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A practical synthesis of *N*-allyl/propargyl-substituted 5-fluorouracils

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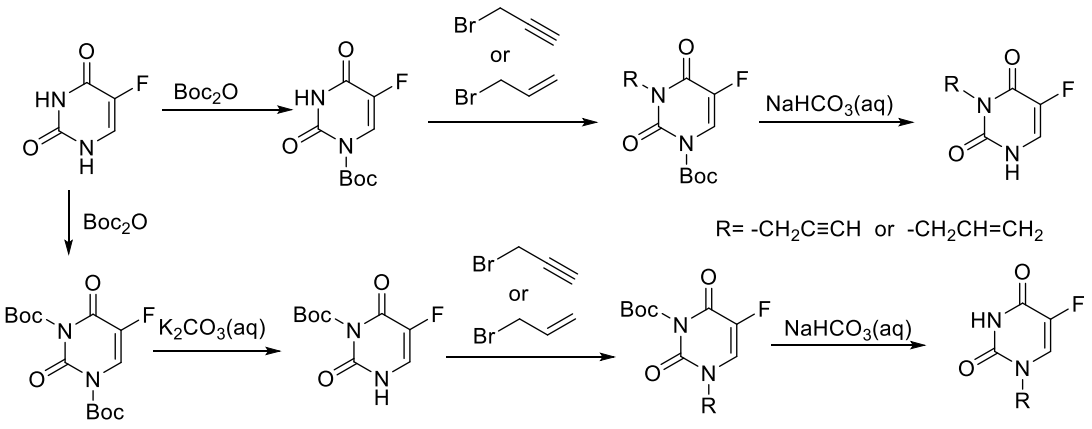
Abstract

Monosubstituted *N*-allyl/propargyl-5-fluorouracils are versatile intermediates for the structural modification of 5-fluorouracils derivatives. However, the regioselective synthesis of these monosubstituted 5-fluorouracils is a challenge. Thus, in the current research work, a practical method for synthesizing N_1/N_3-allyl/propargyl-5-fluorouracils was developed with di-tertbutyl dicarbonate acting as a protective reagent. The process is easy to operate, gives a good regioselectivity, satisfying yields and a simple post-treatment.



Keywords: 5-Fluorouracil, allyl, propargyl, regioselective synthesis

Introduction

5-Fluorouracil (5-FU, **1**) is an antimetabolite acting as a bioisostere of the natural uracil in living body, and has been widely used in the treatment of colorectal cancer and several solid tumors.[1] 5-FU derivatives incorporating pharmacologically active natural or synthetic molecules, such as 5-FU linked with podophyllotoxin, colchicine, parthenolide, coumarins, thymoquinone, emodin, camptothecin, cisplatin, oxaliplatin, tamibarotene and chalcone, have attracted much attention of many researchers in the field of medicinal chemistry.[2] Recently, many structural modifications have been focused on merging a particular pharmacologically active molecule at the N_1 or N_3 position of 5-FU using a triazole linkage in order to achieve a higher bioactivity. For example, 5-FU derivatives, incorporating the bioactive molecules parthenolide **3a**, thymoquinone **3b**, or glucose derivative **3c** incorporating the click triazole linker, have shown potential anticancer activities.[3–5] Moreover, 5-FU with triazole-linked polyheterocyclic compound **3d** has been reported to exhibit a superior antibacterial activity (Figure 1).[6]

