Supplementary Material

"Design, Synthesis and Evaluation of Tetrahydropyrrolo[1,2-*c*]pyrimidines as Capsid Assembly Inhibitors for HBV treatment"

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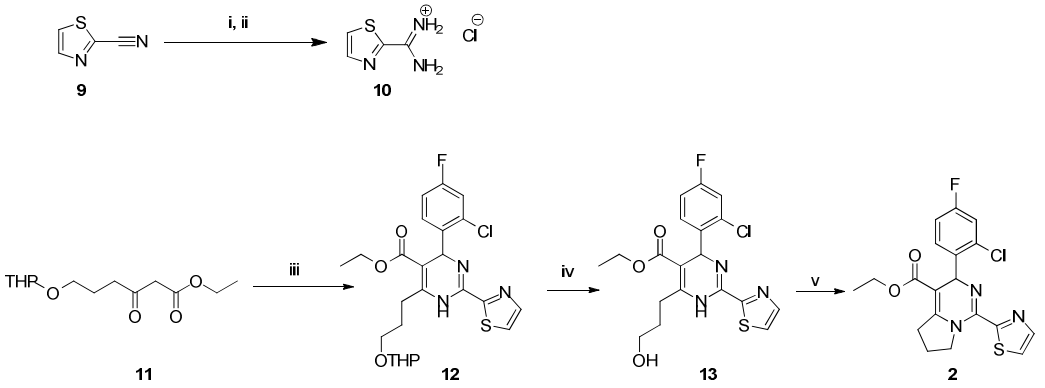
1. Chemical synthesis:

Unless otherwise stated, all reagents and anhydrous solvents were of the highest grade available and were purchased from commercial sources and used without further purification. All NMR spectra were recorded on Bruker Advance III 400 MHz FT-NMR spectrometer with a 5 mm BBO (F) probe or a Varian 400 MHz spectrometer with a $^{1}H/^{19}F/^{31}P/^{13}C$ 5 mm PFG 4Nuc probe. ^{1}H chemical shifts (δ) were reported in parts per million with MeOH-d_4, DMSO-d_6, or $CDCl_3$ as the

reference standard. Signal multiplicities are represented by s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quadruplet), br (broad), bs (broad singlet), and m (multiplet). Analytical LC-MS analyses were conducted using Shimadzu LC-20AB pumps and an SPD-M20 PDA detector set at 220 and 254 nm, and the MS detection was performed with a MS-2010EV Micromass Platform LC spectrometer in electrospray ionization mode. Analytical SFC-MS analyses were conducted using Mettler pumps and an Agilent G1315B detector set at 190-370 nm, and the MS detection was performed with an Agilent 6110 detector following the detailed column and eluting conditions specified below. Preparative reversed-phase (RP) HPLC was performed using a Gilson 322 pump, a Gilson 156 UV detector set at 220 and 254 nm, and a Gilson GX-281 liquid handler, following the detailed column and eluting conditions specified below. Normal-phase silica gel preparative purification was performed using an automated Combi-flash companion from ISCO with pre-packed silica gel cartridges supplied by Santai Technologies Inc. and Agela Inc. SFC separation was performed using a Berger SFC Analytic system following the detailed column and eluting conditions specified below. Qualitative (±) optical rotation data were collected using a PDR-chiral advanced laser in-line polarimeter (model ALP2002). Analytical thin-layer chromatography (TLC) was performed using SGF254 TLC plates (0.2-0.25 mm) supplied by Combinol Reagent (Yantai) Co., Ltd. Preparative TLC was performed using SGF254 TLC plates (0.4-0.5 mm) supplied by Yucheng Chemical (Shanghai) Co., Ltd. All of the compounds were established by a variety of LC/MS, HRMS, and NMR analytical techniques, and purities were >95% for all final products.

Example 1: Exemplification of General Synthesis compound **2**.

Scheme 1: The synthetic route for compound **2**



Step 1. amino(thiazol-2-yl)methaniminium chloride (10): To a solution of thiazole-2-carbonitrile (220 g, 2 mol, 1eq) in 1.2 L MeOH was added NaOMe (5.4 g, 0.1 mol, 0.05 eq) at 10 ℃, stirred for 0.5 h, TLC showed the thiazole-2-carbonitrile was disappeared, NH_4Cl (130 g, 2.4.0 mol,1.2 eq) was added. the reaction temperature was raised to 65℃ and stirred for 16 hrs. TLC monitored and LCMS showed the reaction was completed, filtered to afford 21 g NH_4Cl solid, the filtrate was evaporated to give the crude product. 320 g of pure compound **10** was obtained by further slurring with 2 L EtOAc for 2 hrs. ^{1}H NMR (400 MHz, DMSO-*d6*) δ: 9.80 (br. s., 4H), 8.37 (d, *J*=2.8 Hz, 1H), 8.25 (d, *J*=2.8 Hz, 1H); HRMS (EI): m/z calcd for $C_4H_6N_3S$ $[M+H]^+$: 129.0277, found: 129.0356.

Step 2. ethyl 4-(2-chloro-4-fluorophenyl)-6-(3-((tetrahydro-2H-pyran-2-yl)oxy) propyl)-2-(thiazol-2-yl)-1,4-dihydropyrimidine-5-carboxylate (12): To a solution of compound **11** (700 mg, 2.7mmol) in EtOH (20 mL) was added 2-chloro-4-fluorobenzaldehyde (545mg,2.7mmol), thiazole-2-carboximidamide hydrochloride (880 mg, 5.4 mmol) and AcONa (664 mg, 8.1 mmol). The resulting mixture was stirred at 100℃ overnight. The mixture was evaporated and extracted with ethyl acetate three times. The residue was purified by chromatography to give the ethyl 4-(2-chloro-4-fluorophenyl)-6-(3-((tetrahydro-2H-pyran-2-yl)oxy)propyl)-2-(thiazol-2-yl)-1,4-dihydropyrimidine-5-carboxylate **(12)** (500 mg, 61%); HRMS (EI): m/z calcd for $C_{24}H_{27}ClFN_3O_4S$ $[M+H]^+$: 508.1395, found: 508.1395.

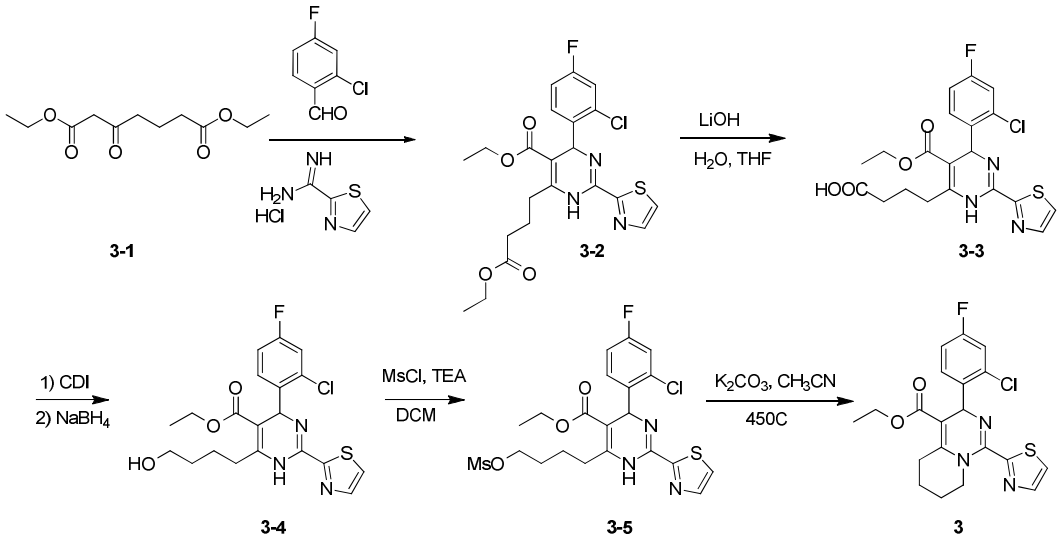
Step 3. ethyl 4-(2-chloro-4-fluorophenyl)-6-(3-hydroxypropyl)-2-(thiazol-2-yl)-

1,4-dihydropyrimidine-5-carboxylate (13): To a solution of ethyl 4-(2-chloro-4-fluorophenyl)-6-(3-((tetrahydro-2H-pyran-2-yl)oxy)propyl)-2-(thiazol-2-yl)-1,4-dihydropyrimidine-5-carboxylate (103mg, 0.2mmol) in EtOH (10mL) was added p-TsOH (114mg, 0.6mmol). The resulting mixture was stirred for 30min. The mixture was added $NaHCO_3$ to adjust pH=8 and extracted with ethyl acetate three times. The residue was purified by chromatography to give ethyl 4-(2-chloro-4-fluorophenyl)-6-(3-hydroxypropyl)-2-(thiazol-2-yl)-1,4-dihydropyrimidine-5-carboxylate **(13)** (85 mg, 85%). HRMS (EI): m/z calcd for $C_{19}H_{19}ClFN_3O_3S$ $[M+H]^+$: 424.0820, found: 424.0820.

