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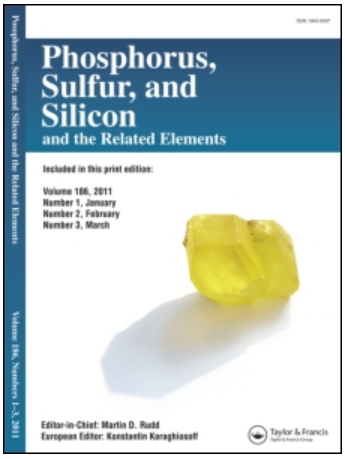

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Synthesis and Structure-Antitumor Activity Relationship of Sulfonyl 5-Fluorouracil Derivatives

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Online publication date: 28 December 2009

To cite this Article Yan, Xiaowei , Hou, Yong , Chen, Fan , Zhao, Kejian and Hu, Maolin(2010) 'Synthesis and Structure-Antitumor Activity Relationship of Sulfonyl 5-Fluorouracil Derivatives', Phosphorus, Sulfur, and Silicon and the Related Elements, 185: 1, 158 — 164
To link to this Article: DOI: 10.1080/10426500902754260
URL: http://dx.doi.org/10.1080/10426500902754260

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Phosphorus, Sulfur, and Silicon, 185:158–164, 2010
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ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500902754260

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SYNTHESIS AND STRUCTURE–ANTITUMOR ACTIVITY RELATIONSHIP OF SULFONYL 5-FLUOROURACIL DERIVATIVES

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Novel sulfonyl 5-fluorouracil derivatives 2 (5-fluoro-1-(arylsulfonyl)pyrimidine-2,4(1H,3H)-diones) have been synthesized via the reaction of 5-fluorouracil with sulfonyl chloride. Their chemical structures were confirmed by means of ^{1}H NMR, ^{13}C NMR, IR, mass spectra, and elemental analyses, and, in the case of 2a, its structure was established by single crystal X-ray diffraction. Some of the compounds were assayed for anticancer (HL-60 and BEL-7402 cells) activities. Structure–activity relationship (SAR) analysis discovered that the anticancer activity was related to the configuration, and that electron-withdrawing groups at 2-position or 4-position on the aryl group of arylsulfonyl derivatives of 5-fluorouracil could enhance the anticancer activity against the BEL-7402 cells.

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Keywords Anticancer activities; crystal structure; sulfonyl 5-fluorouracil derivatives

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INTRODUCTION

Compounds that exhibit the functionality of 5-fluorouracil (5-FU) have been extensively employed in the area of pharmaceuticals,[1] which is reflected by their use as antiviral,[2] antitumor,[3] and antibacterial[4] agents. The high profile of biological applications of compounds with 5-FU derivative has prompted extensive study for their synthesis and biological properties.[5] The common feature of these prodrugs is that they are all N1-modified derivatives through different biodegradable linkages.

Received 4 December 2008; accepted 30 December 2008.

We acknowledge financial support from the National Natural Science Foundation of China (No. 20571057), the Wenzhou Technology Project Foundation of China (No. S20060026), and the National Center for Drug Screening, Shanghai, China, for evaluation of antitumor activities.

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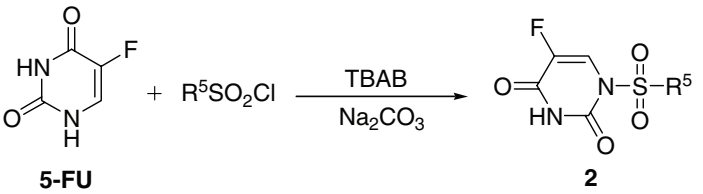
Sulfonamide compounds have been widely used for the treatment of bacterial or viral infections around the world because of their low cost, low toxicity, and excellent activity against common bacterial diseases. Moreover, sulfonamides represent an important class of medicinally important molecules and are known to possess wide varieties of biological activities, including antimalarial, saluretics, carbonic anhydrase inhibitors, antithyroid agents, antitumor drugs, etc.[6–8]

In accordance with the continuing interest in the synthesis of 5-FU derivatives,[9] we herein have synthesized a variety of sulfonyl 5-FU derivatives by the reaction of 5-FU with sulfonyl chloride and evaluated their biological activities. In this article we report the synthesis and biological activities of some new 5-fluoro-1-(arylsulfonyl)pyrimidine-2,4(1*H*,3*H*)-diones.

