (s, 3H, CH_3), 3.70–3.75 (m, 2H, CH_2), 3.77 (s, 3H, CH_3), 4.59 (d, 1H, $^2J_{HH}$ = 13.2 Hz, CH_2), 5.85 (d, 1H, $^2J_{HH}$ = 13.2 Hz, CH_2), 6.84 (d, 2H, $^3J_{HH}$ = 8.4 Hz), 7.06 (d, 2H, $^3J_{HH}$ = 8.4 Hz), 7.15 (s, 1H, CH), 7.28 (bs, 1H, N-H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 34.0, 50.1, 51.4, 54.9, 62.3 (q, $^2J_{CF}$ = 30.0 Hz, C-4), 73.4, 94.1, 113.9, 123.3 (q, $^1J_{CF}$ = 287.5 Hz, CF_3), 128.8, 129.7, 145.0, 150.7, 158.3, 163.6. ^{19}F NMR (188 MHz, $CDCl_3$): –80.1 (s, CF_3). $C_{17}H_{18}F_3N_3O_6$ (417.3): calcd. C 48.93, H 4.35, N 10.07; found C 49.07, H 4.36, N 10.09. LCMS: MH^+, 418.

Methyl 4-methoxy-1-[(4-methoxyphenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (8). White solid, yield: 0.24 g (92%), mp 108–110 °C. IR (KBr, cm^{-1}): ν 1680 (C=O), 1725 (C=O), 3255 (N–H). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.27 (s, 3H, CH_3), 3.75 (s, 3H, CH_3), 3.80 (s, 3H, CH_3), 4.75 (m, 2H), 6.12 (bs, 1H, N-H), 6.88 (d, 2H, $^3J_{HH}$ = 8.5 Hz), 7.19 (d, 2H, $^3J_{HH}$ = 8.5 Hz), 7.76 (s, 1H, CH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 50.1, 50.1, 51.6, 54.9, 87.2 (q, $^2J_{CF}$ = 33.8 Hz, C-4), 96.0, 114.1, 121.9 (q, $^1J_{CF}$ = 286.3 Hz, CF_3), 127.3, 128.7, 145.6, 150.4, 159.2, 163.2. ^{19}F NMR (188 MHz, $CDCl_3$): –82.1 (s, CF_3). $C_{16}H_{17}F_3N_2O_5$ (374.3): calcd. C 51.34, H 4.58, N 7.48; found C 51.48, H 4.56, N 7.51. LCMS: MH^+, 375.

General procedure for the synthesis of compounds (6a-d).

To the solution of compound **5a-d** in CH_2Cl_2 (8 mL) were added triethylamine (27 mg, 0.27 mmol) and nitromethane (0.8 mL, 13.5 mmol) at 0–5 °C. The reaction mixture was stirred at this temperature for 10 h and then poured into 0.1 M hydrochloric acid (5 mL). The organic layer was sepapated, washed with water (5 mL) and dried over Na_2SO_4. The solvent was evaporated and obtained residue was crystallized from toluene (for compound **6a**) or toluene/isopropanol mixture, 3:1 (for compounds **6b-d**).

Methyl 4-(nitromethyl)-2-oxo-3-phenyl-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (6a). White solid, yield: 0.17 g (68%), mp 120–122 °C. IR (KBr, cm^{-1}): ν 1555 (NO_2), 1690 (C=O), 1720 (C=O), 3220 (N–H). ^{1}H NMR (400 MHz, $CDCl_3$): 3.84 (s, 3H, CH_3), 4.56 (dd, 1H, $^2J_{HH}$ = 11.6 Hz, $^3J_{HH}$ = 3.6 Hz, CH_2), 4.65 (dd, 1H, $^2J_{HH}$ = 11.6 Hz, $^3J_{HH}$ = 4.8 Hz, CH_2), 5.36–5.40 (m, 1H, CH), 7.35–7.55 (m, 5H), 7.73 (bs, 1H, NH). ^{13}C NMR (125 MHz, $CDCl_3$): 52.9, 59.6, 75.0, 101.8, 118.9 (q, $^1J_{CF}$ = 275.0 Hz, CF_3), 127.4, 128.6, 129.9, 137.01 (q, $^2J_{CF}$ = 37.5 Hz, C-6), 138.3, 149.7, 162.5. ^{19}F NMR (188 MHz, $CDCl_3$): –65.1 (s, CF_3). $C_{14}H_{12}F_3N_3O_5$ (359.3): calcd. C 46.80, H 3.37, N 11.70; found C 46.72, H 3.36, N 11.73. LCMS: MH^+, 360.