Step 4. ethyl 3-(2-chloro-4-fluorophenyl)-1-(thiazol-2-yl)-3,5,6,7-tetrahydropyrrolo[1,2-*c*]pyrimidine-4-carboxylate (2): To a solution of ethyl 4-(2-chloro-4-fluorophenyl)-6-(3-hydroxypropyl)-2-(thiazol-2-yl)-1,4-dihydropyrimidine-5-carboxylate (70 mg, 0.15mmol) in DCM (5 mL) was added MsCl (26 mg, 0.23 mmol) and TEA (30 mg, 0.3 mmol). The resulting solution was stirred for 2 hs at room temperature. The mixture was purified by pre-TLC to give the **compound 2** (30 mg, 45%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.80 (d, *J*=2.8 Hz, 1H), 7.36 (d, *J*=3.2 Hz, 1H), 7.27-7.32 (m, 2H), 6.96 (d, *J*=2.4 Hz, 1H), 6.17 (s, 1H), 4.36 (m, 1H), 4.23-4.32 (m, 1H), 4.06 (m, 2H), 3.42 (m, 1H), 3.08 (m, 1H), 2.00-2.21 (m, 2H), 1.15 (t, *J*=6.8 Hz, 3H); HRMS (EI): m/z calcd for $C_{19}H_{17}ClFN_3O_2S$ [M+H]+: 406.0714, found: 406.0714.

Example 2: Exemplification of General Synthesis compound **3**.

Scheme 2: The synthetic route for compound **3**



Step 1. ethyl 4-(2-chloro-4-fluorophenyl)-6-(4-ethoxy-4-oxobutyl)-2-(thiazol-2-yl)-1,4-dihydropyrimidine-5-carboxylate (3-2): A mixture of 2-chloro-4-fluorobenz aldehyde (1.08 g, 6.8 mmol), thiazole-2-carboximidamide hydrochloride salt (1.9 g, 5.8 mmol, 50% purity), diethyl 3-oxoheptanedioate (1.34 g, 5.8 mmol) and NaOAc (1.1 g, 17.4 mmol) in ethanol (50 mL) was stirred at 90 °C for 15 h. The mixture was concentrated to give a crude product. The crude product was dissolved in dichloromethane (100 mL) and H_2O (100 mL). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to give a crude product. The crude product was purified by column chromatography on silica gel (Petroleum ether : EtOAc = 3:1) to give ethyl4-(2-chloro-4-fluorophenyl)-6-(4-ethoxy-4-oxobutyl)-2 -(thiazol-2-yl) -1,4-dihydropyrimidine-5-carboxylate (**compound 3-2**) (1.5 g, yield: 52%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (br. s., 1H), 8.01 (d, *J*=2.8 Hz, 1H), 7.62 (d, *J*=3.2 Hz, 1H), 7.32 (dd, *J*=6.4, 8.56 Hz, 1H), 7.09-7.13 (m, 1H), 6.88-6.93 (m, 1H), 6.18 (s, 1H), 4.47 (q, *J*=7.2 Hz, 2H), 4.14-4.20 (m, 2H), 2.82-3.10 (m, 2H), 2.46 (t, *J*=6.8 Hz, 2H), 2.06 (br. s., 2H), 1.44 (t, *J*=7.2 Hz, 3H), 1.11 (t, *J*=6.8 Hz, 3H); HRMS (EI): m/z calcd for $C_{22}H_{23}ClFN_3O_4S$ [M+H]+: 480.1082, found: 480.2040.

Step 2. 4-(6-(2-chloro-4-fluorophenyl)-5-(ethoxycarbonyl)-2-(thiazol-2-yl)-3,6-dihydropyrimidin-4-yl)butanoic acid (3-3): A mixture of ethyl

4-(2-chloro-4-fluorophenyl)-6-(4-ethoxy-4-oxobutyl)-2-(thiazol-2-yl)-1,4-dihydropyrimidine-5-carboxylate (1.5 g, 3.1 mmol) and lithium hydroxide (394 mg, 9.3 mmol) in THF (20 mL) and H_2O (20 mL) was stirred at 15 °C for 15 h. 1N aq. HCl solution was added to the mixture until pH = 3. The mixture was extracted with dichloromethane (3 x 50 mL). The combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to give 4-(6-(2-chloro-4-fluorophenyl) -5-(ethoxycarbonyl)-2-(thiazol-2-yl)-3,6 -dihydropyrimidin-4-yl)butanoic acid (**compound 3-3**, 1.3 g, yield: 92.9%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.94 (br. s., 1H), 7.85 (br. s., 1H), 7.33-7.42 (m, 2H), 7.17-7.22 (m, 1H), 5.99 (s, 1H), 3.93 (q, *J*=7.03 Hz, 2H), 2.77-3.06 (m, 2H), 2.01-2.09 (m, 2H), 1.76-1.84 (m, 2H), 1.04 (t, *J*=2.8 Hz, 3H); HRMS (EI): m/z calcd for $C_{20}H_{19}ClFN_3O_4S$ [M+H]+: 452.0769, found: 452.0685.

Step 3. ethyl 4-(2-chloro-4-fluorophenyl)-6-(4-hydroxybutyl)-2-(thiazol-2-yl) -1,4-dihydropyrimidine -5-carboxylate (3-4): To a mixture of 4-(6-(2-chloro-4-fluorophenyl)-5-(ethoxycarbonyl)-2-(thiazol-2-yl)-3,6-dihydropyrimidin-4-yl)butanoic acid (500 mg, 1.11 mmol) in dry dichloromethane (20 mL) was added 1,1'-carbonyldiimidazole (360 mg, 2.22 mmol). After stirred at 15 °C for 0.5 h, the mixture was poured into the solution of $NaBH_4$ (420 mg, 11.1 mmol) in methanol (20 mL). After stirred at 15 °C for 0.5 h, the mixture was diluted with H_2O (10 mL) and dichloromethane (20 mL), the aqueous phase was extracted with dichloromethane (2 × 20 mL). The combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to give a crude product. The crude product was purified by column chromatography on silica gel (Petroleum ether : EtOAc = 3:1) to give ethyl 4-(2-chloro-4-fluorophenyl)-6-(4-hydroxybutyl)-2-(thiazol-2-yl)-1,4-dihydropyrimidine-5-carboxylate (**compound 3-4**, 300 mg, yield: 61.7%); HRMS (EI): m/z calcd for $C_{20}H_{21}ClFN_3O_3S$ [M+H]+: 438.0976, found: 438.1036.

Step 4. ethyl4-(2-chloro-4-fluorophenyl)-6-(4-((methylsulfonyl)oxy)butyl)-2 -(thiazol-2-yl)-1,4-dihydropyrimidine-5-carboxylate (3-5): A mixture of ethyl4-(2-chloro-4-fluorophenyl)-6-(4-hydroxybutyl)-2-(thiazol-2-yl)-1,4- dihydropyrimidine -5-carboxylate (300 mg, 0.68 mmol), methanesulfonyl chloride (118 mg, 1.03 mmol)

and triethylamine (206 mg, 2.04 mmol) in dry dichloromethane (10 mL) was stirred at 15 °C for 15 h. The mixture was concentrated to give a crude product. The crude product was purified by flash chromatography on silica gel to give ethyl4-(2-chloro-4-fluorophenyl)-6-(4-((methylsulfonyl)oxy)butyl)-2-(thiazol-2-yl)-1,4-dihydropyrimidine-5-carboxylate (**compound 3-5**, 130 mg, yield: 36.8%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.83 (dd, *J*=2.8, 7.2 Hz, 1H), 7.44-7.53 (m, 1H), 7.30-7.36 (m, 1H), 7.13 (td, *J*=3.26, 8.4 Hz, 1H), 6.85-7.03 (m, 1H), 6.06-6.28 (m, 1H), 4.28-4.37 (m, 2H), 3.97-4.10 (m, 2H), 3.04 (d, *J*=4.4 Hz, 3H), 2.83-3.02 (m, 2H), 1.81-1.98(m,4H), 1.12 (d, *J*=2.4, 3H); HRMS (EI): m/z calcd for $C_{21}H_{23}ClFN_3O_5S_2$ [M+H]+: 516.0752, found: 516.0748.

Step 5. ethyl3-(2-chloro-4-fluorophenyl)-1-(thiazol-2-yl)-5,6,7,8-tetrahydro-3H-pyrido[1,2-c]pyrimidine-4-carboxylate (3): A mixture of ethyl4-(2-chloro-4-fluorophenyl)-6-(4-((methylsulfonyl)oxy)butyl)-2-(thiazol-2-yl)-1,4-dihydro pyrimidine-5-carboxylate (130 mg, 0.25 mmol) and potassium carbonate (69 mg, 0.5 mmol) in acetonitrile (3 mL) was stirred at 45 °C for 1 h. The mixture was concentrated to give a crude product. The crude product was diluted with H_2O (5 mL) and dichloromethane (10 mL). The aqueous phase was extracted with dichloromethane (3x10 mL). The combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to give a crude product. The crude product was purified by pre-TLC (Petroleum ether : EtOAc = 2:1) to give The crude product was purified by pre-HPLC to give ethyl3-(2-chloro-4-fluorophenyl)-1-(thiazol-2-yl) -5,6,7,8 -tetrahydro -3H-pyrido[1,2-c]pyrimidine-4-carboxylate (**compound 3**, 35 mg, yield: 33.2%). ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.95 (d, *J*=3.2 Hz, 1H), 7.73 (d, *J*=3.2 Hz, 1H), 7.38 (dd, *J*=6.4, 8.0 Hz, 1H), 7.28 (dd, *J*=2.4, 8.4 Hz, 1H), 7.09 (dt, *J*=2.4, 8.0 Hz, 1H), 6.12 (s, 1H), 4.20-4.30 (m, 1H), 4.03-4.17 (m, 2H), 3.61 (m, 1H), 3.44 (d, *J*=4.0, 1H), 3.00-3.13 (m, 1H), 2.04-2.17 (m, 1H), 1.93 (m, 2H), 1.75-1.86 (m, 1H), 1.18 (m, 3H); HRMS (EI): m/z calcd for $C_{20}H_{19}ClFN_3O_2S$ [M+H]+: 420.0871, found: 420.0871.