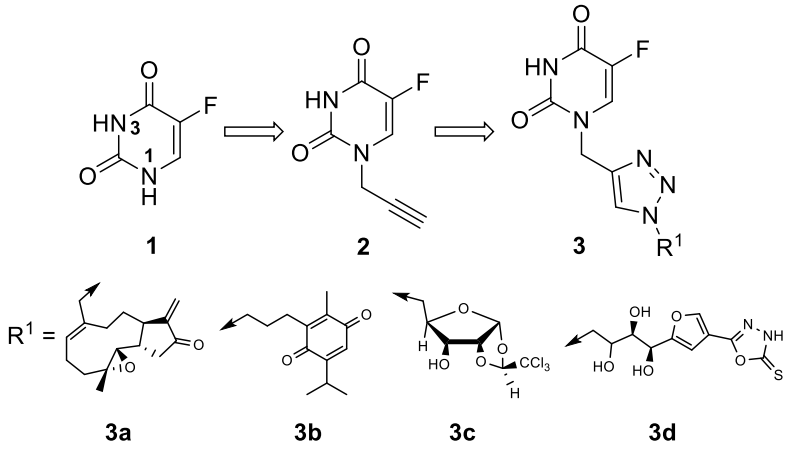
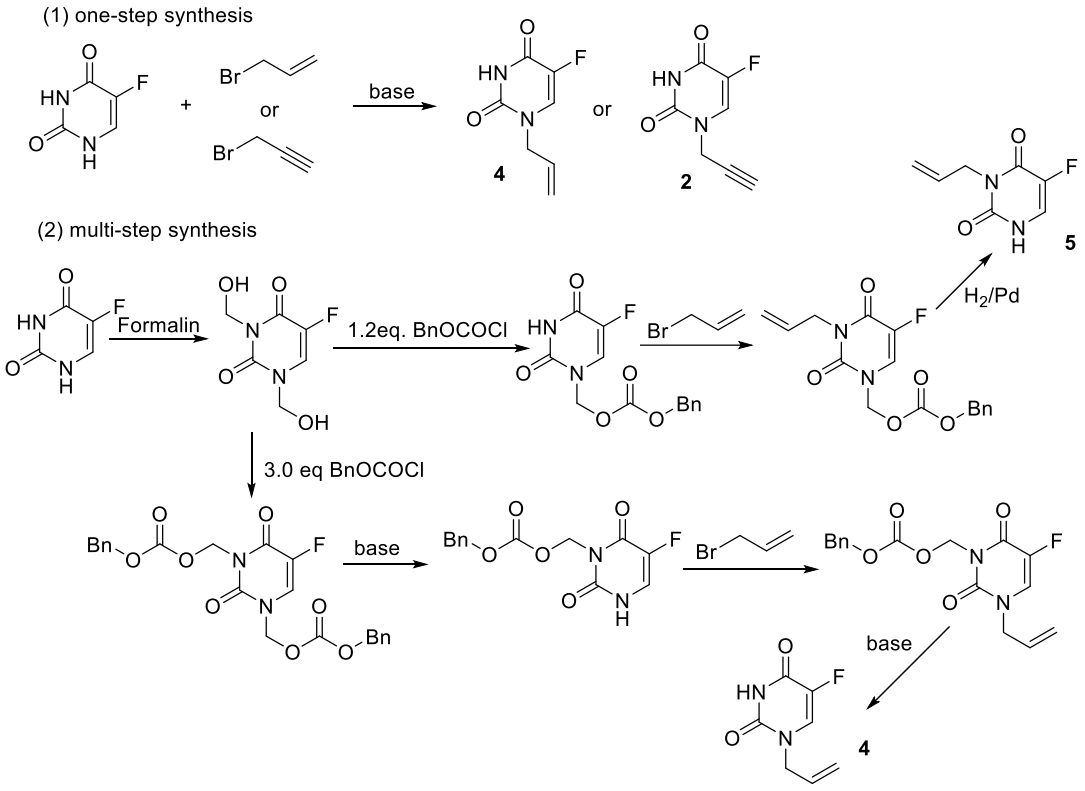


Figure 1. Chemical structures of 5-FU, 1-propargyl-3*H*-5-FU, and its triazole derivatives.

Since triazole moieties have been developed as versatile pharmacophoric linkers, connecting two biological units into one molecule called hybrids,[7-8] alkyne or alkene-decorated 5-FUs, especially 1-propargyl-5-FU **2**, have been used as a key intermediate to furnish various isoxazole or triazole-functionalized 5-FU derivatives **3** via 1,3-dipolar cycloaddition reactions with nitrile oxides or azide dipoles.

