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An Efficient Synthesis of PARP Inhibitors Containing a 4-Trifluoromethyl Substituted 3,6,7,7a-Tetrahydro-1*H*-pyrrolo[3,4-*d*]pyrimidine-2,5-dione Scaffold

Abstract

Poly(ADP-ribose) polymerases (PARPs) are key enzymes in the DNA repair pathway. Inhibitors of these enzymes belong to a new type of anticancer drugs that selectively kill cancer cells by targeting the homologous recombination genetic defects. This study presents a new synthetic approach to PARP inhibitors containing a 4-trifluoromethyl substituted 3,6,7,7a-tetrahydro-1*H*-pyrrolo[3,4-*d*]pyrimidine-2,5-dione scaffold. The method is based on a practical one-step cyclocondensation of 2-(2-oxo-1,2,3,4-tetrahydropyrimidin-4-yl)acetic acid derivatives *via* the Curtius rearrangement of the corresponding acyl azides formed *in situ* upon the treatment with diphenylphosphoryl azide. The resulting products have been found to possess a potent inhibitory effect on PARP-1 and PARP-2 isoforms of poly(ADP-ribose) polymerases. The structure–activity analysis has revealed that the N1-aryl substituent is crucial to the selectivity and high potency towards PARP-2, and that the *p*-fluorobenzyl group is the optimal group for the non-selective and potent PARP-1 and PARP-2 inhibition.

Keywords: Curtius rearrangement; heterocyclization; trifluoromethyl group; pyrrolo[3,4-*d*]pyrimidines; poly(ADP-ribose) polymerase inhibitors

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Ефективний синтез інгібіторів PARP на основі 4-трифторометилзаміщеного скафолду 3,6,7,7a-тетрагідро-1*H*-піроло[3,4-*d*]піримідин-2,5-діону

Анотація

Полі(АДФ-рибоза)-полімерази (PARP) є ключовими ензимами в процесах репарації ДНК. Інгібітори цих ензимів належать до нового типу протипухлинних препаратів, які вибірково вражають ракові клітини, націлюючись на генетичні дефекти гомологічної рекомбінації. У роботі наведено новий синтетичний підхід до інгібіторів PARP, що містять 4-трифторометилзаміщений скафолд 3,6,7,7a-тетрагідро-1*H*-піроло[3,4-d]піримідин-2,5-діону. Метод базується на практичній одностадійній циклоконденсації похідних 2-(2-оксо-1,2,3,4-тетрагідропіримідин-4-іл)оцтової кислоти за допомогою перегрупування Курціуса відповідних ацилазидів, утворених *in situ* за обробки кислот дифенілфосфорилазидом. Визначено, що одержані продукти виявляють значний інгібувальний ефект на ізоформи PARP-1 і PARP-2 полі(АДФ-рибоза)-полімераз. Аналізом взаємозв'язку між структурою та активністю доведено, що N1-арильний замісник має суттєве значення для селективності та високої активності до PARP-2, а *пара*-фторобензильна група є оптимальною для вираженого невибіркового інгібування PARP-1 та PARP-2.

Ключові слова: перегрупування Курціуса; гетероциклізація; трифлуорометильна група; піроло[3,4-*d*]піримідини; інгібітори полі(АДФ-рибоза)-полімерази

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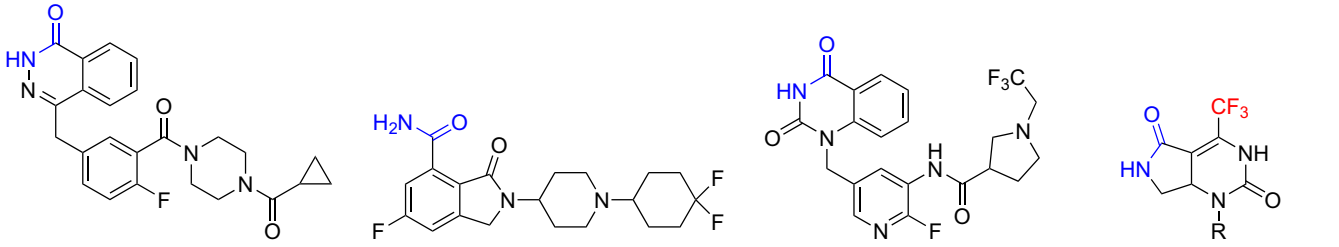
■ Introduction

Poly(ADP-ribose) polymerase (PARP) has evolved as a promising molecular target in the cancer-targeted chemotherapy due to its pivotal role in restoring the genomic integrity [1]. The knowledge of its functions has led to the development of PARP inhibitors, which exert their anticancer activity by interrupting DNA repair mechanisms [2]. Several compounds (olaparib, niraparib, talazoparib, and rucaparib) have already been marketed for treating advanced ovarian cancer and breast cancer patients [3]. As a monotherapy, PARP inhibitors have been shown to selectively kill tumors harboring mutations or deletions in DNA repair genes related to homologous recombination pathways, such as BRCA-1 and BRCA-2. This phenomenon referred to as "synthetic lethality" has been successfully translated to clinical practice and now exemplifies a "personalized" approach to the cancer therapy [4].

A poly(ADP-ribose) polymerase family has 18 nuclear and cytoplasmic enzymes that cleave NAD+ to nicotinamide and ADP-ribose to form long and branched ADP-ribose polymers on target proteins, including topoisomerases, histones and PARP itself, and thus impact diverse cellular processes (replication, transcription, differentiation, gene regulation, protein degradation). In the family, PARP1 and PARP2 are the most attractive therapeutic targets for the anticancer drug development. In fact, the vast majority of PARP inhibitors developed to date demonstrate a lack of specificity for any given PARP isoform. This raises the challenging problem of developing small molecule PARP inhibitors with a high isoform selectivity as better-tolerated drugs [5]. PARP-1 accounts for more than 90% of the cellular PARP activity, thus representing a primarily targeted PARP isozyme for the therapeutic intervention. However, none of the currently FDA-approved PARP inhibitors selectively inhibits PARP-1. Moreover, olaparib (**Figure**), the most clinically successful drug, demonstrates superior (5-fold) inhibition of PARP-2 [6]. Compound NMS-P118 is one of the most PARP-1 selective clinical candidates (~150-fold selectivity over PARP-2) endowed with a pronounced anticancer activity in preclinical studies [7]. *Zhao et al.* identified compound **11a** with a nearly 40-fold PARP-2/PARP-1 selectivity [8].