Compound 1: ethyl4-(2-chloro-4-fluorophenyl)-2-(thiazol-2-yl)-1,3-diazabicyclo

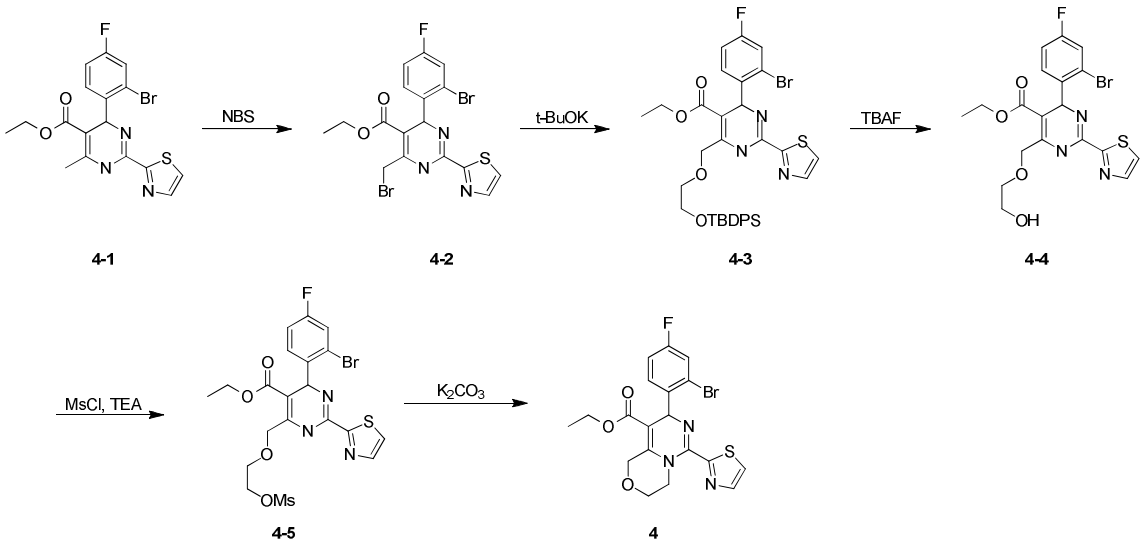
[4.2.0]octa -2,5-diene-5-carboxylate was prepared by the common procedure as compound 3 starting with diethyl 3-oxopentanedioate, 2-chloro-4-fluorobenzaldehyde and thiazole-2-carboximidamide hydrochloride salt.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80-7.88 (m, 1H), 7.53 (d, *J*=3.2 Hz, 1H), 7.35-7.42 (m, 1H), 7.33 (dd, *J*=2.4, 8.0 Hz, 1H), 6.88-7.13 (m, 1H), 5.99-6.27 (m, 1H), 4.07 (m, 2H), 3.01-3.09 (m, 2H), 1.99-2.06 (m, 2H), 1.13 (m, 3H); HRMS (EI): m/z calcd for $C_{18}H_{15}ClFN_3O_2S$ [M+H]+: 392.0558, found: 392.0558.

^{13}C NMR (101 MHz, CHLOROFORM-d) δ 165.2, 162.3, 161.5 (d, *J* = 251.5), 157.5, 145.3, 143.6, 138.5(d, *J* = 4.0), 130.4(d, *J* = 8.1), 123.6(d, *J* = 10.1), 122.4, 120.2(d, *J* = 24.2), 114.8(d, *J* = 20.2), 95.6, 59.9, 57.6, 55.5, 29.5, 14.4.

Example 3: Exemplification of General Synthesis compound **4**.

Scheme 3: The synthetic route for compound **4**



Step 1. ethyl 4-(2-bromo-4-fluorophenyl)-6-(bromomethyl)-2-(thiazol-2-yl) -1,4-dihydropyrimidine-5-carboxylate(4-2): To a suspension of ethyl 4-(2-bromo -4-fluorophenyl)-6-methyl-2- (thiazol-2-yl)-1,4- dihydropyrimidine-5-carboxylate (5 g, 11.78 mmol) in CCl_4 (50 mL) was added NBS (2.3 g, 12.96 mmol), AIBN (97 mg, 0.59 mmol) at room temperature under N_2. The reaction was warmed up to 70 ^{o}C and stirred for 30 min. Then the reaction was cooled to room temperature and concentrated. The residue was washed with H_2O (10 mL), extracted with EtOAc (10

mL x 3). The combined organic liquid was dried, filtered, concentrated. The residue was purified by column chromatography with elute (Petroleum ether : Ethyl acetate = 5:1) to give the **compound 4-2**. (2.4 g, yield: 39%). ^{1}H NMR (400 MHz,$CDCl_3$) δ 7.84 (d, *J* = 3.2 Hz, 1H), 7.56 - 7.49 (m, 1H), 7.48 - 7.37 (m, 1H), 7.32 (dd, *J* = 2.4, 8.0 Hz, 1H), 7.09 - 6.93 (m, 1H), 6.22 - 6.02 (m, 1H), 4.12 (m, 1H), 4.06 (s, 2H), 1.16 (m, 3H); HRMS (EI): m/z calcd for $C_{17}H_{14}Br_2FN_3O_2S$ [M+H]+: 501.9158, found: 501.9158.

Step 2. ethyl 4-(2-bromo-4-fluorophenyl)-6-((2-((tert-butyldiphenylsilyl) oxy)ethoxy) methyl)-2-(thiazol-2-yl)-1,4-dihydropyrimidine-5-carboxylate(4-3): To a solution of 2-((tert-butyldiphenylsilyl)oxy)ethanol (1.07 g, 3.57 mmol) in THF (10 mL) was added potassium 2-methylpropan-2-olate (400 mg, 3.57 mmol) at room temperature under N_2. The reaction was stirred for 30 min. Then to the reaction was added ethyl 4-(2-bromo-4- fluorophenyl)-6-(bromomethyl)-2-(thiazol-2-yl)-1,4-dihydropyrimidine-5-carboxylate (600 mg, 1.19 mmol). The mixture reaction was stirred at room temperature overnight. After that time, the reaction was concentrated. The residue was washed with H_2O (10 mL), extracted with EtOAc (10 mL x 3). The combined organic liquid was dried, filtered, concentrated. The residue was used to next steps without further purification. (**compound 4-3**, 840 mg, crude), HRMS (EI): m/z calcd for $C_{35}H_{37}BrFN_3O_4SSi$ [M+H]+: 722.1441, found: 722.1424/724.1428.

Step 3. ethyl 4-(2-bromo-4-fluorophenyl)-6-((2-hydroxyethoxy)methyl) -2-(thiazol-2-yl) -1,4-dihydropyrimidine-5-carboxylate(4-4): To a solution of ethyl 4-(2-bromo-4-fluorophenyl)-6-((2-((tert-butyldiphenylsilyl)oxy)ethoxy)methyl)-2-(thiazol-2-yl)-1,4-dihydropyrimidine-5-carboxylate (840 mg, 1.16 mmol) in THF (10 mL) was added a solution of TBAF (10 mmol, 10 mL, 1M in THF) at room temperature under N_2. The reaction was stirred overnight. Then the reaction was concentrated, washed with H_2O (10 mL), extracted with EtOAc (10 mL x 3). The combined organic liquid was dried, filtered, concentrated. The residue was purified by column chromatography with elute (Petroleum ether: EtOAc = 1:1) to give the **compound 4-4**. (300 mg, yield: 53%).^{1}H NMR (400 MHz,$CDCl_3$) δ 9.08 (br. s., 1H), 7.82 (d, *J* = 3.2 Hz, 1H), 7.43 (d, *J* = 3.2 Hz, 1H), 7.36 - 7.29 (m, 2H), 6.97 (dt, *J* =

2.4, 8.4 Hz, 1H), 6.18 (s, 1H), 4.96 (d, *J* = 2.4 Hz, 2H), 4.11 - 3.97 (m, 2H), 3.90 (br. s., 2H), 3.84 - 3.69 (m, 2H), 2.71 (br. s., 1H), 1.13 (m, 3H); HRMS (EI): m/z calcd for $C_{19}H_{19}BrFN_3O_4S$ [M+H]+: 484.0264, found: 484.0264.

Step 4. ethyl 4-(2-bromo-4-fluorophenyl)-6-((2-((methylsulfonyl)oxy) ethoxy)methyl) -2-(thiazol-2-yl)-1,4-dihydropyrimidine-5-carboxylate(4-5): To a solution of ethyl 4-(2-bromo-4 -fluorophenyl)-6-((2-hydroxyethoxy)methyl)-2-(thiazol-2-yl)-1,4-dihydropyrimidine-5-carboxylate (280 mg, 0.58 mmol), triethylamine (176 mg, 1.74 mmol) in DCM (3 mL) was added methanesulfonyl chloride (132 mg, 1.16 mmol) at room temperature under N_2. The reaction was stirred overnight. Then the reaction was concentrated, washed with H_2O (10 mL), extracted with EtOAc (10 mL x 3). The combined organic liquid was dried, filtered, concentrated. The residue was purified by column chromatography with elute (Petroleum ether : EtOAc = 3:1) to give the **compound 4-5**. (150 mg, yield: 46%). ^{1}H NMR (400 MHz,$CDCl_3$) δ 8.95 (br. s., 1H), 7.83 (d, *J* = 3.2 Hz, 1H), 7.47 (d, *J* = 3.2 Hz, 1H), 7.40 - 7.31 (m, 2H), 7.00 (dt, *J* = 2.4, 8.4 Hz, 1H), 6.20 (s, 1H), 5.09 - 4.92 (m, 2H), 4.58 - 4.44 (m, 2H), 4.13 - 4.00 (m, 2H), 4.00 - 3.90 (m, 2H), 3.17 (s, 3H), 1.15 (t, *J* = 3.2 Hz, 3H); HRMS (EI): m/z calcd for $C_{20}H_{21}BrFN_3O_6S_2$ [M+H]+: 564.0125, found: 564.0123.