Given the proved applications of allyl or propargyl-containing 5-FUs in the development of the bioactive 5-FU derivatives, extensive research has been focused on the synthesis of 1-propargyl-5-FU **2** and 1-allyl-5-FU **4**. A common method for the preparation of N_1-substituted 5-FUs (**2** and **4)** was through nucleophilic substitution of 5-FU with bromopropyne or bromopropylene in the presence of a base such as K_2CO_3, NaH or DBU (Scheme 1, eq 1).[3, 9-12] Although this method provides a simple and direct route to propargyl or allyl-monosubstituted 5-FUs, the poor regioselectivity and low reaction yields are still challenging problems. In a modified method, the combination of $Pd(PPh_3)_4$/1,1'-Bis(diphenylphosphino)ferrocene(DPPF) and allyl acetate was used instead of bromopropylene, giving N_1-allyl-5-FU **4** in a moderate yield.[13] Alternatively, a multiple-step pathway could be used to synthesize the monosubstituted 5-FUs, where 5-FU was first transformed into the key intermediates featuring N_1-$CH_2OCOOBn$ or N_3-$CH_2OCOOBn$ by multiple steps, followed by allylation and deprotection to give allyl-substituted 5-FUs **4** and **5** (Scheme 1, eq 2).[14] Although multiple methods have been

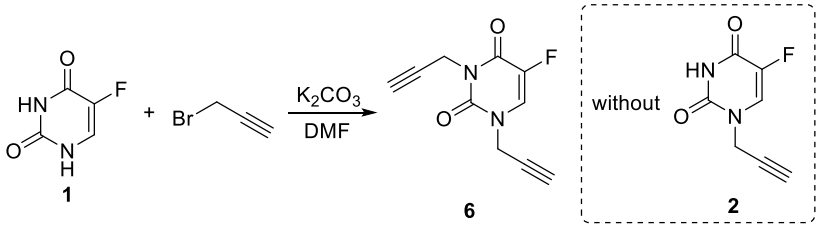
utilized for the synthesis of propargyl/allyl-substituted 5-FUs, there are some disadvantages such as low reaction yields,[10-12] using an expensive catalyst[13] and complex synthetic procedures.[14] Furthermore, few of these methods were involved in the preparation of N_3-substituted 5-FUs (**7** and **5**). Therefore, it is still of interest to develop a general and efficient method for the synthesis of allyl/propargyl-monosubstituted 5-FUs.



Scheme 1. 1) One-step synthesis of 5-FUs **2** and **4**, and 2) multi-step synthesis of 5-FUs **4** and **5**.