Recently, we have reported that the 4-trifluoromethyl-substituted 3,6,7,7a-tetrahydro-1*H*-pyrrolo[3,4-*d*]pyrimidine-2,5-dione core may serve as a scaffold for designing a novel class of PARP inhibitors, due primarily to the presence of the endocyclic amide fragment in the pyrrolidone ring, which resembles a key structural motif of the majority of PARP's nicotinamide site ligands [9]. This suggestion was supported by a molecular docking study, which additionally revealed that the trifluoromethyl group in position 4 of the novel scaffold may significantly contribute to the binding with the PARP enzyme NAD+ binding site due to the C···F orthogonal dipolar interaction with the backbone peptide fragment. As a result,



Olaparib (ref [6])
IC_{50} (PARP-1): 5 nM
IC_{50} (PARP-2): 1 nM

NMS-P118 (ref [7])
K_D (PARP-1): 0.03 μM
K_D (PARP-2): 3.93 μM

Compound 1 1a (ref [8])
IC_{50} (PARP-1): 467 nM
IC_{50} (PARP-2): 11.5 nM

Compounds 1a,b (ref [9])
a: R = PMP
IC_{50} (PARP-2): 0.46 μM
b: R = PFB
IC_{50} (PARP-2): 1.12 μM

Figure. Selected PARP-1 and PARP-2 inhibitors. PMP – *p*-methoxyphenyl; PFB – *p*-fluorobenzyl

compounds **1a,b** demonstrated a potent inhibition of the PARP-2 enzyme. In this work, we characterized a new series of 3,6,7,7a-tetrahydro-1*H*-pyrrolo[3,4-*d*]pyrimidine-2,5-dione derivatives in the *in vitro* PARP-1 and PARP-2 radiometric assay to gain deeper insight into the inhibition selectivity of the isoforms and a preliminary structure-activity relationship.

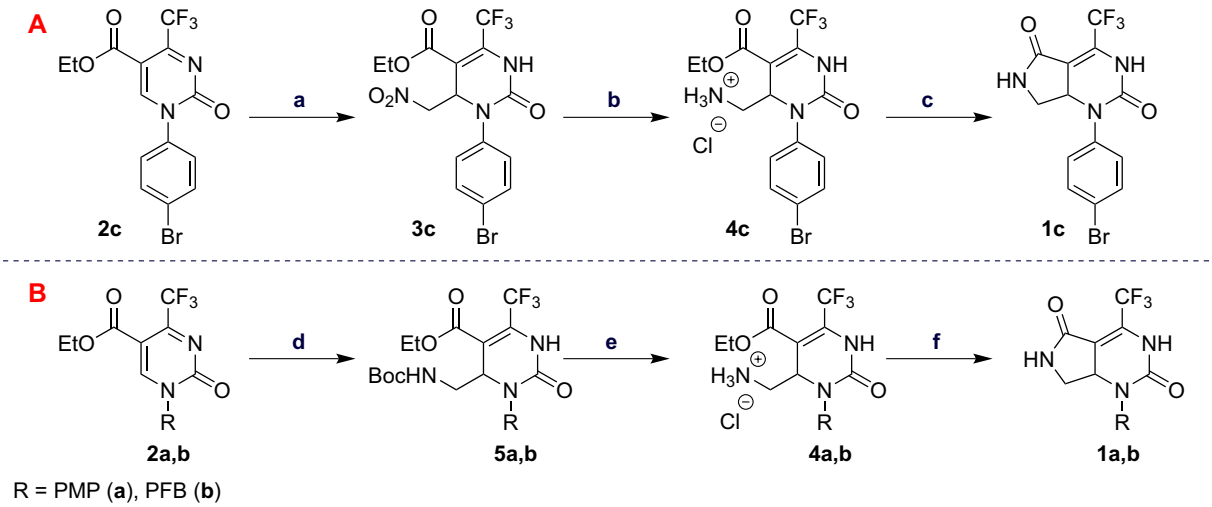
■ Results and discussion

Synthesis

The method previously developed for the preparation of 4-bromophenyl substituted 3,6,7,7a-tetrahydro-1*H*-pyrrolo[3,4-*d*]pyrimidine-2,5-dione **1c** relied on regioselective nitromethane addition to ethyl carboxylate **2c**, chemoselective nitro group reduction in the adduct **3c** and subsequent intramolecular cyclocondensation of the resulting amine intermediate **4c** (**Scheme 1**, A) [10]. The main drawbacks of this approach were the low thermal stability of nitro compound **3c**, which easily underwent a retro nitro-Michael reaction to the starting reactants, and facile saturation of the C=C double bond in the 1*H*-pyrrolo[3,4-*d*]pyrimidine-2,5-dione system under a number of reducing conditions tested for step ***b***. It was found that reduction of the nitro group with zinc dust in acetic acid furnished amino ester hydrochloride **4c** in an acceptable 60% yield. Finally, compound **1c** was obtained in 83% yield after the treatment with aqueous NaOH at room temperature. This method is unsuitable for synthesizing N1-alkyl substituted derivatives due to an insufficient reactivity of N1-alkyl pyrimidones **2** in the nitromethane addition step.

The second approach (**Scheme 1**, B) was based on the visible-light-mediated hydroaminoalkylation of pyrimidin-2(1*H*)-ones **2a,b** by the *aza*-Giese-type reaction with potassium *N*-Boc-aminomethyltrifluoroborate in the presence of an acridinium dye as a photocatalyst [9]. Further transformation of the radical addition products **5a,b** enabled the synthesis of amine hydrochlorides **4a,b** and, eventually, 3,6,7,7a-tetrahydro-1*H*-pyrrolo[3,4-*d*]pyrimidine-2,5-dione derivatives **1a,b**, which showed promise as inhibitors of poly-(ADP-ribose) polymerase (PARP) enzymes (IC_{50} 0.46–1.12 μM for PARP-2 in a fluorometric assay). The method requires chromatographic purification of intermediates **5** due to the formation of by-products derived from the radical side reactions.