Step 5. ethyl 8-(2-bromo-4-fluorophenyl)-6-(thiazol-2-yl)-1,3,4,8-tetrahydropyrimido [6,1-c][1,4]oxazine-9-carboxylate (4): To a solution of ethyl 4-(2-bromo-4-fluorophenyl)-6-((2-((methylsulfonyl)oxy)ethoxy)methyl)-2-(thiazol -2-yl)-1,4-dihydropyrimidine-5-carboxylate (140 mg, 0.24 mmol) in CH_3CN (5 mL) was added K_2CO_3 (68 mg, 0.50 mmol) at room temperature under N_2. Then the reaction was refluxed overnight. After that time, the reaction was filtered, concentrated. The residue was washed with H_2O (10 mL), extracted with EtOAc (10 mL x 3). The combined organic liquid was dried, filtered, concentrated. The residue was purified by column chromatography with elute (PE : EtOAc = 3:1) to give the **compound 4**. (64 mg, yield: 52%). ^{1}H NMR (400 MHz,$CDCl_3$) δ 7.82 (d, *J* = 3.6 Hz, 1H), 7.42 - 7.34 (m, 2H), 7.31 - 7.27 (m,1H), 7.01 (dt, *J* = 2.4, 8.4 Hz, 1H), 6.14 (s, 1H), 5.29 (m, 1H), 5.00 (m, 1H), 4.80 (d, *J* = 4.0, 1H), 4.15 - 4.05 (m, 2H), 4.04 -

3.97 (m, 1H), 3.96 - 3.86 (m, 1H), 3.64 (d, *J* = 3.6, 1H), 1.14 (t, *J* = 7.2 Hz, 3H). HRMS (EI): m/z calcd for $C_{19}H_{17}BrFN_3O_3S$ [M+H]+: 468.0356, found: 468.0356.

Compound 5: ethyl 8-(2-bromo-4-fluorophenyl)-6-(thiazol-2-yl)-2,3,4,8-tetrahydro-1H-pyrazino[1,2-c]pyrimidine-9-carboxylate was prepared by the common procedure as compound 4 starting with 2-((4-methoxybenzyl)amino)ethanol, and ethyl 4-(2-bromo-4-fluorophenyl)-6-(bromomethyl)-2-(thiazol-2-yl)-1,4-dihydropyrimidine -5-carboxylate. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J=3.2 Hz, 1H), 7.42 - 7.33 (m, 2H), 7.28 (d, J=5.6 Hz, 1H), 6.99 (d, J=2.5, Hz, 1H), 6.14 (s, 1H), 4.75 - 4.64 (m, 1H), 4.58 - 4.29 (m, 2H), 4.15 - 3.97 (m, 2H), 3.52 - 3.30 (m, 2H), 3.17 - 3.04 (m, 1H), 1.14 (t, J=7.2 Hz, 3H); HRMS (EI): m/z calcd for $C_{19}H_{18}BrFN_4O_2S$ [M+H]+: 465.0381, found: 465.0378.

Compound 6: ethyl8-(2-bromo-4-fluorophenyl)-3-oxo-6-(thiazol-2-yl)-2,3,4,8 -tetrahydro-1H-pyrazino[1,2-c]pyrimidine-9-carboxylate was prepared by the common procedure as compound 4. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* =3.2 Hz, 1H), 7.46 (d, *J* =3.2 Hz, 2H), 7.36 (d, *J*=2.4, 1H), 7.05 - 6.97 (m, 1H), 6.97 - 6.90 (m, 1H), 6.00 (d, *J* = 8.4 Hz, 1H), 5.72 (s, 1H), 5.52 (d, *J* = 4.4 Hz, 1H), 4.42 (d, *J* = 16.8 Hz, 1H), 4.23 (m, 2H), 3.47 (d, *J* = 1.6 Hz, 1H), 1.28 (t, *J* = 7.2 Hz, 3H); HRMS (EI): m/z calcd for $C_{19}H_{16}BrFN_4O_3S$ [M+H]+: 479.0111, found: 479.0111.

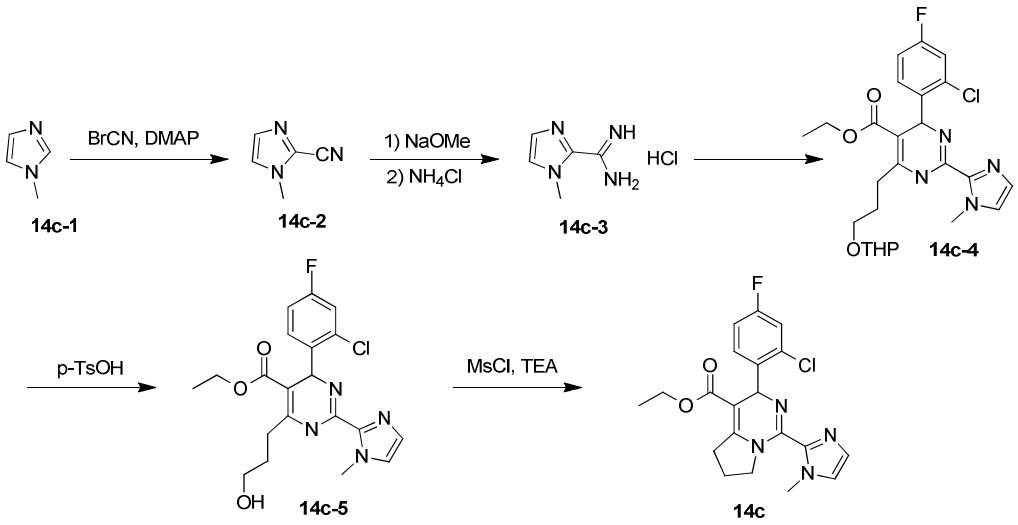
Compound 7: ethyl 2-acetyl-8-(2-bromo-4-fluorophenyl)-6-(thiazol-2-yl)-2,3,4,8 -tetrahydro-1H-pyrazino[1,2-c]pyrimidine-9-carboxylate was prepared by the procedure starting with compound 5, and Ac_2O. HRMS (m/z): Calcd. for $C_{21}H_{20}BrFN_4O_3S$ [M+H]: 507.0424, found 507.0424; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J=3.2 Hz, 1H), 7.44 (d, J=3.2 Hz, 1H), 7.38 (dd, J=2.8, 8.0 Hz, 1H), 7.20 (d, *J*=6.0, 1H), 6.99 (d, J=2.4 Hz, 1H), 6.17 (s, 1H), 5.15 - 4.90 (m, 2H), 4.89 - 4.82 (m, 1H), 4.19 - 4.04 (m, 2H), 3.96 - 3.86 (m, 1H), 3.77 - 3.67 (m, 2H), 2.89 (s, 3H), 1.18 (t, J=7.2 Hz, 3H).

Compound 8: ethyl 8-(2-bromo-4-fluorophenyl)-2-(methylsulfonyl)-6-(thiazol-2-yl) -2,3,4,8-tetrahydro-1H-pyrazino[1,2-c]pyrimidine-9-carboxylate was prepared by the procedure starting with compound 5 and MsCl. ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.84 (d, J=3.2 Hz, 1H), 7.44 (d, J=3.2 Hz, 1H), 7.38 (d, J=2.4, 1H), 7.20 (d, J=6.0 Hz,

1H), 6.99 (d, J=2.5 Hz, 1H), 6.17 (s, 1H), 5.14 - 4.90 (m, 2H), 4.90 - 4.82 (m, 1H), 4.20 - 4.04 (m, 2H), 3.96 - 3.85 (m, 1H), 3.76 - 3.66 (m, 2H), 2.89 (s, 3H), 1.18 (t, J=7.2 Hz, 3H); HRMS (EI): m/z calcd for $C_{20}H_{20}BrFN_4O_4S_2$ [M+H]+: 543.0093, found: 543.0090.

Example 4: Exemplification of General Synthesis compound **14c**.

Scheme 4: The synthetic route for compound **14c**



Step 1. 1-methyl-1H-imidazole-2-carbonitrile (14c-2): Under N_2, a solution of DMAP (14.8g, 121.95 mmol) in DMF (200 mL) was cooled to 10°C and BrCN (12.92 g, 121.95 mmol) was added. The reaction was exotherms to 20°C and a pale yellow precipitate of CAP forms. The mixture was then allowed to 10°C and 1-methyl-1H-imidazole (4 g, 48.78 mmol) was added. The mixture was stirred at 40°C for 16 h. Then the mixture was cooled to room temperature and poured into 0.1M aq. $NaHCO_3$ (1000 mL) and stirred 30 min. The solution was extracted with EtOAc (500 mL x 3). The combined organic liquid was dried, filtered, concentrated. The residue was purified by column chromatography with elute (Petroleum ether : EtOAc = 20:1) to give the **compound 14c-2**. (1.5 g, yield: 29%). ^{1}H NMR (400 MHz,$CDCl_3$) δ 7.18 (s, 1H), 7.08 (s, 1H), 3.87 (s, 3H).