Methyl 3-(4-chlorophenyl)-4-(nitromethyl)-2-oxo-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (6b). White solid, yield: 0.18 g (67%), mp 132–134 °C. IR (KBr, cm^{-1}): ν 1555 (NO_2), 1695 (C=O), 1715 (C=O), 3230 (N–H). ^{1}H NMR (400 MHz, $CDCl_3$): 3.85 (s, 3H, CH_3), 4.55 (dd, 1H, $^2J_{HH}$ = 12.0 Hz, $^3J_{HH}$ = 4.0 Hz, CH_2), 4.64 (dd, 1H, $^2J_{HH}$ = 12.0 Hz, $^3J_{HH}$ = 5.2 Hz, CH_2), 5.31–5.34 (m, 1H, CH), 7.35 (d, 2H, $^3J_{HH}$ = 8.8 Hz), 7.40–7.45 (bs, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 52.6, 59.1, 74.6, 101.4, 118.3 (q, $^1J_{CF}$ = 275.0 Hz, CF_3), 128.4, 129.6, 134.0, 136.3, 136.5 (q, $^2J_{CF}$ = 37.5 Hz, C-6), 149.3, 162.1. ^{19}F NMR (188 MHz, $CDCl_3$): –65.0 (s, CF_3). $C_{14}H_{11}ClF_3N_3O_5$ (393.7): calcd. C 42.71, H 2.82, N 10.67; found C 42.63, H 2.81, N 10.69. LCMS: MH^+, 394.

Methyl 3-(4-bromophenyl)-4-(nitromethyl)-2-oxo-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (6c). White solid, yield: 0.21 g (70%), mp 156–158 °C. IR (KBr, cm^{-1}): ν 1550 (NO_2), 1690 (C=O), 1720 (C=O), 3230 (N–H). ^{1}H NMR (400 MHz, $CDCl_3$): 3.85 (s, 3H, CH_3), 4.53 (dd, 1H, $^2J_{HH}$ = 12.0 Hz, $^3J_{HH}$ = 3.6 Hz, CH_2), 4.64 (dd, 1H, $^2J_{HH}$ = 12.0 Hz, $^3J_{HH}$ = 5.2 Hz, CH_2), 5.31–5.33 (m, 1H, CH), 7.28 (d, 2H, $^3J_{HH}$ = 8.8 Hz), 7.58 (d, 2H, $^3J_{HH}$ = 8.8 Hz), 7.63 (s, 1H, NH). ^{13}C NMR (125 MHz, $CDCl_3$): 53.0, 59.4, 75.0, 101.8, 118.7 (q, $^1J_{CF}$ = 275.0 Hz, CF_3), 122.4, 129.1, 133.0, 137.0 (q, $^2J_{CF}$ = 37.5 Hz, C-6), 137.3, 149.7, 162.5. ^{19}F NMR (188 MHz, $CDCl_3$): –65.0 (s, CF_3). $C_{14}H_{11}BrF_3N_3O_5$ (438.2): calcd. C 38.38, H 2.53, N 9.59; found C 38.25, H 2.52, N 9.61. LCMS: MH^+, 438.

Methyl 3-(4-methoxyphenyl)-4-(nitromethyl)-2-oxo-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (6d). White solid, yield: 0.15 g (55%), mp 140–142 °C. IR

(KBr, cm^{-1}): ν 1545 (NO_2), 1690 (C=O), 1725 (C=O), 3225 (N–H). ^1H NMR (400 MHz, $CDCl_3$): 3.80 (s, 3H, CH_3), 3.83 (s, 3H, CH_3), 4.58 (dd, 1H, $^2J_{HH}$ = 12.4 Hz, $^3J_{HH}$ = 3.2 Hz, CH_2), 4.63 (dd, 1H, $^2J_{HH}$ = 12.4 Hz, $^3J_{HH}$ = 4.0 Hz, CH_2), 5.23–5.25 (m, 1H, CH), 6.94 (d, 2H, $^3J_{HH}$ = 8.4 Hz), 7.29 (d, 2H, $^3J_{HH}$ = 8.4 Hz), 7.69 (s, 1H, NH). ^{13}C NMR (125 MHz, $CDCl_3$): 52.5, 55.2, 59.5, 74.7, 101.1, 114.7, 118.4 (q, $^1J_{CF}$ = 275.0 Hz, CF_3), 128.4, 130.4, 136.7 (q, $^2J_{CF}$ = 36.3 Hz, C-6), 149.6, 159.0, 162.2. ^{19}F NMR (188 MHz, $CDCl_3$): –64.9 (s, CF_3). $C_{15}H_{14}F_3N_3O_6$ (389.3): calcd. C 46.28, H 3.62, N 10.79; found C 46.19, H 3.63, N 10.76. LCMS: MH^+, 390.