With the aim of developing a practical general approach to the desired heterocyclic system **1**, lacking the above-mentioned limitations, we used stable (2-oxo-1,2,3,4-tetrahydropyrimidin-4-yl)acetic acid derivatives **6a–j** (**Scheme 2**) as key intermediates in this work. Latter compounds were obtained in high yields from readily available pyrimidin-2(1*H*)-ones **7a–j** according to our reported procedure based on the regioselective decarboxylative malonic acid addition [11]. As found out, acids **6** can be easily converted into target compounds **1** in a single step by the interaction with diphenylphosphoryl azide and triethylamine under heating in toluene. The reaction proceeds *via* the Curtius rearrangement of the corresponding



R = PMP (**a**), PFB (**b**)

Scheme 1. Previously reported methods for the preparation of compounds **1a–c**. *Reagents and conditions*: (**a**) $MeNO_2$ (5 equiv), Et_3N (0.1 equiv), CH_2Cl_2, 0–5 °C, 10 h, 70% yield; (**b**) 1. Zn, AcOH, 25 °C, 8 h; 2. 4M HCl in dioxane, 60% yield; (**c**) NaOH, MeOH/H_2O, 25 °C, 2 h, 83% yield; (**d**) $BocNHCH_2BF_3K$ (1.5 equiv), acridinium photocatalyst (3 mol%), acetone/MeOH (5:1), blue light irradiation, 25 °C, 16 h, 59–64% yield; (**e**) 1M HCl in dioxane, 25 °C, 6 h, 77–86% yield; (**f**) NaOH, EtOH, 60 °C, 6 h, 71–76% yield.
Boc – *tert*-butyloxycarbonyl; PFB – *p*-fluorobenzyl; PMP – *p*-methoxyphenyl

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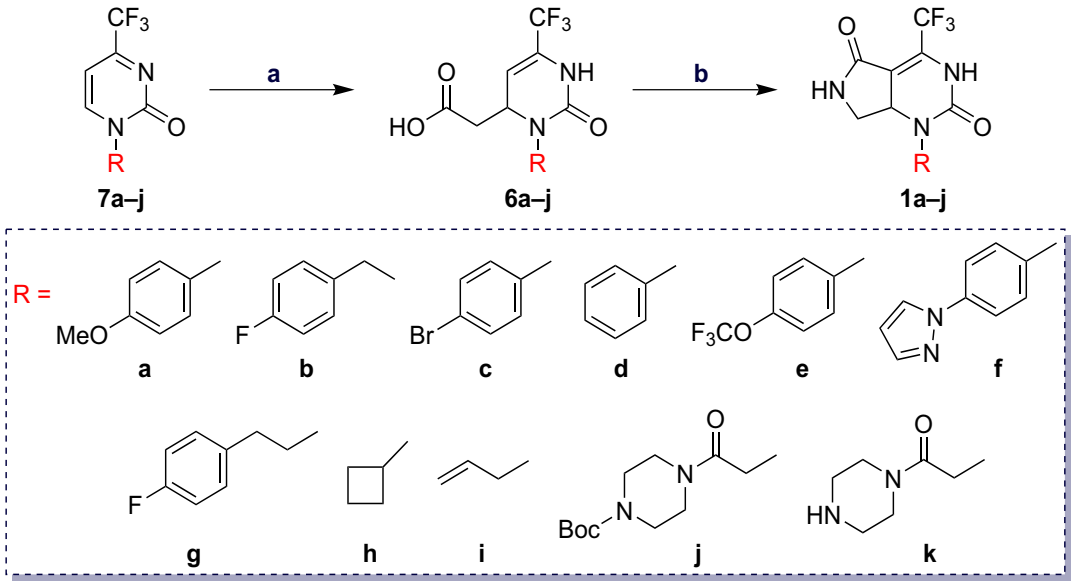

Scheme 2. The approach elaborated to 3,6,7,7a-tetrahydro-1*H*-pyrrolo[3,4-*d*]pyrimidine-2,5-diones. *Reagents and conditions*: (**a**) malonic acid (5 equiv), Et_3N (1 equiv), DMSO, 80 °C 18 h, 59–79 % yield; (**b**) $(PhO)_2PON_3$ (1.2 equiv), Et_3N (1.5 equiv), toluene, 80 °C, 6 h, 42–63 % yield. Boc – *tert*-butyloxycarbonyl

in situ generated acyl azides and the subsequent intramolecular cyclocondensation of the resulting isocyanates to 3,6,7,7a-tetrahydro-1*H*-pyrrolo[3,4-*d*]pyrimidine-2,5-diones. Thus, the target compounds **1a–j** featuring diverse N1-alkyl and N1-aryl substituents were obtained in 42–63% yields. The removal of the *N*-Boc-protection in product **1j** led to piperazine-containing compound **1k** in 87% yield. None of the synthetic steps in the novel approach required the chromatographic purification of both the intermediate and final products.

Biological activity

The results of studying the inhibitory activity for compounds **1a–i,k** against PARP-1 and PARP-2 enzymes are presented in **Table** (represented as the residual enzyme activity after the incubation with the inhibitors in the concentration of 10 μM). The results of the radiometric PARP inhibitory assay revealed that the N1-aryl-substitution within the 3,6,7,7a-tetrahydro-1*H*-pyrrolo-[3,4-d]pyrimidine-2,5-dione system (compounds **1a,c–f**) led to the complete PARP-2 inhibition in this concentration, while the activity of PARP-1 enzyme was in the range of 23.85–50.21%. The substitution by a N1-*p*-fluorobenzyl group gave rise to a potent and merely isoform non-selective inhibitor (compound **1b**). When R is a N1-*p*-fluorophenethyl group, compound **1g** exhibited a moderate selectivity and a good potency (up to 1.22% and 17.48% of the remaining activity of PARP-2 and PARP-1, respectively). The introduction of simple N1-alkyl groups, such as cyclobutyl or allyl substituents, in compounds **1h,i**, or a piperazine amide fragment in compound **1k** resulted in a weaker non-selective inhibition with 8.59–35.2% of the remaining enzyme activity.

Table. The remaining enzyme activity (%, n = 2: data 1 and data 2, relative to DMSO control) after the incubation of 10 μM of compounds **1a–i,k** with PARP-1 and PARP-2

Compound	PARP-1 activity (data 1; data 2), %	PARP-2 activity (data 1; data 2), %
1a	50.21; 49.18	6.92; 6.51
1b	6.29; 6.72	-2.62; 0.21
1c	33.57; 30.56	-2.08; 1.08
1d	41.64; 39.22	5.11; 5.87
1e	40.82; 39.32	3.90; 3.79
1f	25.05; 23,85	-3.20; -0.95
1g	17.48; 14.35	2.08; 1.22
1h	26.9; 26.3	21.22; 19.3
1i	20.81; 19.84	9.58; 8.59
1k	35.2; 33.27	18.27; 17.89

■ Conclusions

A series of 3,6,7,7a-tetrahydro-1*H*-pyrrolo[3,4-*d*]pyrimidine-2,5-diones has been synthesized using a novel practical approach, and their inhibitory activity against PARP-1 and PARP-2 isoforms has been evaluated. Among all the compounds tested, derivatives **1a–g** have exhibited a potent enzyme inhibitory activity with the complete inhibition at a concentration of 10 μM, and **1a,d-f** have demonstrated specificity to PARP-2 (up to 41.64 of the remaining PARP-1 activity at the same concentration). These findings can provide promising structural chemotypes for the development of novel PARP inhibitors with a high potency and specificity.