Step 2. 1-methyl-1H-imidazole-2-carboximidamide hydrochloride(14c-3): To a solution of 1-methyl-1H-imidazole-2-carbonitrile (500 mg, 4.67 mmol) in MeOH (10 mL) was added NaOMe (504 mg, 9.35 mmol) at room temperature under N_2. The

reaction was stirred for 60 min. Then NH_4Cl (990 mg, 18.68 mmol) was added to the solution and heated up to 80°C for 12 h. The reaction was cooled to room temperature and filtered. The solid was washed with MeOH (5 mL x 2). The combined organic liquid was concentrated. The crude product was washed with EtOAc (10 mL x 3) and filtered. The precipitate was washed with EtOAc (5 mL x 3) and dissolved in MeOH (10 mL). The solution was filtered and concentrated to give the **compound 14c-3**. (600 mg, 80%). ^1H NMR (400 MHz,$CDCl_3$) δ 8.38 (s, 3H), 7.53 (s, 1H), 7.14 (s, 1H), 3.89 (s, 3H).

Step 3. ethyl 4-(2-chloro-4-fluorophenyl)-2-(1-methyl-1H-imidazol-2-yl)-6-(3-((tetrahydro-2H-pyran-2-yl)oxy)propyl)-1,4-dihydropyrimidine-5-carboxylate(14c-4): 2-chloro-4-fluorobenzal dehyde (456 mg, 2.87 mmol), 1-methyl-1H-imidazole-2-carboximidamide hydrochloride (600 mg, 3.73 mmol), ethyl 3-oxo-6-((tetrahydro-2H-pyran-2-yl)oxy)hexanoate (740 mg, 2.87 mmol) and sodium acetate (588 mg, 7.18 mmol) were dissolved in anhydrous EtOH (10mL) at room temperature. Then the mixture reaction was refluxed for 12h under N_2. After that time, the reaction was completed, cooled to room temperature, concentrated. The residue was washed with H_2O (20 mL), extracted with EtOAc (20 mL x 3). The combined organic liquid was dried over Na_2SO_4, filtered, concentrated. The residue was purified by column chromatography with elute (DCM, EtOH = 20:1) to give the **compound 14c-4**. (700 mg, 50%). LCMS (m/z): Calcd. for $C_{25}H_{30}ClFN_4O_4$, 504.1, found 527.1 (M + Na).

Step 4. ethyl 4-(2-chloro-4-fluorophenyl)-6-(3-hydroxypropyl)-2-(1-methyl-1H-imidazol-2-yl)-1,4-dihydropyrimidine-5-carboxylate(14c-5): A mixture of ethyl 4-(2-chloro-4-fluorophenyl)-2-(1-methyl-1H-imidazol-2-yl)-6-(3-((tetrahydro-2H-pyr an-2-yl)oxy)propyl)-1,4-dihydropyrimidine-5-carboxylate (700 mg, 1.39 mmol) and $TsOH \cdot H_2O$ (527 mg, 2.78 mmol) in EtOH (10 mL) was stirred at room temperature for 2 h. Then the mixture was washed with water and extracted with EtOAc. The organic layer was concentrated to give the **compound 14c-5** (500 mg, 85.7%), which was used for next step without further purification.

Step 5. ethyl 3-(2-chloro-4-fluorophenyl)-1-(1-methyl-1H-imidazol-2-yl)-3,5,6,7

-tetrahydropyrrolo[1,2-c]pyrimidine-4-carboxylate(14c): To a mixture of ethyl 4-(2-chloro-4-fluorophenyl)-6-(3-hydroxypropyl)-2-(1-methyl-1H-imidazol-2-yl)-1,4 -dihydropyrimidine-5-carboxylate (500 mg, 1.19 mmol) and TEA (606 mg, 6.0 mmol) in DCM (20 mL) was added MsCl (458 mg, 4.0 mmol) dropwise. The resulting mixture was stirred at 25 ^{o}C for 16 h. The mixture was washed with water and then dried over Na_2SO_4, filtered and concentrated to give the crude product, which was purified by column to give ethyl 3-(2-chloro-4-fluorophenyl)-1-(1-methyl-1H -imidazol-2-yl)-3,5,6,7-tetrahydropyrrolo[1,2-c]pyrimidine-4-carboxylate (**compound 14c**, 57 mg, 11.9%). ^{1}H NMR (400 MHz,$CDCl_3$) δ 7.33 - 7.26 (m, 1H), 7.12 (d, J=6.8 Hz, 1H), 6.98 (br. s., 1H), 6.92 (t, J=7.2 Hz, 1H), 6.84 (s, 1H), 6.20 (s, 1H), 4.21 (d, J=8.0 Hz, 1H), 4.04 (q, J=6.8 Hz, 2H), 3.96 (br. s., 1H), 3.63 (br. s., 3H), 3.44 - 3.31 (m, 1H), 3.10 (m, 1H), 2.15 - 1.91 (m, 2H), 1.13 (t, J=7.2 Hz, 3H); HRMS (EI): m/z calcd for $C_{20}H_{20}ClFN_4O_2$ [M+H]+: 403.1259, found: 403.1256.

Compound 14a: ethyl 3-(2-chloro-4-fluorophenyl)-1-(isothiazol-3-yl)-3,5,6,7 -tetrahydropyrrolo[1,2-c]pyrimidine-4-carboxylate was prepared by the procedure starting with 2-chloro-4-fluorobenzaldehyde, isothiazole-3-carboximidamide hydrochloride and ethyl 3-oxo-6-((tetrahydro-2H-pyran-2-yl)oxy)hexanoate. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.56 (d, J=5.02 Hz, 1H), 7.67 (br. s., 1H), 7.34 (d, J=6.2, 8.0 Hz, 1H), 7.08-7.14 (m, 1H), 6.93 (d, J=2.4 Hz, 1H), 6.21 (s, 1H), 4.18-4.29 (m, 1H), 3.97-4.13 (m, 3H), 3.39 (d, J=4.0, Hz, 1H), 3.02-3.16 (m, 1H), 1.96-2.19 (m, 2H), 1.15 (t, J=7.2 Hz, 3H); HRMS (EI): m/z calcd for $C_{19}H_{17}ClFN_3O_2S$ [M+H]+: 406.0714, found: 406.0714.

Compound 14b: ethyl 3-(2-chloro-4-fluorophenyl)-1-(1-methyl-1H-pyrazol-4-yl) -3,5,6,7-tetrahydropyrrolo[1,2-c]pyrimidine-4-carboxylate was prepared by the procedure starting with 2-chloro-4-fluorobenzaldehyde, ethyl 3-oxo-6-((tetrahydro-2H-pyran-2-yl) oxy)hexanoate and 1-methyl-1H-pyrazole-4-carboxi midamide hydrochloride. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 8.05 (s, 1H), 7.67 (s, 1H), 7.30-7.41 (m, 2H), 7.08-7.20 (m, 1H), 5.91 (s, 1H), 3.89-4.02 (m, 3H), 3.76-3.84 (m, 4H), 3.20-3.30 (m, 2H), 2.99 (m, 1H), 1.94-2.14 (m, 1H), 1.06 (t, J=7.2 Hz, 3H). HRMS (EI): m/z calculated for $C_{20}H_{20}ClFN_4O_2$ [M+H$^+$]: 404.1337; found 404.1333

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.3, 160.5(d, *J* = 249.4), 155.1, 153.9, 140.8, 140.1, 138.5(d, *J* = 3.7), 133.8(d, *J* = 10.3), 131.1(d, *J* = 8.8), 129.5, 117.0(d, *J* = 24.2), 114.2(d, *J* = 21.3), 108, 59.8, 56.4, 51.5, 40.2, 30.6, 22.4, 14.2.

Compound 14d: ethyl 3-(2-chloro-4-fluorophenyl)-1-(oxazol-2-yl)-3,5,6,7 -tetrahydropyrrolo [1,2-c]pyrimidine-4-carboxylate was prepared by the procedure starting with 2-chloro -4-fluorobenzaldehyde, oxazole-2-carboximidamide hydrochloride and ethyl 3-oxo-6- ((tetrahydro-2H-pyran-2-yl)oxy)hexanoate. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.31 (d, J=6.0 Hz, 1H), 7.20 (s, 1H), 7.11 (dd, J=2.6, 8.4 Hz, 1H), 6.92 (dt, J=2.5, 8.0 Hz, 1H), 6.25 (s, 1H), 4.32 (m, 1H), 4.23 - 4.11 (m, 1H), 4.04 (m, 2H), 3.38 (m, 1H), 3.07 (m, 1H), 2.22 - 2.11 (m, 1H), 2.10 - 1.99 (m, 1H), 1.14 (t, J=7.2 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.2, 161.5(d, *J* = 249.4), 155.1, 153.9, 140.8, 140.1, 138.5(d, *J* = 3.7), 133.8(d, *J* = 10.3), 131.1(d, *J* = 8.8), 127.9, 117.0(d, *J* = 24.2), 114.2(d, *J* = 21.3), 95.5, 59.8, 56.4, 51.5, 30.6, 22.4, 14.2. HRMS(EI): m/z calculated for $C_{19}H_{17}ClFN_3O_3$ [M+H$^+$] : 390.1021, found: 390.1009.