General procedure for the synthesis of compounds 3, 9, 10a,b.

To the solution of compound **2b, 6c, 7c,e** (2.3 mmol) in acetic acid (10 mL) zinc dust (1.2 g, 18.4 mmol) was added under stirring at 20–25 °C. The reaction mixture was stirred at this temperature for 8 h. After that the solid was filtered and clear solution was evaporated in rotor vacuum. The residue was dissolved in 4M HCl solution in dioxane (5 mL) and volatiles were evaporated. The product was purified by column chromatography using $CHCl_3$/MeOH mixture (6:1) as eluent.

Ethyl 4-(aminomethyl)-1-methyl-2-oxo-6-phenyl-4-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate hydrochloride (3). White solid, yield: 0.67 g (74%), mp 148–150 °C. IR (KBr, cm^{-1}): ν 1710 (C=O), 1720 (C=O), 3230 (N–H), 3280 (NH_3^+). ^1H NMR (300 MHz, DMSO-d_6): δ 0.54 (t, 3H, $^3J_{HH}$ = 6.9 Hz, CH_3), 2.70 (s, 3H, CH_3), 3.17 (d, 1H, $^2J_{HH}$ = 12.6 Hz, CH_2), 3.50–3.80 (m, 3H, $2CH_2$), 7.36–7.45 (m, 2H, Ph), 7.48–7.52 (m, 3H, Ph), 8.32 (bs, 3H, NH_3^+), 8.60 (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ 12.8, 32.0, 41.1, 60.3, 61.8 (q, $^2J_{CF}$ = 28.7 Hz, C-4), 94.0, 124.5 (q, $^1J_{CF}$ = 288.7 Hz, CF_3), 127.4, 128.2, 128.5, 128.6, 129.1, 134.3, 150.9, 154.0, 165.4. ^{19}F NMR (188 MHz, DMSO-d_6): –80.5 (s, CF_3). $C_{16}H_{19}ClF_3N_3O_3$ (393.8): calcd. C 48.80, H 4.86, N 10.67; found C 48.96, H 4.88, N 10.64. LCMS: MH^+, 358.

Methyl 4-(aminomethyl)-3-(4-bromophenyl)-2-oxo-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate hydrochloride (9). White solid, yield: 0.61 g (60%), mp 168–170 °C. IR (KBr, cm^{-1}): ν 1690 (C=O), 1730 (C=O), 3240-3310 (N–H). ^1H NMR (400 MHz, DMSO-d_6): δ 3.04 (bs, 2H, CH_2), 3.72 (s, 3H, CH_3), 4.96–5.01 (m, 1H, CH), 7.52 (d, 2H, $^3J_{HH}$ = 8.4 Hz), 7.63 (d, 2H, $^3J_{HH}$ = 8.4 Hz), 8.09 (bs, 3H, NH_3^+), 10.48 (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ 52.4, 56.9, 62.0, 103.7, 119.0 (q, $^1J_{CF}$ = 276.3 Hz, CF_3), 119.7, 129.2, 131.9, 135.3 (q, $^2J_{CF}$ = 35.0 Hz, C-6), 139.0, 149.9, 162.8. ^{19}F NMR (188 MHz, DMSO-d_6): –63.3 (s, CF_3). $C_{14}H_{14}BrClF_3N_3O_3$ (444.6): calcd. C 37.82, H 3.17, N 9.45; found C 37.93, H 3.16, N 9.48. LCMS: MH^+, 408.