Experimental part

Chemistry, general experimental information

All chemicals were obtained from Enamine LTD and used without further purification. Solvents were purified according to the standard procedures. Melting points were uncorrected. ^{19}F NMR, ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian Mercury-400 (^{13}C: 101 MHz; ^{19}F: 376 MHz) or Bruker Avance DRX-500/600 (^{13}C: 126 MHz, 151 MHz; ^{19}F: 470 MHz) or Mercury+ 300 Varian (^{13}C: 76 MHz, 302 MHz; ^{19}F: 188 MHz) spectrometers with TMS or CCl_3F as an internal standard. Multiplets were assigned as *s* (singlet), *d* (doublet), *t* (triplet), *q* (quartet), *m* (multiplet) and *br. s* (broad singlet). Mass spectrometric detection of samples was performed with an Infinity 1260 UHPLC system (Agilent Technologies, Waldbronn, Germany) coupled to a 6224 Accurate Mass TOF LC/MS system (Agilent Technologies, Singapore). Compounds **6b,i** and **7a–f,i** were prepared according to the literature procedures [11].

Biological assay conditions and protocol

The research was performed by the Reaction Biology Corporation according to the standard assay protocol recommended by the developer (https://www.reactionbiology.com/services/target-specific-assays/parp-assays). The reaction buffer was 50 mM Tris-HCl (pH 8.0), 50 mM NaCl, 10 mM $MgCl_2$, 1 mM DTT, 1% DMSO, and 20 μg/mL activated DNA. The ^{32}P-NAD$^+$ ([adenylate-^{32}P]-Nicotinamide Adenine Dinucleotide) concentration was 10 μM. Compounds were tested in a single-dose duplicate mode in a concentration of 10 μM. The control compound, PJ34, was tested in a 10-dose IC_{50} mode with a 3-fold serial dilution starting at 10 μM. The resulting IC_{50} values were in accordance with the published data: 13.5 nM (PARP-1) and 9.5 nM (PARP-2). PARP substrates were core histones (PARP-1) and histone H3.3 (PARP-2).

The substrate was prepared in the Reaction Buffer freshly obtained. The indicated PARP was delivered into the substrate solution and gently mixed. Compounds were delivered in DMSO into the reaction mixture using an Acoustic Technology (Echo 550, LabCyte Inc. Sunnyvale, CA) in the nanoliter range and incubated 20 min at room temperature. ^{32}P-NAD$^+$ was delivered into the reaction mixture to initiate the reaction. The mixture was incubated for 2 h at room temperature and then delivered to filter-paper and washed with 0.75% phosphoric acid for detection.

The data were analyzed using the Excel and GraphPad Prism software. The PARP activity data were expressed as the percent of the remaining PARP activity in test samples (data 1 and data 2) compared to vehicle (dimethyl sulfoxide) reactions. IC_{50} values and curve fits were obtained using the Prism4 Software (GraphPad).

The synthesis of compounds 1a-j

To a solution of compounds **6a–j** (1 mmol) and diphenylphosphoryl azide (0.33 g, 1.2 mmol) in toluene (10 mL), triethylamine (0.15 g, 1.5 mmol) was added. The mixture was stirred at 80 °C for 6 h. After completion of the reaction, the mixture was cooled to room temperature and evaporated to dryness under reduced pressure. The residue obtained was treated with saturated solution of sodium hydrogen carbonate (20 mL). The solid was filtered, washed with water (20 mL), methyl *tert*-butyl ether (10 mL), dried on air and purified by recrystallization from acetonitrile to obtain the corresponding product as a white solid.

1-(4-Methoxyphenyl)-4-(trifluoromethyl)-3,6,7,7a-tetrahydro-1H-pyrrolo[3,4-d]pyrimidine-2,5-dione (**1a**)

Yield – 0.18 g (56%). M. p. >250 °C. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 2.94 (1H, t, J = 8.5 Hz), 3.20 (1H, t, J = 8.8 Hz), 5.26 (1H, s), 3.76 (3H, s), 6.94 (2H, d, J = 8.4 Hz), 7.27 (2H, d, J = 8.4 Hz), 8.16 (1H, s), 10.10 (1H, s). ^{13}C NMR (126 MHz, DMSO-d_6), δ, ppm: 45.8, 55.7, 55.8, 110.0, 114.5, 119.5 (q, J = 275.8 Hz), 127.6 (q, J = 38.4 Hz), 128.6, 131.6, 153.2, 158.5, 164.1. ^{19}F NMR (376 MHz, DMSO-d_6), δ, ppm: –62.1 (s). HRMS (ESI): m/z calcd for $C_{14}H_{13}F_3N_3O_3$ $[M+H]^+$ 328.0904, found 328.0906.

1-(4-Fluorobenzyl)-4-(trifluoromethyl)-3,6,7,7a-tetrahydro-1H-pyrrolo[3,4-d]pyrimidine-2,5-dione (**1b**)

Yield – 0.23 g (62%). M. p. >250 °C. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 3.15 (1H, t, J = 8.3 Hz), 3.54 (1H, t, J = 8.5 Hz), 4.22 (1H, d, J = 15.4 Hz), 4.51–4.55 (1H, m), 4.68 (1H, d, J = 15.5 Hz), 7.17 (2H, t, J = 8.7 Hz), 7.38 (2H, dd, J = 8.4, 5.5 Hz), 8.17 (1H, s), 9.97 (1H, s). ^{13}C NMR (126 MHz, DMSO-d_6), δ, ppm: 45.7, 46.5, 54.5, 109.2, 115.8 (d, J = 21.4 Hz), 120.4 (q, J = 276.1 Hz), 127.4 (q, J = 38.2 Hz), 130.4 (d, J = 8.2 Hz), 133.3 (d, J = 3.0 Hz), 153.6, 162.0 (d, J = 243.2 Hz), 164.2. ^{19}F NMR (470 MHz, DMSO-d_6), δ, ppm: –115.2 (t, J = 7.4 Hz, 1F), –61.8 (s, 3F). HRMS (ESI): m/z calcd for $C_{14}H_{12}F_4N_3O_2$ $[M+H]^+$ 330.0860, found 330.0855.