Compound 14e: ethyl 3-(2-chloro-4-fluorophenyl)-1-(pyridin-2-yl)-3,5,6,7 -tetrahydropyrrolo[1,2-c]pyrimidine-4-carboxylate was prepared by the procedure starting with 2-chloro-4-fluorobenzaldehyde, picolinimidamide hydrochloride and ethyl 3-oxo-6 -((tetrahydro-2H-pyran-2-yl)oxy)hexanoate. ^{1}HNMR (400 MHz, DMSO-d_6) δ 8.55 (d, J=4.5 Hz, 1H), 7.86 (dt, J=1.5, 7.8 Hz, 1H), 7.59 (d, J=7.5 Hz, 1H), 7.48 - 7.40 (m, 2H), 7.37 (dd, J=2.8, 8.8 Hz, 1H), 7.19 (dt, J=2.5, 8.5 Hz, 1H), 6.06 - 6.00 (m, 1H), 4.03 - 3.89 (m, 3H), 3.63 - 3.54 (m, 1H), 3.25 (td, J=6.5, 18.1 Hz, 1H), 3.03 (td, J=8.7, 17.8 Hz, 1H), 2.02 - 1.91 (m, 2H), 1.14 - 1.01 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3, 161.4(d, *J* = 248.7), 154.1, 153.0, 150.8, 148.1, 138.8(d, *J* = 3.7), 137.2, 133.6(d, *J* = 10.3), 131.3(d, *J* = 8.8), 124.6, 124.4, 116.8(d, *J* = 24.2), 114.3(d, *J* = 21.3), 95.8, 59.7, 56.5, 50.7, 30.7, 22.3, 14.2. HRMS(EI): m/z calculated for $C_{21}H_{19}ClFN_3O_2$ [M+H$^+$] : 400.1228, found: 400.1223.

Compound 14f: ethyl 3-(2-chloro-4-fluorophenyl)-1-(5-fluoropyridin-2-yl)-3,5,6,7 -tetrahydropyrrolo[1,2-c]pyrimidine-4-carboxylate was prepared by the procedure starting with 2-chloro-4-fluorobenzaldehyde, 5-fluoropicolinimidamide and ethyl

3-oxo-6- ((tetrahydro-2H-pyran-2-yl)oxy)hexanoate. ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.48 (d, *J*=2.69 Hz, 1H), 7.57-7.70 (m, 3H), 7.47 (dd, *J*=6.11, 8.80 Hz, 1H), 7.19 (dd, *J*=2.45, 8.80 Hz, 1H), 7.06 (dt, *J*=2.69, 8.44 Hz, 1H), 6.12 (s, 1H), 4.03 (q, *J*=7.01 Hz, 2H), 3.69-3.82 (m, 2H), 3.32-3.38 (m, 1H), 3.12 (td, *J*=8.77, 17.91 Hz, 1H), 1.87-2.20 (m, 2H), 1.13 (t, *J*=7.09 Hz, 3H); HRMS(EI): m/z calculated for $C_{21}H_{18}ClF_2N_3O_2$ [M+H$^+$]: 418.1134, found: 418.1126.

^{13}C NMR (101 MHz, $CDCl_3$) δ 161.3, 159.4(d, *J* = 240.6), 153.6, 153.0, 150.8, 148.1, 138.8(d, *J* = 3.7), 135.2, 133.6(d, *J* = 10.3), 131.3(d, *J* = 8.8), 124.6, 124.4, 116.8(d, *J* = 24.2), 114.3(d, *J* = 21.3), 96.8, 59.7, 56.5, 50.7, 30.7, 22.3, 14.2.

Compound 14g: ethyl 3-(2-chloro-4-fluorophenyl)-1-(3,5-difluoropyridin-2-yl) -3,5,6,7 -tetrahydropyrrolo[1,2-c]pyrimidine-4-carboxylate was prepared by the procedure starting with 2-chloro-4-fluorobenzaldehyde, amino(3,5 -difluoropyridin-2-yl)methaniminium chloride and ethyl 3-oxo-6-((tetrahydro-2H-pyran-2-yl)oxy)hexanoate. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.54 (d, *J*=2.0 Hz, 1H), 8.09 (dt, *J*=2.0, 9.2 Hz, 1H), 7.45 (dd, *J*=6.0, 8.4 Hz, 1H), 7.38 (dd, *J*=2.4, 8.4 Hz, 1H), 7.21 (dt, *J*=2.4, 8.4 Hz, 1H), 6.02 (s, 1H), 3.90-4.03 (m, 2H), 3.52-3.54 (m, 1H), 3.34-3.38 (m, 1H), 3.23-3.27 (m, 1H), 3.05-3.10 (m, 1H), 1.91-2.03 (m, 2H), 1.08 (t, *J*=7.2 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.2, 161.5(d, *J* = 248.7), 159.3(dd, *J* = 238.7, 6.1), 156.6(dd, *J* = 242.4, 7.1), 153.2, 146.0(d, *J* = 6.1), 138.7(d, *J* = 6.1), 133.8(d, *J* = 4.4), 133.6(d, *J* = 3.7), 131.2(d, *J* = 8.8), 116.8(d, *J* = 24.9), 114.4(d, *J* = 21.3), 112.8(d, *J* = 22.2), 112.7(d, *J* = 21.2), 96.0, 59.8, 56.7, 49.5, 30.8, 22.0, 14.2. HRMS(EI): m/z calculated for $C_{21}H_{17}ClF_3N_3O_2$ [M+H$^+$]: 436.1040, found: 436.1030.

Compound 14h: ethyl 3-(2-chloro-4-fluorophenyl)-1-(5-fluoropyrimidin-2-yl) -3,5,6,7-tetrahydropyrrolo[1,2-c]pyrimidine-4-carboxylate was prepared by the procedure starting with 2-chloro-4-fluorobenzaldehyde, 5-fluoropyrimidine -2-carbox imidamide hydrochloride and ethyl 3-oxo-6-((tetrahydro-2H-pyran-2-yl)oxy) hexanoate. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.66 (s, 2H), 7.42 (m, 1H), 7.07 (m, 1H), 6.94 (m, 1H), 6.29 (s, 1H), 4.08 - 4.02 (m, 2H), 3.95 – 3.93 (m, 1H), 3.52 - 3.50 (m, 1H), 3.52 - 3.50 (m, 1H),3.20-3.13 (m, 1H), 2.10-2.03 (m, 2H), 1.16 - 1.03 (m, 3H).

HRMS(EI): m/z calculated for $C_{20}H_{17}ClF_2N_4O_2$ [M+H$^+$]: 419.1086, found: 419.1079.

^{13}C NMR (101 MHz, $CDCl_3$) δ 162.2, 161.3, 160.4(d, *J* = 240.6), 153.6, 153.0, 150.8, 148.6, 148.2, 135.2, 133.6(d, *J* = 10.3), 124.4, 116.8(d, *J* = 24.2), 114.3(d, *J* = 21.3), 96.8, 59.7, 56.5, 50.7, 30.7, 22.3, 14.2.

Compound 14i: ethyl-3-(2-chloro-4-fluorophenyl)-1-cyclopropyl-3,5,6,7 -tetrahydropyrrolo[1,2-c]pyrimidine-4-carboxylate was prepared by the procedure starting with 2-chloro-4-fluorobenzaldehyde, cyclopropane carboximidamide hydrochloride and ethyl 3-oxo-6-((tetrahydro-2H-pyran-2-yl)oxy)hexanoate. HRMS (EI): m/z calculated for $C_{19}H_{20}ClFN_2O_2$ [M+H] $^+$: 363.1276, found: 363.1271.

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 7.75 (d, *J*=2.0 Hz, 1H), 8.72 (d, *J*= 9.2 Hz, 1H), 7.45 (d, 8.4 Hz, 1H), 6.02 (s, 1H), 3.90-4.03 (m, 2H), 3.52-3.54 (m, 1H), 3.34-3.38 (m, 1H), 3.23-3.27 (m, 1H), 3.05-3.10 (m, 1H), 1.91-2.03 (m, 2H), 1.08 (t, *J*=7.2 Hz, 3H). 0.98 (m, 1H), 0.40 (m, 2H), 0.28 (m, 2H).

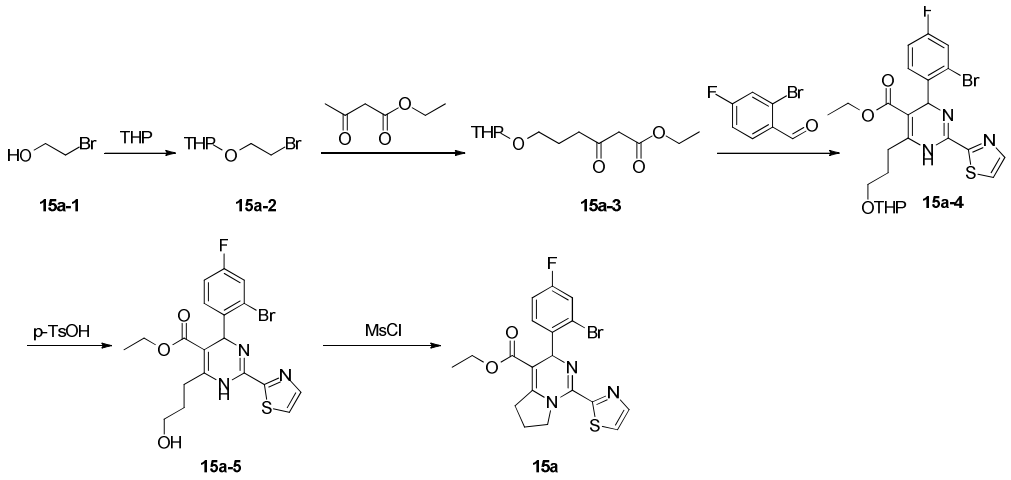
^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2, 161.3(d, *J* = 240.6), 158.6, 154.3, 135.2, 133.6(d, *J* = 10.3), 124.4, 116.8(d, *J* = 24.2), 114.3(d, *J* = 21.3), 96.8, 59.7, 56.5, 50.7, 30.7, 22.3, 14.2, 12.9, 5.9, 5.7.