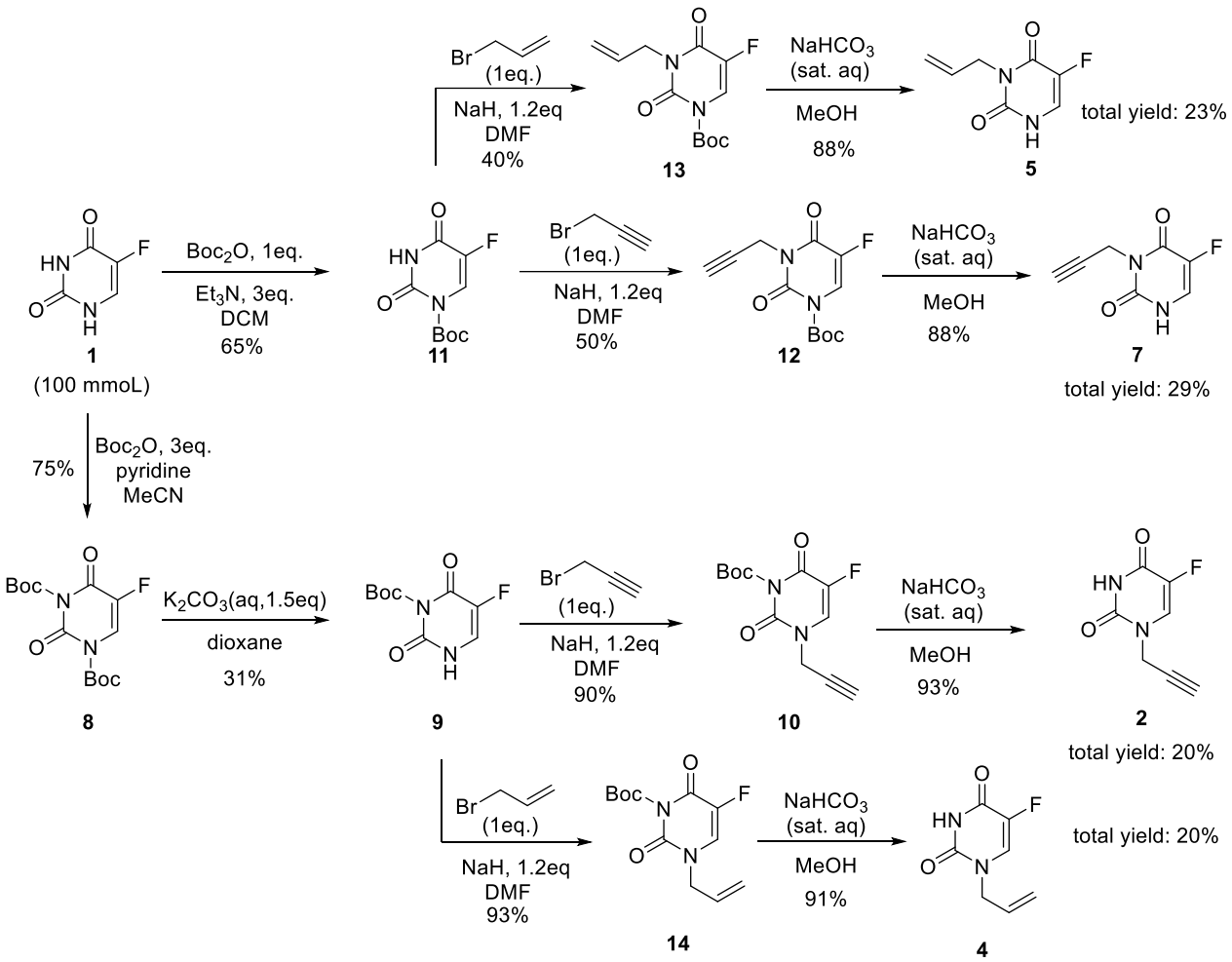
Results and Discussion

The methods reported to synthesize 1-propargyl-5-FU **2** from the reaction of 5-FU and bromopropyne using K_2CO_3 as a base in DMF has problems of a low regioselectivity and a poor yield.[3,9] To improve the regioselectivity and yield, the reaction conditions of 5-FU and bromopropyne with K_2CO_3 (1 equiv to 5-FU) in DMF were optimized (Table S1, see supporting information); however, a single product N_1, N_3-dipropargyl-5-FU **6** was obtained instead of N_1-propargyl-5-FU **2**. Interestingly, no trace of compound **2** was detected by ^{1}H-NMR analysis of the isolated product (Scheme 2).



Scheme 2. The reaction of 5-FU and bromopropyne with K_2CO_3 as a base.

Usually, the proton N_1-H of 5-FU is much more reactive than that of the N_3 position. A plausible reaction mechanism was assumed, where the proton at the N_1 position of 5-FU was firstly replaced by propargyl, and the resulting intermediate significantly improved the reaction activity of the proton at the N_3 position. Therefore, there was no single substitution product **2**, but always the double substitution product **6**. While this reaction was carried out with 5-FU and bromopropylene, it was observed that N_1, N_3-diallyl-5-FU and N_1-allyl-5-FU were both generated. In this reaction mechanism, N_1-allyl-5-FU is formed in the first step, and then a double substituted product is generated.