1-(4-Bromophenyl)-4-(trifluoromethyl)-3,6,7,7a-tetrahydro-1H-pyrrolo[3,4-d]pyrimidine-2,5-dione (**1c**)

Yield – 0.21 g (57%). M. p. >250 °C. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 2.85–2.94 (1H, m),

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3.25–3.31 (1H, m), 5.34 (1H, br. s), 7.32 (2H, d, *J* = 7.0 Hz), 7.59 (2H, d, *J* = 7.6 Hz), 8.22 (1H, s), 10.23 (1H, s). ^{13}C NMR (126 MHz, DMSO-d_6), δ, ppm: 45.1, 54.6, 109.7 (d, *J* = 2.6 Hz), 119.0 (q, *J* = 276.3 Hz), 119.5, 126.9 (q, *J* = 38.8 Hz), 128.8, 131.6, 137.7, 152.3, 163.3. ^{19}F NMR (470 MHz, DMSO-d_6), δ, ppm: –61.55 (s). HRMS (ESI): *m/z* calcd for $C_{13}H_9BrF_3N_3O_2$ $[M+H]^+$ 375.9903, found 375.9900.

1-Phenyl-4-(trifluoromethyl)-4a,6,7,7a-tetrahydro-1H-pyrrolo[3,4-d]pyrimidine-2,5-dione (**1d**)

Yield – 0.18 g (61%). M. p. >250 °C. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 2.89 (1H, t, *J* = 8.2 Hz), 3.28 (1H, t, *J* = 8.7 Hz), 5.31 – 5.39 (1H, m), 7.25–7.45 (5H, m), 8.19 (1H, s), 10.17 (1H, s). ^{13}C NMR (126 MHz, DMSO-d_6), δ, ppm: 45.8, 55.3, 110.1, 119.5 (q, *J* = 275.7 Hz), 127.2, 127.4, 127.6 (q, *J* = 39.8 Hz), 129.3, 138.9, 153.0, 164.0. ^{19}F NMR (470 MHz, DMSO-d_6), δ, ppm: –61.6 (s). HRMS (ESI): *m/z* calcd for $C_{13}H_{11}F_3N_3O_2$ $[M+H]^+$ 298.0798, found 298.0796.

1-(4-(Trifluoromethoxy)phenyl)-4-(trifluoromethyl)-3,6,7,7a-tetrahydro-1H-pyrrolo[3,4-d]pyrimidine-2,5-dione (**1e**)

Yield – 0.24 g (63%). M. p. >250 °C. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 2.91 (1H, t, *J* = 8.2 Hz), 3.33 (1H, t, *J* = 8.5 Hz), 5.36 (1H, br. s), 7.39 (2H, d, *J* = 8.5 Hz), 7.49 (2H, d, *J* = 8.8 Hz), 8.20 (1H, s), 10.23 (1H, s). ^{13}C NMR (126 MHz, DMSO-d_6), δ, ppm: 45.6, 55.1, 110.1 (d, *J* = 2.4 Hz), 119.4 (q, *J* = 276.0 Hz), 120.4 (q, *J* = 256.3 Hz), 121.8, 127.4 (q, *J* = 38.5 Hz), 128.9, 137.8, 147.0 (d, *J* = 1.9 Hz), 152.9, 163.8. ^{19}F NMR (470 MHz, DMSO-d_6), δ, ppm: –61.6 (s, 1F), –56.9 (s, 1F). HRMS (ESI): *m/z* calcd for $C_{14}H_{10}F_6N_3O_3$ $[M+H]^+$ 382.0621, found 382.0625.

1-(4-(1H-Pyrazol-1-yl)phenyl)-4-(trifluoromethyl)-3,6,7,7a-tetrahydro-1H-pyrrolo[3,4-d]pyrimidine-2,5-dione (**1f**)

Yield – 0.19 g (52%). M. p. >250 °C. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 2.91–2.99 (1H, m), 3.31–3.39 (2H, m), 5.37 (1H, br. s), 6.55 (1H, t, *J* = 2.2 Hz), 7.47 (2H, d, *J* = 8.4 Hz), 7.75 (1H, d, *J* = 1.7 Hz), 7.85 (2H, d, *J* = 8.4 Hz), 8.13 (1H, s), 8.49 (1H, d, *J* = 2.2 Hz), 10.11 (1H, s). ^{13}C NMR (76 MHz, DMSO-d_6), δ, ppm: 45.3, 54.9, 109.7, 117.9, 118.2, 119.1 (q, *J* = 276.1 Hz), 126.2, 127.1 (q, *J* = 38.5 Hz), 127.8, 135.9, 138.3, 141.9 (d, *J* = 2.8 Hz), 152.6, 163.6. ^{19}F NMR (376 MHz, DMSO-d_6), δ, ppm: –62.0 (s). HRMS (ESI): *m/z* calcd for $C_{16}H_{13}F_3N_5O_2$ $[M+H]^+$ 364.1016, found 364.1021.

1-(4-Fluorophenethyl)-4-(trifluoromethyl)-3,6,7,7a-tetrahydro-1H-pyrrolo[3,4-d]pyrimidine-2,5-dione (**1g**)

Yield – 0.21 g (61%). M. p. >250 °C. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 2.59–3.00 (2H, m), 3.00–3.24 (2H, m), 3.49–3.81 (2H, m), 4.70 (1H, s), 6.91–7.22 (2H, m), 7.22–7.50 (2H, m), 8.19 (1H, s), 9.82 (1H, s). ^{13}C NMR (126 MHz, DMSO-d_6), δ, ppm: 32.0, 45.6, 54.2, 109.0, 115.5 (d, *J* = 21.0 Hz), 119.4 (q, *J* = 275.9 Hz), 127.4 (q, *J* = 37.9 Hz), 131.0, 131.1, 135.6, 153.2, 161.4 (d, *J* = 242.7 Hz), 164.2. ^{19}F NMR (470 MHz, DMSO-d_6), δ, ppm: –116.8 (s, 1F), –61.8 (s, 3F). HRMS (ESI): *m/z* calcd for $C_{15}H_{14}F_4N_3O_2$ $[M+H]^+$ 344.1017, found 344.1011.