Compound 14j: ethyl 3-(2-bromo-4-fluorophenyl)-1-morpholino-3,5,6,7 -tetrahydropyrrolo [1,2-c]pyrimidine-4-carboxylate was prepared by the procedure starting with 2-chloro -4-fluorobenzaldehyde, morpholine-4-carboximidamide hydrobromide and ethyl 3-oxo-6- ((tetrahydro-2H-pyran-2-yl)oxy)hexanoate. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (dd, J=2.4, 8.4 Hz, 1H), 7.33 - 7.27 (m, 1H), 7.12 - 7.05 (m, 1H), 5.90 (s, 1H), 4.61 (br. s., 7H), 4.01 (q, J=6.8 Hz, 2H), 3.83 (t, J=7.2, 2H), 3.75 - 3.66 (m, 5H), 3.17 - 3.05 (m, 3H), 2.96 (br. s., 2H), 2.15 - 2.04 (m, 2H), 1.12 (t, J=7.2 Hz, 4H). HRMS(EI): m/z calculated for $C_{20}H_{23}BrFN_3O_3$ [M+H$^+$]: 452.0985, found: 452.0980.

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.2, 160.3(d, *J* = 240.6), 157.6, 152.3, 135.2, 133.6, 124.4, 116.8(d, *J* = 24.2), 114.3(d, *J* = 21.3), 96.8, 66.5, 59.7, 56.5, 50.9, 50.7, 30.7, 22.3, 14.2.

Example 5: Exemplification of General Synthesis compound **15a**.

Scheme 5: The synthetic route for compound **15a**



Step 1. 2-(2-bromoethoxy)tetrahydro-2H-pyran(15a-2): To a solution of 2-bromoethanol (12.5 g, 0.1 mol) in DCM (30 mL) was added THP (12.6 g, 0.15 mol) and p-TsOH(250 mg ,1.3 mmol) . The mixture reaction was stirred overnight at room temperature. Then the reaction was evaporated and purified by chromatography to give the **compound 15a-2**. (1.5 g, yield: 29%). ^{1}H NMR (400 MHz,$CDCl_3$) δ 4.68 (t, *J*=3.2 Hz, 1H), 4.03 (t, *J*=6.2, 1H), 3.90 (m, 1H), 3.73-3.82 (m, 1H), 3.45-3.58 (m, 3H), 1.80-1.91 (m, 1H), 1.70-1.79 (m, 1H), 1.51-1.63 (m, 4H).

Step 2. ethyl 3-oxo-6-((tetrahydro-2H-pyran-2-yl)oxy)hexanoate(15a-3): To the stirred suspension of sodium hydride(400 mg) in THF (30mL) were added compound ethyl 3-oxobutanoate (936 mg, 7.2 mmol) dissolved in THF (10 mL) at -40^{o}C .The mixture was stirred at -20 ^{o}C for thirty minutes. The reaction mixture became clear. Then 4 mL n-BuLi were added and the reaction mixture was stirred at 0 ^{o}C for 15 minutes. Then compound 2-(2-bromoethoxy)tetrahydro-2H-pyran (1 g, 4.8 mmol) dissolved in THF (10 mL). The reaction mixture was stirred at 0 ^{o}C for 2 hours and then at room temperature overnight. 100 mL saturated NH_4Cl solution was added and the mixture extracted three times with portions of 100 mL ethyl acetate. The combined organic layers were evaporated in vacuo and purified by chromatography to give the **compound 15a-3** (700 mg, 56%). ^{1}H NMR (400 MHz,$CDCl_3$) δ 4.50-4.61 (m, 1H), 4.20 (q, *J*=6.8 Hz, 2H), 3.69-3.89 (m, 2H), 3.32-3.57 (m, 4H), 2.58-2.75 (m, 2H), 1.91 (m, 2H), 1.75-1.84 (m, 1H), 1.63-1.75 (m, 2H), 1.51-1.57 (m, 3H), 1.23-1.33 (m, 3H).

Step 3. ethyl 4-(2-bromo-4-fluorophenyl)-6-(3-((tetrahydro-2H-pyran-2-yl)oxy) propyl)-2-(thiazol-2-yl)-1,4-dihydropyrimidine-5-carboxylate(15a-4): To a solution of ethyl 3-oxo-6 -((tetrahydro-2H-pyran-2-yl)oxy)hexanoate (700 mg, 2.7 mmol) in EtOH (20 mL) was added 2-bromo-4-fluorobenzaldehyde (426.6 mg,2.7 mmol), thiazole-2-carboximidamide hydrochloride (880 mg, 5.4 mmol) and AcONa(664 mg, 8.1 mmol). The resulting mixture was stirred at 100 ^{o}C overnight. The mixture was evaporated and extracted with ethyl acetate three times. The residue was purified by chromatography to give the product (**15a-4**) (500mg, 61%). HRMS(EI): m/z calculated for $C_{24}H_{27}BrFN_3O_4S$ $[M+H]^+$: 552.0890, found: 552.0890.

Step 4. ethyl 4-(2-bromo-4-fluorophenyl)-6-(3-hydroxypropyl)-2-(thiazol-2-yl) -1,4-dihydropyrimidine-5-carboxylate(15a-5): To a solution of ethyl 4-(2-bromo-4 -fluorophenyl)-6-(3-((tetrahydro-2H-pyran-2-yl)oxy)propyl)-2-(thiazol-2-yl)-1,4 -dihydropyrimidine-5-carboxylate (101.12 mg, 0.2 mmol) in EtOH (10 mL) was added p-TsOH (114 mg, 0.6 mmol). The resulting mixture was stirred for 30 min. The mixture was added $NaHCO_3$ to adjust Ph = 8 and extracted with ethyl acetate three times. The residue was purified by chromatography to give **compound 15a-5**. HRMS(EI): m/z calculated for $C_{19}H_{19}BrFN_3O_3S$ $[M+H]^+$: 468.0315, found: 468.0315.

Step 5. ethyl 3-(2-bromo-4-fluorophenyl)-1-(thiazol-2-yl)-3,5,6,7 -tetrahydropyrrolo [1,2-c]pyrimidine-4-carboxylate(15a): To a solution of ethyl 4-(2-bromo-4-fluorophenyl)-6-(3-hydroxypropyl)-2-(thiazol-2-yl)-1,4-dihydro pyrimidine-5-carboxylate (55 mg, 0.13 mmol) in DCM (10 mL) was added MsCl (74.1 mg, 0.39 mmol) and Et_3N(65.7 mg, 0.65 mmol).. The resulting mixture was stirred for 3 hours. The mixture was added water and extracted with ethyl acetate for three times. The residue was purified by chromatography to give the **15a** (20 mg, 37%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J=3.2 Hz, 1H), 7.37 (d, J=3.2 Hz, 1H), 7.28-7.32 (m, 1H), 7.12 (dd, J=2.4, 8.0 Hz, 1H), 6.92 (m, 1H), 6.19 (s, 1H), 4.20-4.45 (m, 2H), 4.01-4.11 (m, 2H), 3.40 (m, 1H), 3.06 (m, 1H), 1.93-2.29 (m, 2H), 1.14 (t, J=7.2 Hz, 3H).

^{13}C NMR (101 MHz, CHLOROFORM-d) δ 165.3, 163.8, 160.0(d, *J* = 250.5), 153.6, 143.8, 142.0, 139.0(d, *J* = 3.7), 129.5(d, *J* = 8.1), 122.2(d, *J* = 9.5), 121.7, 119.1(d,

J = 24.2), 113.7(d, *J* = 20.5), 94.4, 58.7, 57.5, 50.4, 29.5, 21.6, 13.2. HRMS(EI): m/z calculated for $C_{19}H_{17}BrFN_3O_2S$ $[M+H]^+$: 450.0287, found: 450.0282.

Compound 15b: ethyl 3-(2-chloro-3-fluorophenyl)-1-(thiazol-2-yl)-3,5,6,7 -tetrahydropyrrolo [1,2-c]pyrimidine-4-carboxylate was prepared by the procedure starting with 2-chloro-3-fluorobenzaldehyde, ethyl 3-oxo-6-((tetrahydro-2H-pyran-2-yl)oxy)hexanoate and thiazole-2-carboximidamide hydrochloride. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J=3.2 Hz, 1H), 7.85 (d, J=3.2 Hz, 1H), 7.39 - 7.21 (m, 3H), 6.06 (s, 1H), 4.34 (m, 1H), 4.21 - 4.11 (m, 1H), 4.01 - 3.91 (m, 2H), 3.31 - 3.22 (m, 1H), 3.00 (m, 1H), 2.14 - 1.98 (m, 2H), 1.06 (t, J=7.2 Hz, 3H); HRMS(EI): m/z calculated for $C_{19}H_{17}ClFN_3O_2S$ $[M+H]^+$: 406.0714, found: 406.0714.