Scheme 3. Synthetic route of *N*-monosubstituted allyl/propargyl-5-FU

Then, the synthesis of the monosubstituted 5-FUs by a muti-step method was evaluated with a strategy of protection/alkylation/deprotection. Since the *N*-protecting groups were commonly used to prepare pyrimidine derivatives, such as benzoyl, trichloroethoxyformyl, benzyloxyformyl, benzyl and diphenylmethyl moieties, different N-protecting methods were tested and ultimately di-tertbutyl dicarbonate (Boc_2O) was selected as the N-protecting reagent of the starting material 5-FU **1**. After several optimizations of the reaction conditions, N_1-Boc-substituted intermediate **11** was directly obtained in 65% yield, by the regioselective reaction of 5-FU **1** and 1.0 equiv of Boc_2O, with Et_3N as a base. In contrast, N_3-monosubstituted 5-FU **9** needed

a reaction sequence of N_1,N_3-diBoc protection and regioselective deprotection of N_1-Boc group. In detail, N_1,N_3-diBoc-5-FU **8** was provided by reacting 5-FU **1** and 3.0 equiv of Boc_2O with pyridine as a base, followed by the regioselective deprotection of N_1-Boc group to give the desired N_3-progargyl-5-FU **9**. Then the subsequent propargylation of intermediates **11** and **9** were performed with bromopropyne, and finally, the desired N_3-propargyl-5-FU and N_1-propargyl-5-FU (**7** and **2**) were prepared after deprotection of the Boc group, with total yields of 29% and 20%, respectively (Scheme 3). Using the same procedure, when bromopropylene was used instead of bromopropyne, the corresponding allyl-substituted-5-FUs, **4** and **5**, were obtained with total yields of 20% and 23%, respectively (Scheme 3).

Conclusions

In summary, the developed method uses 5-FU as starting material and Boc anhydride as a protective reagent to regioselectively produce N_1/N_3-Boc-5-FU, and provides a practical synthesis of allyl/propargyl-monosubstituted-5-FUs. This method is easy to operate, leads to a good regioselectivity, satisfying yield and simple post-treatment. The produced allyl/propargyl-functionalized 5-FUs can have wide applications in the subsequent preparation of diverse 5-FU derivatives with specific pharmacological activities.

Experimental Section

General. Melting points were recorded using the XRC-1 apparatus and are uncorrected. IR spectra were obtained on a Thermo Nicolet Avatar 370 FT-IR spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker AVANCE III spectrometer at 500 MHz and 600 MHz using TMS as the internal standard. HRMS spectra were recorded on a Waters GCT Premier instrument with EI mode. All the chemicals and solvents were analytical reagents and commercially available and used as received.

Synthesis of 1-Boc-5-FU (11).[15] A mixture of 5-FU (13.0 g, 100 mmol), Boc anhydride (22.0 g, 100 mmol), and triethylamine (43.4 mL) in DCM (200 mL) was stirred at 20 °C until 5-FU disappeared by TLC monitoring. The solvent was concentrated under vacuum, and the crude product was purified by column chromatography to obtain **11**, white solid, 15.0 g, yield 65%, mp 148-150 °C [lit[15] 149-150 °C].^{1}H NMR (600 MHz, DMSO-d_6) δ 11.95(br, 1H, NH), 8.19(d, *J* 7.2 Hz, 1H, ArH), 1.52(s, 9H, $C(CH_3)_3$); ^{13}C NMR (151 MHz, DMSO-d_6) δ 157.5(d, *J* 27.0 Hz), 147.9, 146.6, 140.3(d, *J* 234.3 Hz), 125.0(d, *J* 37.1 Hz), 86.5, 27.8.