RESULTS AND DISCUSSION

To synthesize our target compounds **2**, we used the modified Schotten–Baumann conditions. A typical procedure involves adding the sulfonyl chloride slowly into an amine solution in a biphasic system of organic solvents and a basic (Na_2CO_3) aqueous solution,[10] which is shown in Scheme 1. In this route, acetone and ethyl acetate were used as the organic co-solvents and tetrabutylammonium bromide (TBAB) was used as the phase transfer catalyst. The target compound **5** precipitated completely at a pH of 3, while most of byproducts still remained in the solution.



5-FU **2**

2a: R^5 = 2-Cl-3-pyridine
2b: $R^5 = C_6H_5$
2c: $R^5 = 4\text{-}MeC_6H_4$
2d: $R^5 = 4\text{-}BrC_6H_4$
2e: $R^5 = 3\text{-}NO_2C_6H_4$
2f: $R^5 = 2\text{-}NO_2C_6H_4$
2g: $R^5 = 3\text{-}COOHC_6H_4$
2h: $R^5 = 4\text{-}MeCONHC_6H_4$
2i: $R^5 = 4\text{-}CF_3C_6H_4$

Scheme 1

A single crystal of **2a** was grown from acetone, and acetic ether (1:1, v/v) was confirmed by X-ray diffraction analysis as shown in Figure 1. Diffraction data were collected at 25(2)°C using a graphite monochromated Mo Kα ($\lambda = 0.071073$ nm) radiation with a ω-scan technique. Determination of the crystal class, orientation matrix, and cell dimensions was performed according to the established procedures. Lorentz polarization and absorption corrections were applied. Empirical absorption corrections were performed with SADABS program.[11] Most of the non-hydrogen atoms were located using direct methods, and those remaining were derived by subsequent Fourier syntheses. All non-hydrogen atoms were refined anisotropically, and all hydrogen atoms were held stationary and included in the final stage of full-matrix least-squares refinement based on F^2 using

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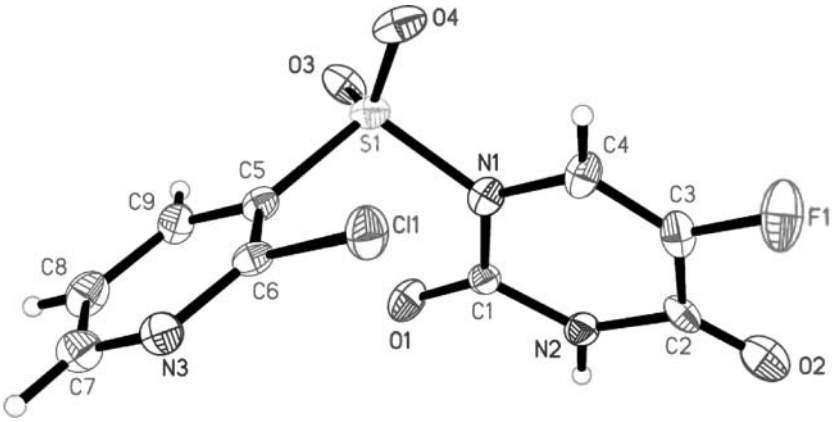

Figure 1 ORTEP drawing of the compound **2a** showing the atom numbering scheme.

SHELXS-97 and SHELXL-97 program packages.[12] Crystal data are summarized in Table I. The crystallographic data was deposited at CCDC.[13]

A displacement ellipsoid plot with the numbering is shown in Figure 1. The selected bond distances and bond angles are listed in Table II. In the crystal structure of **2a**, the bond lengths and angles are within normal ranges. The pyridine ring (C5, C6, C7, C8, C9, N3) is essentially planar with an r.m.s. deviation of 0.0099 Å. The uracil ring (C1, C2, C3,

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Table I Crystal data and summary of data collection and structure refinement of **2a**