1-Cyclobutyl-4-(trifluoromethyl)-3,6,7,7a-tetrahydro-1H-pyrrolo[3,4-d]pyrimidine-2,5-dione (**1h**)

Yield – 0.13 g (47%). M. p. >250 °C. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 1.45–1.75 (2H, m), 2.03–2.10 (2H, m), 2.39–2.47 (2H, m), 3.20 (1H, t, *J* = 8.4 Hz), 3.72 (1H, t, *J* = 8.4 Hz), 4.04 (1H, p, *J* = 8.9 Hz), 4.74 (1H, s), 8.16 (1H, s), 9.64 (1H, s). ^{13}C NMR (101 MHz, DMSO-d_6), δ, ppm: 15.1, 28.3, 28.4, 47.3, 51.1, 54.9, 108.8, 119.4 (q, *J* = 276.2 Hz), 127.2 (q, *J* = 38.4 Hz), 153.0, 164.1. ^{19}F NMR (376 MHz, DMSO-d_6), δ, ppm: –62.2 (s). HRMS (ESI): *m/z* calcd for $C_{11}H_{13}F_3N_3O_2$ $[M+H]^+$ 276.0954, found 276.0959.

1-Allyl-4-(trifluoromethyl)-3,6,7,7a-tetrahydro-1H-pyrrolo[3,4-d]pyrimidine-2,5-dione (**1i**)

Yield – 0.11 g (42%). M. p. >250 °C. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 3.21 (1H, t, *J* = 8.3 Hz), 3.53–3.63 (2H, m), 4.10 (1H, dd, *J* = 15.7, 5.0 Hz), 4.65 (1H, dq, *J* = 7.8, 4.1 Hz), 5.20 (1H, d, *J* = 10.2 Hz), 5.27 (1H, d, *J* = 17.1 Hz), 5.72–5.86 (1H, m), 8.17 (1H, s), 9.86 (1H, s). ^{13}C NMR (126 MHz, DMSO-d_6), δ, ppm: 45.6, 46.3, 54.2, 109.3, 118.9, 119.4 (q, *J* = 276.3 Hz), 127.4 (d, *J* = 38.5 Hz), 133.0, 153.2, 164.2. ^{19}F NMR (376 MHz, DMSO-d_6), δ, ppm: –62.3 (s). HRMS (ESI): *m/z* calcd for $C_{11}H_{11}F_3N_3O_2$ $[M+H]^+$ 262.0798, found 262.0802.

tert-Butyl 4-(2-(2,5-dioxo-4-(trifluoromethyl)-2,3,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-d]pyrimidin-1-yl)acetyl)piperazine-1-carboxylate (**1j**)

Yield – 0.28 g (63%). M. p. >250 °C. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 1.41 (9H, s), 3.15 (1H, t, *J* = 8.4 Hz), 3.38 (8H, q, *J* = 19.9 Hz), 3.61 (1H, t, *J* = 8.5 Hz), 3.77 (1H, d, *J* = 17.0 Hz), 4.40 (1H, d, *J* = 17.0 Hz), 4.74–4.83 (1H, m), 8.17 (1H, s), 9.88 (1H, s). ^{13}C NMR (126 MHz, DMSO-d_6), δ, ppm: 28.5, 41.6, 44.3, 44.8, 45.6, 55.0, 79.7, 109.3, 119.5 (q, *J* = 276.0 Hz), 127.4 (q, *J* = 38.6 Hz), 153.8, 154.3, 164.2, 166.3. ^{19}F NMR (470 MHz, DMSO-d_6), δ, ppm: –61.8 (s). HRMS (ESI): *m/z* calcd for $C_{18}H_{25}F_3N_5O_5$ $[M+H]^+$ 448.1802, found 448.1805.

The synthesis of 1-(2-oxo-2-(piperazin-1-yl)ethyl)-4-(trifluoromethyl)-3,6,7,7a-tetrahydro-1*H*-pyrrolo[3,4-d]pyrimidine-2,5-dione hydrochloride (1k)

Compound **1j** (0.2 g, 0.45 mmol) was treated with 4M HCl in dioxane (5 mL), and the resulting

mixture was stirred at room temperature for 6 h. Methyl *tert*-butyl ether (10 mL) was added to the mixture. The solid was collected by filtration and washed with methyl *tert*-butyl ether (2×10 mL) to give compound **1k**.

A beige solid. Yield – 0.15 g (87%). M. p. >250 °C. ^{1}H NMR (302 MHz, DMSO-d_6), δ, ppm: 2.97–3.19 (5H, m), 3.57–3.73 (5H, m), 3.82 (1H, d, J = 17.1 Hz), 4.44 (1H, d, J = 17.0 Hz), 4.68–4.82 (1H, m), 8.23 (1H, s), 9.60 (2H, br. d, J = 29.5 Hz), 9.90 (1H, s). ^{13}C NMR (76 MHz, DMSO-d_6), δ, ppm: 41.1, 42.4 (d, J = 7.1 Hz), 44.3, 45.3, 54.6, 109.0 (d, J = 2.3 Hz), 119.0 (q, J = 276.1 Hz), 126.9 (q, J = 38.3 Hz), 153.4, 163.8, 165.9. ^{19}F NMR (188 MHz, DMSO-d_6), δ, ppm: –61.7 (s). HRMS (ESI): m/z calcd for $C_{13}H_{17}F_3N_5O_3$ $[M+H]^+$ 348.1278, found 348.1280.

The synthesis of compounds 6a,c–h,j

To the solution of compounds **7a,c–h,j** (3 mmol) and malonic acid (1.56 g, 15 mmol, 5 equiv) in DMSO (10 mL), triethylamine (0.3 g, 3 mmol) was added. The mixture was stirred at 80 °C for 18 h. After completion of the reaction, the mixture was cooled, diluted with 0.4M hydrochloric acid (20 mL), and the product was extracted with dichloromethane (3×20 mL). The combined organic layers were washed with brine (2×20 mL), dried over anhydrous sodium sulfate, and the solvent was evaporated. The residue obtained was crystallized from hexane/methyl *tert*-butyl ether (1:5) to give the corresponding product as a white solid.

2-(3-(4-Methoxyphenyl)-2-oxo-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidin-4-yl)acetic acid (**6a**)

Yield – 0.75 g (76%). M. p. 194–195 °C. ^{1}H NMR (302 MHz, DMSO-d_6), δ, ppm: 2.46 (2H, d, J = 5.9 Hz), 3.76 (3H, s), 4.56–4.77 (1H, m), 5.53–5.77 (1H, m), 6.95 (2H, d, J = 8.4 Hz), 7.26 (2H, d, J = 8.4 Hz), 9.60 (1H, s), 12.41 (1H, s). ^{13}C NMR (76 MHz, DMSO-d_6), δ, ppm: 38.43, 55.31, 56.19, 102.57 (d, J = 5.5 Hz), 114.20, 119.86 (q, J = 272.3 Hz), 126.99 (q, J = 34.6 Hz), 132.88, 129.63, 151.52, 157.96, 171.21. ^{19}F NMR (376 MHz, DMSO-d_6), δ, ppm: –69.7 (s). HRMS (ESI): m/z calcd for $C_{14}H_{14}F_3N_2O_4$ $[M+H]^+$ 331.0900, found 331.0897.