Synthesis of 1-Boc-3-propargyl-5-FU (12).[10] 1-Boc-5-FU (4.6 g, 20 mmol) was mixed with 60% NaH (0.96 g, 24 mmol) in DMF (50 mL) and stirred for 45 min at 0–5 °C. Bromopropyne (2.4 g, 20 mmol) was added dropwise and then stirred at rt until no reactant was detected by TLC. The mixture was poured into ice-water, extracted with ethyl acetate, and washed with water. The organic layer was dried with anhydrous magnesium sulfate, concentrated under vacuum, and purified by column chromatography to obtain **12**, white solid, 2.7 g, yield 50%, mp 125-127 °C; IR (KBr) cm^{-1}: 215, 2984, 1712, 1683, 1356, 1211, 863, 670; ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.34(d, *J* 6.6 Hz, 1H, ArH), 4.53(s, 2H, N-CH_2-C), 3.22(s, 1H, C≡CH), 1.55(s, 9H, $C(CH_3)_3$); ^{13}C NMR (151 MHz, DMSO-d_6) δ 156.2(d, *J* 27.2 Hz), 147.8, 146.2, 139.7(d, *J* 232.7 Hz), 124.5(d, *J* 37.0 Hz), 87.2, 78.6, 74.2, 31.2, 27.7; HRMS calcd for $C_{12}H_{13}FN_2O_4$: 268.0859, found 268.0857.

Synthesis of 3-propargyl-5-FU (7).[16]A mixture of 1-Boc-3-propargyl-5-FU (1.5 g, 5.6 mmol), saturated $NaHCO_3$ (10 mL) in methanol (20 mL) was stirred at 45 °C for 45 min. The solvent was concentrated under vacuum to

remove methanol and extracted with DCM (25 mL × 3). The organic layer was dried with anhydrous magnesium sulfate, concentrated under vacuum, and purified by column chromatography to obtain **7**, as white solid, 0.83 g, yield 88%; mp 172–173 °C [lit[16] 187-188 °C]; IR (KBr) cm^{-1}: 3320, 3226, 2346, 1718, 1448, 1209, 933, 772; ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.29(br, 1H, NH), 7.92(t, *J* 5.8 Hz, 1H, ArH), 4.50(d, *J* 2.2 Hz, 2H, N-CH_2-C), 3.16(t, *J* 2.4 Hz, 1H, C≡CH). ^{13}C NMR (151 MHz, DMSO-d_6) δ 157.0(d, *J* 26.0 Hz), 149.6, 139.7(d, *J* 226.7 Hz), 126.0(d, *J* 31.6 Hz), 79.1, 73.6, 30.2; HRMS calcd for $C_7H_5FN_2O_2$: 168.0335, found 168.0331.

Synthesis of 1-Boc-3-allyl-5-FU (13). Similar procedure with the synthesis of **12** using bromopropylene (2.4 g, 20 mmol) instead of bromopropyne to obtain 1-Boc-3-allyl-5-FU **13**, white solid, 2.2 g, yield 40%, mp 70-72 °C, IR (KBr) cm^{-1}: 3230, 2976, 1715, 1658, 1467, 1223, 805, 770; ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.31(d, *J* = 6.9 Hz, 1H, ArH), 5.83-5.78(m, 1H, C=CH), 5.18-5.12(m, 2H, CH_2=C), 4.39(d, *J* 5.2 Hz, 2H, N-CH_2-C), 1.54(s, 9H, C(CH_3)$_3$); ^{13}C NMR (151 MHz, DMSO-d_6) δ 156.6(d, *J* 26.7 Hz), 148.0, 146.5, 139.8(d, *J* 232.2 Hz), 132.1, 124.0(d, *J* 37.1 Hz), 117.6, 86.9, 43.7, 27.7; HRMS calcd for $C_{12}H_{15}FN_2O_4$: 270.1016, found 270.1018.