Formal	$C_9\ H_5ClFN_3O_4S$
Temperature (K)	298(2)
Wavelength (Å)	0.71073
Crystal system	Orthorhombic
Space group	P b c a
a (Å)	10.1156 (9)
b (Å)	15.0665 (14)
c (Å)	15.2151 (14)
α (°)	90
β (°)	90
γ (°)	90
Volume ($Å^3$)	2318.9 (4)
Z	4
Calculated density (Mg mm^{-3})	1.751
Absorption coefficient (mm^{-1})	0.537
F(000)	1232
Crystal size (mm)	$0.31 \times 0.14 \times 0.11$
θ Range for data collection (°)	2.68–25.02
Limiting indices ≤ 19	$-11 \leq h \leq 12, -14 \leq k \leq 17, -14 \leq l \leq 18$
Reflections collection/unique	11370 / 2040 [R(int) = 0.0343]
Completeness to $\theta = 25.19°$	100.0%
Absorption correction	Semi-empirical from equivalents
Refinement method	Full-matrix least-squares on F^2
Goodness-of fit on F^2	1.062
Final R indices [I $>2\sigma$ (I)]	$R_1 = 0.0749$, $wR_2 = 0.1615$
Largest diffusion peak and hole (e A^{-3})	0.386 and −0.514

Table II Selected bond lengths (Å) and bond angles (°)

Cl(1)−C(6)	1.728(5)	N(1)−C(4)	1.395(6)
S(1)−O(4)	1.412(4)	N(1)−C(1)	1.402(6)
S(1)−O(3)	1.414(4)	N(2)−C(1)	1.375(6)
S(1)−N(1)	1.707(4)	N(2)−C(2)	1.383(6)
S(1)−C(5)	1.768(4)	N(3)−C(6)	1.314(6)
F(1)−C(3)	1.342(5)	N(3)−C(7)	1.342(6)
O(1)−C(1)	1.201(5)	C(2)−C(3)	1.451(7)
O(2)−C(2)	1.210(5)	C(3)−C(4)	1.318(7)
C(4)−N(1)−C(1)	122.4(4)	O(4)−S(1)−N(1)	103.8(2)
C(1)−N(1)−S(1)	118.6(3)	C(1)−N(2)−C(2)	128.6(4)
O(1)−C(1)−N(2)	123.3(4)	O(1)−C(1)−N(1)	123.2(4)
N(2)−C(1)−N(1)	113.5(4)	O(2)−C(2)−N(2)	122.1(5)
O(2)−C(2)−C(3)	125.7(5)	N(2)−C(2)−C(3)	112.2(4)
N(1)−S(1)−C(5)	103.99(19)	C(4)−C(3)−C(2)	123.1(4)

C4, N1, and N2) comparable to that found in a previous similar study is puckered, with an r.m.s. deviation of 0.0276 Å,[14] and makes a dihedral angle of 82.31(0.12)° with the pyridine ring. The electron-withdrawing effect of the S atom and thiophene groups is observed in this structure, which reduces the planarity of the uracil ring.[15]

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Sulfonyl 5-FU derivatives **2** have been investigated for their anticancer activities against human HL-60 and Bel-7402 cell lines. The antitumor activities in vitro for these compounds were evaluated by SRB method for BEL-7402 cells, and MTT method for HL-60 cells. The results of these assays are shown in Tables III and IV (see the Supplemental Materials available online). The results indicated that among the tested compounds, almost all of the newly prepared compounds showed a moderate to good inhibiting effect on the growth of the HL-60 and BEL-7402 cells at different concentrations of 10^{-4} mol/L, 10^{-5} mol/L, 10^{-6} mol/L, 10^{-7} mol/L, and 10^{-8} mol/L, which might indicated that the sulfonyl derivatives biodegradable linkage was better than peptide derivatives and which could be more easily to released 5-FU.[9,16] The inhibition effect of all the compounds against the HL-60 cells was different from that of the BEL-7402 cells, which suggested that these compounds possibly had different inhibition mechanisms against various tumor cells.[17]

By inspection of the chemical structure of **2** (Scheme 1 and Table IV), it was observed that the substitutes of the phenyl affected the anticancer activity against the BEL-7402 cells. Replacement of electron-withdrawing groups [−Br (**2d**), $-CF_3$ (**2j**)] at 4-position on phenyl ring by electron-donating groups [($-CH_3$ (**2c**), $-NHCOCH_3$ (**2h**)] resulted in the obvious decrease of anticancer activity under 10^{-4} mol/L and 10^{-5} mol/L. Similarly, the nitro group at 2-position (**2f**) had more anticancer activity under 10^{-4} mol/L and 10^{-5} mol/L than at 3-position (**2e**). This might explain why sulfonyl derivatives of 5-FU with electron-withdrawing groups at 2-position or 4-position on phenyl ring showed better anticancer activity against the BEL-7402 cells.