2-(3-(4-Bromophenyl)-2-oxo-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidin-4-yl)acetic acid (**6c**)

Yield – 0.79 g (69%). M. p. 189–190 °C. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 2.47 (2H, d, J = 5.8 Hz), 4.85 (1H, br. s, J = 6.6 Hz), 5.64 (1H, br. s), 7.35 (2H, d, J = 8.1 Hz), 7.59 (2H, d, J = 8.2 Hz), 9.72 (1H, s), 12.42 (1H, s). ^{13}C NMR (126 MHz, DMSO-d_6), δ, ppm: 38.4, 55.7, 102.9 (d, J = 5.2 Hz), 119.6, 119.8 (q, J = 272.1 Hz), 126.9 (q, J = 34.9 Hz), 130.4, 131.8, 139.6, 151.1, 171.0. ^{19}F NMR (376 MHz, DMSO-d_6), δ, ppm: –69.6 (s). HRMS (ESI): m/z calcd for $C_{13}H_{11}BrF_3N_2O_3$ $[M+H]^+$ 379.9900, found 378.9895.

2-(2-Oxo-3-phenyl-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidin-4-yl)acetic acid (**6d**)

Yield – 0.71 g (79%). M. p. 116–117 °C. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 2.42–2.49 (2H, m), 4.82 (1H, d, J = 6.3 Hz), 5.63 (1H, d, J = 4.8 Hz), 7.30 (1H, t, J = 7.2 Hz), 7.33–7.46 (4H, m), 9.66 (1H, s), 12.45 (1H, s). ^{13}C NMR (126 MHz, chloroform-d), δ, ppm: 38.8, 56.3, 103.2 (d, J = 5.2 Hz), 120.3 (q, J = 272.4 Hz), 127.3 (d, J = 14.1 Hz), 127.4, 128.7, 129.4, 140.7, 151.8, 171.5. ^{19}F NMR (376 MHz, DMSO-d_6): δ –69.6 (s). HRMS (ESI): m/z calcd for $C_{13}H_{12}F_3N_2O_3$ $[M+H]^+$ 301.0795, found 301.0799.

2-(2-Oxo-3-(4-(trifluoromethoxy)phenyl)-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidin-4-yl) acetic acid (**6e**)

Yield – 0.82 g (71%). M. p. 176–177 °C. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 2.47 (2H, d, J = 5.8 Hz), 4.79–4.93 (2H, m), 5.60–5.70 (1H, m), 7.40 (2H, d, J = 8.5 Hz), 7.51 (2H, d, J = 8.5 Hz), 9.74 (1H, s), 12.42 (1H, s). ^{13}C NMR (126 MHz, DMSO-d_6), δ, ppm: 38.31, 55.81, 102.85 (d, J = 5.1 Hz), 119.76 (q, J = 272.1 Hz), 120.07 (q, J = 256.3 Hz), 121.48, 126.90 (q, J = 35.0 Hz), 130.17, 139.30, 146.63, 151.24, 171.02. ^{19}F NMR (376 MHz, DMSO-d_6), δ, ppm: –69.6 (s, 1F), –57.4 (s, 1F). HRMS (ESI): m/z calcd for $C_{14}H_{11}F_6N_2O_4$ $[M+H]^+$ 385.0618, found 385.0620.

2-(3-(4-(1H-Pyrazol-1-yl)phenyl)-2-oxo-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidin-4-yl) acetic acid (**6f**)

Yield – 0.68 g (62%). M. p. 204–205 °C. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 2.46–2.52 (2H, m), 4.86–4.90 (1H, m), 5.62–5.68 (1H, m), 6.56 (1H, t, J = 2.2 Hz), 7.49 (2H, d, J = 8.6 Hz), 7.76 (1H, d, J = 1.7 Hz), 7.87 (2H, d, J = 8.4 Hz), 8.52 (1H, d, J = 2.5 Hz), 9.72 (1H, br. s), 12.43 (1H, s). ^{13}C NMR (126 MHz, DMSO-d_6), δ, ppm: 38.93, 56.38, 108.43, 119.25, 103.29 (d, J = 5.1 Hz), 120.27 (q, J = 272.1 Hz), 127.38 (q, J = 34.9 Hz), 128.32, 129.83, 138.54, 138.62, 141.58, 151.78, 171.58. ^{19}F NMR (376 MHz, DMSO-d_6): δ –69.6 (s). HRMS (ESI): m/z calcd for $C_{16}H_{14}F_3N_4O_3$ $[M+H]^+$ 367.1013, found 367.1010.

2-(3-(4-Fluorophenethyl)-2-oxo-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidin-4-yl)acetic acid (**6g**)

Yield – 0.72 g (69%). M. p. 132–134 °C. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 2.45 (1H, d, J = 7.8 Hz), 2.63 (1H, dd, J = 15.9, 4.8 Hz), 2.73 (1H, dt, J = 13.8, 6.7 Hz), 2.78–2.89 (1H, m), 3.05–3.17 (1H, m), 3.73–3.85 (1H, m), 4.24–4.34 (1H, m), 5.45 (1H, d, J = 5.3 Hz), 7.08 (2H, t, J = 8.7 Hz), 7.24

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(2H, dd, J = 8.3, 5.5 Hz), 9.39 (1H, s), 12.48 (1H, s). ^{13}C NMR (126 MHz, chloroform-*d*), δ, ppm: 33.0, 46.5, 52.6, 102.8, 115.4 (d, J = 20.9 Hz), 121.3 (q), 127.7 (q, J = 34.7 Hz), 131.0 (d, J = 7.9 Hz), 135.6, 152.6, 160.4, 162.3, 172.0. ^{19}F NMR (470 MHz, DMSO-d_6), δ, ppm: –117.1 (s, 1F), –69.0 (s, 3F). HRMS (ESI): m/z calcd for $C_{15}H_{15}F_4N_2O_3$ $[M+H]^+$ 347.1013, found 347.1010.