Synthesis of 3-allyl-1-5-FU (5).[17] Similar procedure with the synthesis of **7** using 1-Boc-3-allyl-5-FU **13** (2.2 g, 8.0 mmol) instead of 1-Boc-3-propargyl-5-FU **12** to obtain **5**, white solid, 1.2 g, yield 88%; mp 67–68 °C [lit[17] 78.5-80 °C]; IR (KBr) cm^{-1}: 3423, 3216, 1700, 1660, 1580, 1432, 1168, 743; ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.14(br, 1H, NH), 7.88(d, *J* 5.6 Hz, 1H, ArH), 5.85-5.79(m, 1H, C=CH), 5.12-5.07(m, 2H, CH_2=C), 4.37(d, *J* 5.1 Hz, 2H, N-CH_2-C); ^{13}C NMR (151 MHz, DMSO-d_6) δ 157.5(d, *J* 25.5 Hz), 150.0, 139.8(d, *J* 226.1 Hz), 132.5, 125.6(d, *J* 31.6 Hz), 117.1, 42.7; HRMS calcd for $C_7H_7FN_2O_2$: 170.0492, found 170.0499.

Synthesis of 1,3-diBoc-5-FU (8).[18] A mixture of 5-FU (13.0 g, 100 mmol), acetonitrile (100 mL), Boc anhydride (66.0 g, 300 mmol), and pyridine (8 mL) was stirred at 55 °C until no 5-FU was detected by TLC. After concentration under vacuum, the residue was poured into water (50 mL) and extracted with DCM (20 mL × 3), dried over anhydrous magnesium sulfate. The filtrate was concentrated and purified by column chromatography to obtain **8**, white solid, 25.0 g, yield 75%, mp 111-113 °C; IR (KBr) cm^{-1}: 3181, 3020, 2957, 1758, 1723, 1610, 1376, 642; ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.36(d, *J* 7.3 Hz, 1H, ArH), 1.54(s, 9H, C(CH_3)$_3$), 1.53(s, 9H, C(CH_3)$_3$); ^{13}C NMR (151 MHz, DMSO-d_6) δ 154.9(d, *J* 29.0 Hz), 147.2, 146.8, 144.6, 139.5(d, *J* 234.8 Hz), 125.9(d, *J* 37.3 Hz), 87.7, 87.5, 27.7, 27.5; HRMS calcd for $C_{14}H_{19}FN_2O_6$: 330.1227, found 330.1235.

Synthesis of 3-Boc-5-FU (9).[18] 1,3-diBoc-5-FU **8** (10.0 g, 30 mmol) was dissolved in dioxane (50 mL), and the mixture was added with 10 mL aqueous K_2CO_3 (6.2 g, 45 mmol) dropwise. After stirring for 8 h at rt, the mixture was concentrated under vacuum to remove dioxane. Then, water (50 mL) was added and exacted with DCM (20 mL × 3). The organic layer was dried, concentrated and purified by column chromatography to obtain **9**, white solid, 2.4 g, yield 31%, mp 128-130 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.52(br, 1H, NH), 7.98(d, *J* 6.1 Hz, 1H, ArH), 1.52(s, 9H, C(CH_3)$_3$); ^{13}C NMR (151 MHz, DMSO-d_6) δ 155.6(d, *J* 27.8 Hz), 147.9, 147.5, 139.5(d, *J* 228.7 Hz), 127.7(d, *J* 31.9 Hz), 87.0, 27.5; IR (KBr) cm^{-1}: 3197, 3099, 2832, 1732, 1621, 1153, 842, 612; HRMS calcd for $C_9H_{11}FN_2O_4$: 230.0703, found 230.0694.

Synthesis of 3-Boc-1-propargyl-5-FU (10). A similar procedure as the synthesis of **12** using 3-Boc-5-FU **9** (0.5 g, 2.0 mmol) to obtain **10**, white solid, 0.48 g, yield 90%, mp 113-114 °C; IR (KBr) cm^{-1}: 3287, 2964, 1710, 1685, 1452, 1356, 856, 786; ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.34(d, *J* 6.6 Hz, 1H, ArH), 4.53(d, *J* 2.2 Hz, 2H, N-CH_2-C), 3.54(t, *J* 2.2 Hz, 1H, C≡CH), 1.53(s, 9H, C(CH_3)$_3$); 13C NMR (151 MHz, DMSO-d_6) δ 155.0(d, *J* 27.9 Hz), 147.2, 147.1, 139.5(d, *J* 231.7 Hz), 130.4(d, *J* 34.3 Hz), 87.7, 77.9, 77.3, 38.4, 27.5; HRMS calcd for $C_{12}H_{13}FN_2O_4$: 268.0859, found 268.0855.