EXPERIMENTAL

The melting point was measured with a X-4 melting point apparatus. Mass spectra were obtained on a DECAX-3000LCQ DecaXPPlus. The elemental analyses were performed on a Carlo-Erba 1112 Elemental Analyzer. Infrared (IR) spectrum was recorded on a Perkin Elmer 2000 system in the range of 4000−400 cm^{-1} with KBr disk technique.

Nuclear magnetic resonance (NMR) spectra were obtained with Bruker Avance-300 spectrometer with DMSO-d_6 as solvent. The crystallographic data were collected on a Bruker Smart-Apex CCD diffractometer. All chemicals and solvents were purchased from Aldrich and Fluka. Antimicrobial activities of the title compound were evaluated at The National Center for Drug Screening in Shanghai, China.

General Procedure for the Synthesis of Compound 2

A solution of ethyl acetate (10 mL) and acetone (10 mL) with TBAB (0.32 g, 1 mmol) and sulfonyl chloride (5 mmol) was dropped in a water solution (20 mL) of 5-FU (0.65 g, 5 mmol) and Na_2CO_3 (1.59 g, 15 mmol) at 0°C over a period of 30 min. The resulting reaction mixture was left to stand at room temperature overnight. After filtration and separation, the separated aqueous layer was acidified with hydrochloric acid with pH = 3. The white solid was collected by filtration and washed with water and dried.

1-(2-Chloropyridin-3-ylsulfonyl)-5-fluoropyrimidine-2,4(1*H*,3*H*)-dione (2a). Yield: 62%; mp: 183–184°C; IR ν_{max} (KBr)/cm^{-1} 3445 (N—H), 3027 (=C—H), 1733 (C=O), 1676 (C=O), 1394 (S=O), 1186 (S=O); ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ = 12.44 (s, 1H), 8.80 (dd, J = 4.8 Hz, J = 1.8 Hz, 1H), 8.67 (dd, J = 6.4 Hz, J = 1.8 Hz, 1H), 8.50 (d, J = 6.3 Hz, 1H), 7.80 (dd, J = 6.4 Hz, J = 4.8 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6, ppm): δ = 157.0 (d, $J_{C\text{-}F}$ = 27.5 Hz), 155.3, 146.3 (d, $J_{C\text{-}F}$ = 33.4 Hz), 143.5, 140.3(d, $J_{C\text{-}F}$ = 237.8 Hz), 131.4, 123.9, 123.3, 122.8; MS (ESI, m/z,%) 304.2 ([M-H]$^+$, 100); Anal. Calcd. for $C_9H_5N_3SClFO_4$ (%): C 35.35, H 1.64, N 13.75; Found (%): C 35.41, H 1.58, N 13.81.

5-Fluoro-1-(phenylsulfonyl)pyrimidine-2,4(1*H*,3*H*)-dione (2b). Yield: 70%, mp: 191–193°C; IR ν_{max} (KBr)/cm^{-1} 3429 (N—H), 3102 (=C—H), 1709 (C=O), 1394 (S=O), 1181 (S=O). ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ = 12.24 (s, 1H), 8.42 (d, J = 6.3 Hz, 1H), 8.06 (d, J = 7.8 Hz, 2H), 7.71 (d, J = 8.1 Hz, 2H), 7.58 (d, J = 7.2 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6, ppm): δ = 157.2 (d, $J_{C\text{-}F}$ = 27.1 Hz), 146.1, 140.4 (d, J = 236.7 Hz), 136.0, 135.4, 131.8, 129.4, 129.0 (d, $J_{C\text{-}F}$ = 3.8 Hz), 125.6, 122.7 (d, $J_{C\text{-}F}$ = 36.8 Hz); MS (ESI, m/z,%) 269.3 ([M-H]$^+$, 100); Anal. Calcd. for $C_{10}H_7N_2SFO_4$ (%): C 44.44, H 2.60, N 10.37; Found (%): C 44.67, H 2.58, N 10.25.