Methyl 4-(aminomethyl)-1-(4-bromophenyl)-2-oxo-4-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate hydrochloride (10a). White solid, yield: 0.73 g (72%), mp 178–180 °C. IR (KBr, cm^{-1}): ν 1685 (C=O), 1730 (C=O), 3240-3295 (N–H). ^1H NMR (400 MHz,

DMSO-d_6): δ 3.17 (d, 1H, $^2J_{HH}$ = 12.8 Hz, CH_2), 3.67 (s, 3H, CH_3), 4.06 (d, 1H, $^2J_{HH}$ = 12.8 Hz, CH_2), 7.27 (d, 2H, $^3J_{HH}$ = 8.4 Hz, CH_2), 7.67 (d, 2H, $^3J_{HH}$ = 8.4 Hz, CH_2), 7.93 (s, 1H, CH), 8.22 (bs, 3H, NH_3^+), 8.83 (bs, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ 51.9, 62.1 (q, $^2J_{CF}$ = 30.0 Hz, C-4), 79.2, 94.2, 121.1, 124.6 (q, $^1J_{CF}$ = 287.5 Hz, CF_3), 128.9, 132.2, 137.9, 146.7, 149.7, 163.7. ^{19}F NMR (188 MHz, DMSO-d_6): –79.9 (s, CF_3). $C_{14}H_{14}BrClF_3N_3O_3$ (444.6): calcd. C 37.82, H 3.17, N 9.45; found C 37.93, H 3.16, N 9.46. LCMS: MH^+, 409.

Methyl 4-(aminomethyl)-1-[(4-methoxyphenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate hydrochloride (10b). White solid, yield: 0.66 g (70%), mp 127–130 °C. IR (KBr, cm^{-1}): ν 1700 (C=O), 1725 (C=O), 3270-3315 (N–H). ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.95 (d, 1H, $^2J_{HH}$ = 13.0 Hz, CH_2), 3.65 (s, 3H, CH_3), 3.73 (s, 3H, CH_3), 3.82 (d, 1H, $^2J_{HH}$ = 13.0 Hz, CH_2), 4.23 (bs, 3H, NH_3^+), 4.66 (d, 1H, $^2J_{HH}$ = 15.0 Hz, CH_2), 4.78 (d, 1H, $^2J_{HH}$ = 15.0 Hz, CH_2), 6.91 (d, 2H, $^3J_{HH}$ = 8.5 Hz), 7.21 (d, 2H, $^3J_{HH}$ = 8.5 Hz), 7.99 (s, 1H, CH), 8.29 (bs, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ 49.0, 51.5, 55.1, 63.2 (q, $^2J_{CF}$ = 28.8 Hz, C-4), 79.2, 94.1, 113.9, 125.1 (q, $^1J_{CF}$ = 287.5 Hz, CF_3), 128.8, 129.3, 147.3, 151.2, 158.7, 164.0. ^{19}F NMR (188 MHz, DMSO-d_6): –80.1 (s, CF_3). $C_{16}H_{19}ClF_3N_3O_4$ (409.8): calcd. C 46.90, H 4.67, N 10.25; found C 46.85, H 4.69, N 10.27. LCMS: MH^+, 374.

General procedure for the synthesis of compounds 4, 11, 12a,b.

A solution of compound **3, 9, 10a,b** (1.5 mmol, hydrochloride salt) in methanol (15 mL) was added to 0.1N aqueous NaOH (15 mL) at room temperature. The reaction mixture was stirred at room temperature (for compound **9**) or refluxed (for compounds **3, 10a,b**) for 2 h and then evaporated to a half of the volume. The precipitate formed was filtered, washed with water and dried.

3-Methyl-4-phenyl-7a-(trifluoromethyl)-1H,2H,3H,5H,6H,7H,7aH-pyrrolo[3,4-d]pyrimidine-2,5-dione (4). White solid, yield: 0.42 g (90%), mp 240-242 °C (decomp.). IR (KBr, cm^{-1}): ν 1680 (C=O), 3260 (N–H). ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.71 (s, 3H, CH_3), 3.34 (d, 1H, $^2J_{HH}$ = 10.5 Hz, CH_2), 3.61 (d, 1H, $^2J_{HH}$ = 10.5 Hz, CH_2), 7.2–7.5 (m, 5H, Ph), 7.77 (s, 1H, NH), 8.75 (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ 32.1, 46.5, 59.1 (q, $^2J_{CF}$ = 31.3 Hz, C-7a), 99.2, 125.9 (q, $^1J_{CF}$ = 285.0 Hz, CF_3), 127.9, 129.8, 129.9, 131.5, 148.4, 152.9, 165.5. ^{19}F NMR (188 MHz, DMSO-d_6): –83.8 (s, CF_3). $C_{14}H_{12}F_3N_3O_2$ (311.3): calcd. C 54.02, H 3.89, N 13.50; found C 54.22, H 3.90, N 13.45. LCMS: MH^+, 312.