Synthesis of 1-propargyl-5-FU (2).[6] A similar procedure as the synthesis of **7** using 3-Boc-1-propargyl-5-FU **10** (0.48 g, 1.8 mmol) to obtain **2**, colorless crystal, 0.28 g, yield 93%; mp 168–170 °C [lit[6] 169-171 °C]; IR (KBr) cm^{-1}: 3359, 3012, 1670, 1605, 1280, 1136, 923, 806; ^{1}H-NMR (600MHz, DMSO-d_6) δ: 11.94(br, 1H, NH), 8.13(d, *J* 6.6 Hz, 1H, ArH), 4.47(d, *J* 2.2 Hz, 2H, N-CH_2-C), 3.44(t, *J* 2.2 Hz, 1H, C≡CH); ^{13}C NMR (151 MHz, DMSO-d_6) δ

157.3(d, *J* 25.9 Hz), 149.0, 139.8(d, *J* 230.6 Hz), 128.8(d, *J* 34.0 Hz), 78.0, 76.1, 36.9; HRMS Calcd for $C_7H_5FN_2O_2$: 168.0335, found 168.0333.

Synthesis of 3-Boc-1-allyl-5-FU (14). Similar procedure with the synthesis of **10** using 3-Boc-5-FU **9** (0.5 g, 2.0 mmol) and bromopropylene (2.4 g, 20 mmol), to obtain 3-Boc-1-allyl-5-FU **14**, white solid, 0.5 g, yield 93%, mp 123-124 °C; IR (KBr) cm^{-1}: 3053, 2932, 2154, 1689, 1396, 1257, 862, 724; ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.22(d, *J* 6.8 Hz, 1H, ArH), 5.94-5.87(m, 1H, CH=C), 5.26-5.24(m, 2H, C=CH_2), 4.30(d, *J* 5.5 Hz, 2H, N-CH_2-C), 1.52(s, 9H, $C(CH_3)_3$); ^{13}C NMR (151 MHz, DMSO-d_6) δ 155.1(d, *J* 27.8 Hz), 147.5, 147.3, 139.4(d, *J* 230.7 Hz), 132.4, 131.1(d, *J* 33.6 Hz), 119.1, 87.4, 50.7, 27.5; HRMS calcd for $C_{12}H_{15}FN_2O_4$: 270.1016, found 270.1019.

Synthesis of 1-allyl-5-FU (4).[13] Similar procedure with the synthesis of **2** using 3-Boc-1-allyl-5-FU **14** (0.5 g, 2.0 mmol) instead of 1-Boc-3-propargyl-5-FU **10** to obtain **4**, colorless needle crystal, 0.31 g, yield 91%; mp 125–126 °C [lit[13] 101 °C]; IR (KBr) cm^{-1}: 3382, 3200, 1705, 1663, 1573, 1328, 1149, 756; ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.82(br, 1H, NH), 8.02(d, *J* 6.7 Hz, 1H, ArH), 5.91-5.85(m, 1H, C=CH), 5.21-5.16(m, 2H, CH_2=C), 4.25(d, *J* 5.1 Hz, 2H, N-CH_2-C); ^{13}C NMR (151 MHz, DMSO-d_6) δ 157.9(d, *J* 25.8 Hz), 149.8, 140.2(d, *J* 229.4 Hz), 133.1, 130.2(d, *J* 33.2 Hz), 118.2, 49.8; HRMS calcd for $C_7H_7FN_2O_2$: 170.0492, found 170.0500.

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Supplementary Material

The online version of this article contains supplementary materials.

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