5-Fluoro-1-tosylpyrimidine-2,4(1*H*,3*H*)-dione (2c). Yield: 67%, mp: 211–213°C; IR ν_{max} (KBr)/cm^{-1} 3425 (N—H), 3066 (N—H), 1749 (C=O), 1695 (C=O), 1383 (S=O), 1174 (S=O); ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ = 12.20 (s, 1H,), 8.40 (d, J = 6.0 Hz, 1H), 7.94 (d, J = 8.4 Hz, 2H), 7.50 (d, J = 8.1 Hz, 2H), 2.43(s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6, ppm): δ = 157.1 (d, $J_{C\text{-}F}$ = 25.4 Hz), 156.4, 146.2 (d, $J_{C\text{-}F}$ = 27.8 Hz), 140.2(d, $J_{C\text{-}F}$ = 237.2 Hz), 132.9, 129.8, 129.0, 122.7 (d, $J_{C\text{-}F}$ = 36.1 Hz), 21.1; MS (ESI, m/z,%) 283.2 ([M-H]$^+$, 100); Anal. Calcd. for $C_{11}H_9N_2SFO_4$ (%): C 46.48, H 3.17, N 9.86; Found (%): C 46.76, H 3.15, N 9.88.

1-(4-Bromophenylsulfonyl)-5-fluoropyrimidine-2,4(1*H*,3*H*)-dione (2d). Yield: 52%, mp: 201–203°C; IR ν_{max} (KBr)/cm^{-1} 3275 (N—H), 3107 (=C—H), 1731 (C=O), 1664 (C=O), 1568 (C=N), 1381 (S=O), 1185 (S=O); ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ = 12.26 (s, 1H), 8.40 (d, J = 6.6 Hz, 1H), 7.98 (d, J = 8.7 Hz, 2H), 7.93 (d, J = 8.7 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6, ppm): δ = 157.2 (d, $J_{C\text{-}F}$ = 26.9 Hz), 146.6 (d, $J_{C\text{-}F}$ = 66.3 Hz), 140.4 (d, $J_{C\text{-}F}$ = 235.7 Hz), 135.0, 132.5, 131.0, 129.8, 122.6 (d, $J_{C\text{-}F}$ = 38.2 Hz); MS (ESI, m/z,%) 349.1 ([M+2-H]$^+$, 98), 347.1 ([M-H]$^+$, 100); Anal. Calcd. for $C_{10}H_6N_2SBrFO_4$ (%): C 34.43, H 1.72, N 8.03; Found (%): C 34.60, H 1.68, N 7.95.

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5-Fluoro-1-(3-nitrophenylsulfonyl)pyrimidine-2,4(1*H*,3*H*)-dione (2e). Yield: 66%, mp: 194–196°C; IR ν_{max} (KBr)/cm^{-1} 3437 (N—H), 3198 (N=O), 3098 (=C—H), 1736 (C=O), 1697 (C=O), 1536 (C=N), 1391 (S=O), 1189 (S=O); ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ = 12.30 (s, 1H,), 8.75 (t, J = 2.0 Hz, 1H), 8.63–8.66 (m, 1H), 8.46–8.50 (m, 2H), 8.00 (t, J = 8.1 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6, ppm): δ = 157.2 (d, $J_{C\text{-}F}$ = 26.6 Hz), 147.7, 146.2, 140.5 (d, $J_{C\text{-}F}$ = 236.7 Hz), 137.1, 135.3, 131.2, 129.8, 124.3, 122.7 (d, $J_{C\text{-}F}$ = 38.9 Hz); MS (ESI, m/z,%) 314.1 ([M-H]$^+$, 100); Anal. Calcd. for $C_{10}H_6N_3SFO_6$ (%):C 38.08, H 1.90, N 13.33; Found (%):C 38.00, H 2.01, N 13.31.