1-(4-Bromophenyl)-4-(trifluoromethyl)-1*H*,2*H*,3*H*,5*H*,6*H*,7*H*,7a*H*-pyrrolo[3,4-d]pyrimidine-2,5-dione (11). White solid, yield: 0.47 g (83%), mp 228-230 °C (decomp.). IR (KBr, cm^{-1}): ν 1690 (C=O), 1705 (C=O), 3245 (N–H). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.58 (m, 2H, CH_2), 4.90–4.94 (m, 1H, CH), 6.92 (bs, 1H, NH), 7.11 (d, 2H, $^3J_{HH}$ = 7.0 Hz), 7.41 (d, 2H, $^3J_{HH}$ = 7.0 Hz). ^{13}C NMR (125 MHz, DMSO-d_6): δ 46.4, 54.9, 99.04, 116.8, 121.0 (q, $^1J_{CF}$ = 273.8 Hz,

CF_3), 127.8, 130.7, 131.9 (q, $^2J_{CF}$ = 28.8 Hz, C-4), 140.9, 158.3, 165.8. ^{19}F NMR (188 MHz, DMSO-d_6): –64.2 (s, CF_3). $C_{13}H_9BrF_3N_3O_2$ (376.1): calcd. C 41.51, H 2.41, N 11.17; found C 41.38, H 2.42, N 11.20. LCMS: MH^+, 376.

3-(4-Bromophenyl)-7a-(trifluoromethyl)-1H,2H,3H,5H,6H,7H,7aH-pyrrolo[3,4-d]pyrimidine-2,5-dione (12a). Light yellow solid, yield: 0.48 g (85%), mp 218–220 °C (decomp.). IR (KBr, cm^{-1}): ν 1685 (C=O), 1700 (C=O), 3250 (N–H). ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.42–3.47 (m, 1H, CH_2), 3.67–3.70 (m, 1H, CH_2), 7.27 (d, 2H, $^3J_{HH}$ = 8.8 Hz), 7.48 (s, 1H, CH), 7.61 (d, 2H, $^3J_{HH}$ = 8.8 Hz), 8.09 (s, 1H, NH), 8.96 (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ 46.9, 59.3 (q, $^2J_{CF}$ = 30.0 Hz, C-7a), 104.2, 120.2, 125.5 (q, $^1J_{CF}$ = 287.5 Hz, CF_3), 128.7, 131.9, 134.9, 138.6, 151.1, 165.8. ^{19}F NMR (188 MHz, DMSO-d_6): –83.6 (s, CF_3). $C_{13}H_9BrF_3N_3O_2$ (376.1): calcd. C 41.51, H 2.41, N 11.17; found C 41.47, H 2.42, N 11.19. LCMS: MH^+, 376.

3-[(4-Methoxyphenyl)methyl]-7a-(trifluoromethyl)-1*H*,2*H*,3*H*,5*H*,6*H*,7*H*,7a*H*-pyrrolo-[3,4-*d*]pyrimidine-2,5-dione (12b). White solid, yield: 0.47 g (92%), mp 242-245 °C (decomp.). IR (KBr, cm^{-1}): ν 1685 (C=O), 1695 (C=O), 3245 (N–H). ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.33 (d, 1H, $^2J_{HH}$ = 10.8 Hz, CH_2), 3.59 (d, 1H, $^2J_{HH}$ = 10.8 Hz, CH_2), 3.72 (s, 3H, CH_3), 4.52 (d, 1H, $^2J_{HH}$ = 14.8 Hz, CH_2), 4.79 (d, 1H, $^2J_{HH}$ = 14.8 Hz, CH_2), 6.89 (d, 2H, $^3J_{HH}$ = 8.4 Hz), 7.21 (d, 2H, $^3J_{HH}$ = 8.4 Hz), 7.46 (s, 1H, CH), 7.89 (bs, 1H, NH), 8.63 (bs, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ 47.1, 48.9, 55.0, 59.2 (q, $^2J_{CF}$ = 30.0 Hz, C-7a), 102.0, 113.9, 125.4 (q, $^1J_{CF}$ = 287.5 Hz, CF_3), 129.0, 129.6, 135.6, 151.9, 158.6, 166.2. ^{19}F NMR (188 MHz, DMSO-d_6): –83.7 (s, CF_3). $C_{15}H_{14}F_3N_3O_3$ (341.3): calcd. C 52.79, H 4.13, N 12.31; found C 52.68, H 4.14, N 12.34. LCMS: MH^+, 342.

Aknowledgements

This work was supported by the Russian Foundation for Basic Research (grant no. 13-03-90413).

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