2-(3-Cyclobutyl-2-oxo-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidin-4-yl)acetic acid (**6h**)

Yield – 0.49 g (59%). M. p. 157–158 °C. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 1.49–1.65 (2H, m), 2.04–2.23 (5H, m), 2.32–2.46 (1H, m), 4.08 (1H, p, J = 8.4 Hz), 4.34 – 4.43 (1H, m), 5.56 (1H, d, J = 6.0 Hz), 9.37 (1H, s), 12.25 (1H, s). ^{13}C NMR (126 MHz, chloroform-*d*), δ, ppm: 14.7, 27.7, 30.0, 49.6, 50.8, 103.5, 120.3 (q, J = 272.3 Hz), 127.9 (q, J = 34.9 Hz), 152.7, 171.7. ^{19}F NMR (376 MHz, DMSO-d_6), δ, ppm: –69.3 (s). HRMS (ESI): m/z calcd for $C_{11}H_{14}F_3N_2O_3$ $[M+H]^+$ 279.0951, found 279.0955.

2-(3-(2-(4-(tert-Butoxycarbonyl)piperazin-1-yl)-2-oxoethyl)-2-oxo-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidin-4-yl)acetic acid (**6j**)

Yield – 0.88 g (65%). M. p. 221–222 °C (decomp.). ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 1.41 (9H, s), 2.47 (1H, d, J = 16.2 Hz), 2.73 (1H, d, J = 16.1 Hz), 3.20–3.40 (8H, m), 3.99 (1H, d, J = 16.8 Hz), 4.30 – 4.35 (1H, m), 4.40 (1H, d, J = 16.6 Hz), 5.47 (1H, s), 9.36 (1H, s), 12.40 (1H, s). ^{13}C NMR (126 MHz, DMSO-d_6), δ, ppm: 28.5, 41.7, 44.2, 46.4, 53.7, 79.6, 102.7, 102.8, 120.2 (q, J = 272.2 Hz), 127.2 (q, J = 34.5 Hz), 152.6, 154.3, 167.0, 172.1. ^{19}F NMR (376 MHz, DMSO-d_6), δ, ppm: –69.6 (s). HRMS (ESI): m/z calcd for $C_{18}H_{26}F_3N_4O_6$ $[M+H]^+$ 451.1799, found 451.1795.

The synthesis of compounds 7g,h

4-Ethoxy-1,1-difluorobut-3-en-2-one (1.5 g, 10 mmol) and the corresponding *N*-alkylurea (10 mmol) were dissolved in methanol (15 mL), then concentrated hydrochloric acid was added (5 mL). The mixture was refluxed for 12 h. After cooling, the solution was evaporated to the half volume, and then water (10 mL) was added. The precipitate formed was filtered, washed with water (10 mL), diethyl ether (10 mL) and dried on air.

1-(4-Fluorophenethyl)-4-(trifluoromethyl)pyrimidin-2(1H)-one (**7g**)

Using 1-(4-fluorophenethyl)urea (1.82 g, 10 mmol). A white solid. Yield – 1.91 g (67%). M. p. 183–184 °C. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 3.01 (2H, t, J = 7.4 Hz), 4.16 (2H, t, J = 7.4 Hz), 6.81 (1H, d, J = 6.6 Hz), 7.12 (2H, t, J = 8.9 Hz), 7.20–7.29 (2H, m), 8.38 (1H, d, J = 6.6 Hz). ^{13}C NMR (126 MHz, DMSO-d_6), δ, ppm: 33.0, 52.9, 99.1, 115.7 (d, J = 21.2 Hz), 120.0 (q, J = 277.2 Hz), 131.2 (d, J = 8.0 Hz), 134.0 (d, J = 3.3 Hz), 154.7, 154.9, 161.5 (q, J = 35.4 Hz), 161.6 (d, J = 242.3 Hz). ^{19}F NMR (376 MHz, DMSO-d_6), δ, ppm: –116.7 (s, 1F), –70.9 (s, 3F). HRMS (ESI): m/z calcd for $C_{13}H_{11}F_4N_2O$ $[M+H]^+$ 287.0802, found 287.0806.

1-Cyclobutyl-4-(trifluoromethyl)pyrimidin-2(1H)-one (**7h**)

Using 1-cyclobutylurea (1.14 g, 10 mmol). A white solid. Yield – 1.33 g (61%). M. p. 103–105 °C. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 1.60–1.76 (2H, m), 1.76–2.05 (4H, m), 4.30–4.59 (1H, m), 6.83 (1H, d, J = 6.6 Hz), 8.32 (1H, d, J = 6.6 Hz). ^{13}C NMR (126 MHz, DMSO-d_6), δ, ppm: 17.46, 31.49, 54.40, 104.60 (d, J = 11.0 Hz), 120.69 (q, J = 271.7 Hz), 153.64, 160.90 (q, J = 34.7 Hz). ^{19}F NMR (376 MHz, DMSO-d_6), δ, ppm: –70.1 (s). HRMS (ESI): m/z calcd for $C_9H_{10}F_3N_2O$ $[M+H]^+$ 219.0740, found 219.0736.

The synthesis of *tert*-butyl 4-(2-(2-oxo-4-(trifluoromethyl)pyrimidin-1(2*H*)-yl)acetyl)piperazine-1-carboxylate (7j)

To an ice-cooled stirred solution of 4-(trifluoromethyl)pyrimidin-2(1*H*)-one (1.64 g, 10 mmol, 1 equiv) in anhydrous DMF (20 mL), potassium *tert*-butoxide (1.23 g, 11 mmol, 1.1 equiv) was added in one portion, and the mixture was stirred at 0 °C for 15 min. Afterwards, *tert*-butyl 4-(2-chloroacetyl)piperazine-1-carboxylate (2.63 g, 10 mmol, 1 equiv) was added to the mixture. The reaction mixture was warmed to room temperature for over 1 h, stirred at room temperature overnight, and then poured on ice water. The solid was collected by filtration, washed with water (3×30 mL) and cyclohexane (30 mL), and dried on air.

A white solid. Yield – 2.89 g (74%). M. p. 253 °C (decomp.). ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 1.42 (9H, s), 3.31–3.62 (8H, m), 4.95 (2H, s), 6.94 (1H, d, J = 6.6 Hz), 8.48 (1H, d, J = 6.6 Hz). ^{13}C NMR (126 MHz, DMSO-d_6), δ, ppm: 28.5, 42.0, 44.5, 52.0, 79.8, 99.2, 120.0 (q, J = 277.6 Hz), 154.3, 154.8, 156.2, 162.0 (q, J = 35.5 Hz), 164.8. ^{19}F NMR (376 MHz, DMSO-d_6), δ, ppm: –70.2 (s). HRMS (ESI): m/z calcd for $C_{16}H_{22}F_3N_4O_4$ $[M+H]^+$ 391.1588, found 391.1581.

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