5-Fluoro-1-(2-nitrophenylsulfonyl)pyrimidine-2,4(1*H*,3*H*)-dione (2f). Yield: 58%, mp: 199–201°C; IR ν_{max} (KBr)/cm^{-1} 3463 (N—H), 3199 (N=O), 3095 (=C—H), 1709 (C=O), 1539 (C=N), 1393 (S=O), 1189 (S=O); ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ = 12.52 (s, 1H,), 8.40 (dd, J = 8.1 Hz, J = 1.5 Hz, 1H), 8.29 (d, J = 6.3 Hz, 1H), 8.19 (dd, J = 7.5 Hz, J = 1.5 Hz, 1H), 8.00–8.13 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6, ppm): δ = 157.0 (d, $J_{C\text{-}F}$ = 26.9 Hz), 147.4, 146.1, 140.2 (d, $J_{C\text{-}F}$ = 236.9 Hz), 137.3, 134.5, 133.2, 128.3, 125.7, 122.7 (d, $J_{C\text{-}F}$ = 39.4 Hz); MS (ESI, m/z,%) 314.1 ([M-H]$^+$, 100); Anal. Calcd. for $C_{10}H_6N_3SFO_6$ (%):C 38.08, H 1.90, N 13.33; Found (%): C 37.99, H 1.97, N 13.52.

3-(5-Fluoro-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-ylsulfonyl)benzoic acid (2g). Yield: 50%, mp: 214–216°C. IR ν_{max} (KBr)/cm^{-1} 3433 (N—H), 3061 (=C—H, —O—H), 1696 (C=O), 1391 (S=O), 1184 (S=O). ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ = 13.69 (s, 1H), 12.25, 8.52 (t, J = 1.8 Hz, 1H), 8.46 (d, J = 6.0 Hz, 1H), 8.28–8.35 (m, 2H), 7.84 (t, J = 7.8 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6, ppm): δ = 165.5, 157.0, 146.2, 140.5 (d, $J_{C\text{-}F}$ = 239.0 Hz), 136.4, 135.7, 133.1, 131.9, 130.1, 129.8, 122.6 (d, $J_{C\text{-}F}$ = 37.4 Hz). MS (ESI, m/z,%) 313.3 ([M-H]$^+$, 100); Anal. Calcd. for $C_{11}H_7N_2SFO_6$ (%): C 42.34, H 2.23, N 8.92; Found (%): C 42.33, H 2.27, N 8.90.

N-(4-(5-Fluoro-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-ylsulfonyl)phenyl) acetamide (2h). Yield: 73%, mp: 199–200°C; IR ν_{max} (KBr)/cm^{-1} 3338 (N—H), 3049 (=C—H), 1703 (C=O), 1385 (S=O), 1179 (S=O); ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ = 10.57 (s, 1H), 8.18 (d, J = 6.3 Hz, 1H), 7.94 (d, J = 9.0 Hz, 2H), 7.82 (d, J = 8.7 Hz, 2H), 2.10 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6, ppm): δ = 169.4, 159.8, 147.9, 144.9, 141.0 (d, $J_{C\text{-}F}$ = 236.9 Hz), 130.4, 129.5, 121.6 (d, $J_{C\text{-}F}$ = 38.7 Hz), 118.3, 24.2; MS (ESI, m/z,%) 326.1 ([M-1]$^+$, 100); Anal. Calcd. for $C_{12}H_{10}N_3SFO_5$ (%): C 44.38, H 3.06, N 12.84; Found (%): C 44.35, H 3.14, N 13.00.

5-Fluoro-1-(4-(trifluoromethyl)phenylsulfonyl) pyrimidine-2,4(1*H*, 3*H*)-dione (2i). Yield: 76%, mp: 205–206°C; IR ν_{max} (KBr)/cm^{-1} 3488 (N—H), 1663 (C=O), 1388 (S=O), 1176 (S=O); ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ = 8.15 (d, J = 8.4 Hz, 2H), 7.99 (d, J = 8.4 Hz, 2H), 7.87 (d, J = 6.6 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6, ppm): δ = 165.3 (d, $J_{C\text{-}F}$ = 16.8 Hz), 151.0, 142.5 (d, $J_{C\text{-}F}$ = 245.0 Hz), 142.4, 133.2 (q, $J_{C\text{-}F}$ = 31.7 Hz), 129.3, 126.3 (q, $J_{C\text{-}F}$ = 3.7 Hz), 125.2, 121.6, 119.2 (d, $J_{C\text{-}F}$ = 40.2 Hz); MS (ESI, m/z,%) 337.1 ([M-H]$^+$, 100); Anal. Calcd. for $C_{11}H_6N_2SF_4O_4$ (%): C 39.05, H 1.78, N 8.28; Found (%): C 39.11, H 1.73, N 8.28.

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