Compound 15c: ethyl 3-(2-chloro-5-fluorophenyl)-1-(thiazol-2-yl)-3,5,6,7 -tetrahydropyrrolo [1,2-c]pyrimidine-4-carboxylate was prepared by the procedure starting with 2-chloro-5-fluorobenzaldehyde, ethyl 3-oxo-6-((tetrahydro-2H -pyran-2-yl)oxy)hexanoate and thiazole-2-carboximidamide hydrochloride. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J=3.2 Hz, 1H), 7.85 (d, J=3.2 Hz, 1H), 7.49 (dd, J=5.2, 8.40 Hz, 1H), 7.21 - 7.11 (m, 2H), 6.01 (s, 1H), 4.39 - 4.30 (m, 1H), 4.22 - 4.12 (m, 1H), 4.03 - 3.90 (m, 2H), 3.28 (m, 1H), 2.99 (m, 1H), 2.11 - 1.99 (m, 2H), 1.06 (t, J=7.2 Hz, 3H).

^{13}C NMR (101 MHz, CHLOROFORM-d) δ 166.2, 164.6, 161.8(d, *J* = 245.8), 154.8, 145.2, 144.2(d, *J* = 5.9), 143.1, 130.9(d, *J* = 8.1), 127.9(d, *J* = 2.9), 122.8, 116.5(d, *J* = 23.5), 115.4(d, *J* = 23.5), 94.9, 59.8, 56.9, 51.5, 30.6, 22.5, 14.2. HRMS(EI): m/z calculated for $C_{19}H_{17}BrFN_3O_2S$ $[M+H]^+$: 406.0792, found: 406.0786.

Compound 15d: ethyl 3-(2-chloro-6-fluorophenyl)-1-(thiazol-2-yl)-3,5,6,7 -tetrahydropyrrolo [1,2-c]pyrimidine-4-carboxylate was prepared by the procedure starting with 2-chloro-6-fluorobenzaldehyde, ethyl 3-oxo-6-((tetrahydro-2H-pyran-2-yl)oxy)hexanoate and thiazole-2-carboximidamide hydrochloride. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (br. s., 1H), 7.52-7.68 (m, 1H), 7.16-7.25 (m, 2H), 6.92-7.04 (m, 1H), 6.61 (br. s., 1H), 4.49 (br. s., 1H), 4.28 (br. s., 1H), 4.09 (q, *J*=7.2 Hz, 2H), 3.33 (m, 1H), 3.11 (m, 1H), 2.01-2.25 (m, 2H), 1.17 (t, *J*=7.2 Hz, 3H).

^{13}C NMR (101 MHz, CHLOROFORM-d) δ 165.7, 163.2(d, *J* = 250.9), 153.5, 146.7,

143.7 × 2, 135.1(d, *J* = 5.9), 129.3(d, *J* = 10.3), 126.0(d, *J* = 2.9), 124.1, 114.7× 2(d, *J* = 23.47), 96.4, 60.1, 52.3, 51.6, 30.5, 22.3, 14.1. HRMS(EI): m/z calculated for $C_{19}H_{17}ClFN_3O_2S$ $[M+H]^+$: 406.0792, found: 406.0785.

Compound 15e: ethyl 3-(2,4-difluorophenyl)-1-(thiazol-2-yl)-3,5,6,7 -tetrahydropyrrolo [1,2-c]pyrimidine-4-carboxylate was prepared by the procedure starting with 2,4-difluorobenzaldehyde, ethyl 3-oxo-6-((tetrahydro-2H-pyran-2-yl) oxy)hexanoate and thiazole-2-carboximidamide hydrochloride. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J*=3.2 Hz, 1H), 7.39 (d, *J*=3.2 Hz, 1H), 7.28-7.33 (m, 1H), 6.73-6.84 (m, 2H), 6.02 (s, 1H), 4.39-4.43 (m, 1H), 4.22-4.32 (m, 1H), 4.05-4.11 (m, 2H), 3.31-3.37 (m, 1H), 3.00-3.04 (m, 1H), 2.09-2.21 (m, 1H), 1.97-2.09 (m, 1H), 1.18 (t, *J*=7.2 Hz, 3H); HRMS(EI): m/z calculated for $C_{19}H_{17}F_2N_3O_2S$ $[M+H]^+$: 390.1010, found: 390.1010.

Compound 15f: ethyl 3-(3,4-difluorophenyl)-1-(thiazol-2-yl)-3,5,6,7 -tetrahydropyrrolo [1,2-c]pyrimidine-4-carboxylate was prepared by the procedure starting with 3,4-difluorobenzaldehyde, ethyl 3-oxo-6-((tetrahydro-2H -pyran-2-yl)oxy)hexanoate and thiazole-2-carboximidamide hydrochloride. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.92 (br. s., 1H), 7.45 (br. s., 1H), 7.30-7.38 (m, 1H), 7.21 (d, *J*=8.03 Hz, 1H), 6.17 (s, 1H), 4.71 (br. s., 1H), 4.07-4.35 (m, 3H), 3.69 (m, 1H), 3.17 (br. s., 1H), 2.41 (br. s., 1H), 2.21 (br. s., 1H), 1.21 (t, *J*=7.2 Hz, 3H); HRMS(EI): m/z calculated for $C_{19}H_{17}F_2N_3O_2S$ $[M+H]^+$: 390.1010, found: 390.1010.

Compound 15g: ethyl 3-(4-fluoro-2-methylphenyl)-1-(thiazol-2-yl)-3,5,6,7 -tetrahydropyrrolo [1,2-c]pyrimidine-4-carboxylate was prepared by the procedure starting with 4-fluoro-2-methylbenzaldehyde, ethyl 3-oxo-6-((tetrahydro-2H -pyran-2-yl)oxy)hexanoate and thiazole-2-carboximidamide hydrochloride. HRMS(EI): m/z calculated for $C_{20}H_{20}FN_3O_2S$ $[M+H]^+$: 386.1260, found: 386.1262.

Compound 15h: ethyl 3-(4-fluorophenyl)-1-(thiazol-2-yl)-3,5,6,7-tetrahydropyrrolo [1,2-c]pyrimidine-4-carboxylate was prepared by the procedure starting with 4-fluorobenzaldehyde, ethyl 3-oxo-6-((tetrahydro-2H-pyran-2-yl)oxy)hexanoate and thiazole-2-carboximidamide hydrochloride. 1H NMR (400 MHz, $CDCl_3$) δ 7.86 (br. s., 1H), 7.39 (d, *J*=15.04 Hz, 3H), 6.99 (br. s., 2H), 5.83 (br. s., 1H), 4.05-4.50 (m, 4H),

3.34 (br. s., 1H), 2.99 (br. s., 1H), 1.89-2.27 (m, 2H), 1.25 (br. s., 4H). HRMS(EI): m/z calculated for $C_{19}H_{18}FN_3O_2S$ $[M+H]^+$: 372.1104, found: 372.1104.

Compound 15i: ethyl 3-(3-chloropyridin-4-yl)-1-(thiazol-2-yl)-3,5,6,7 -tetrahydropyrrolo [1,2-c]pyrimidine-4-carboxylate was prepared by the procedure starting with 3-chloroisonicotinaldehyde, ethyl 3-oxo-6-((tetrahydro-2H-pyran-2-yl) oxy)hexanoate and thiazole-2-carboximidamide hydrochloride. LCMS m/z 389.0 $[M + H]^+$; 1H NMR (400 MHz, $CDCl_3$) δ 8.58 (s, 1H), 8.43 (d, J=4.8 Hz, 1H), 7.83 (d, J=3.2 Hz, 1H), 7.39 (d, J=3.2 Hz, 1H), 7.24 (d, J=5.2 Hz, 1H), 6.20 (s, 1H), 4.23-4.54 (m, 2H), 4.06 (m, 2H), 3.41 (m, 1H), 3.08 (m, 1H), 1.97-2.28 (m, 2H), 1.14 (t, J=7.2 Hz, 3H).

^{13}C NMR (101 MHz, CHLOROFORM-d) δ 164.9, 163.3, 154.2, 148.8, 148.8, 147.2, 144.7, 142.1, 129.9, 123.0, 121.9, 92.9, 58.9, 55.6, 50.5, 29.6, 21.5, 13.1. HRMS (EI): m/z calculated for $C_{18}H_{17}ClN_4O_2S$ $[M+H]^+$: 389.0839, found: 389.0830.

Compound 15j: ethyl 3-(3,5-difluoropyridin-2-yl)-1-(thiazol-2-yl)-3,5,6,7 -tetrahydropyrrolo [1,2-c]pyrimidine-4-carboxylate was prepared by the procedure starting with 3,5-difluoropicolinaldehyde, ethyl 3-oxo-6-((tetrahydro-2H -pyran-2-yl)oxy)hexanoate and thiazole-2-carboximidamide hydrochloride. ^1H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, *J*=2.0 Hz, 1H), 7.81-7.91 (m, 1H), 7.38 (d, *J*= 3.2 Hz, 1H), 7.17 (m, 1H), 6.26 (s, 1H), 4.36-4.46 (m, 1H), 4.24-4.36 (m, 1H), 4.07 (m, 2H), 3.29-3.42 (m, 1H), 3.06 (m, 1H), 1.99-2.18 (m, 2H), 1.17 (t, *J*=7.2 Hz, 3H).

^{13}C NMR (101 MHz, CHLOROFORM-d) δ 166.3, 164.8, 158.2(dd, *J* = 260.4, 5.1), 154.9, 155.3(dd, *J* = 265.8, 5.9), 147.5(dd, *J* = 13.6, 4.0), 146.0, 143.1, 133.5(dd, *J* = 22.2, 4.5), 122.5, 111.0(dd, *J* = 23.2, 21.2), 94.0, 59.6, 54.7, 51.3, 30.7, 22.3, 14.2. HRMS(EI): m/z calculated for $C_{18}H_{16}F_2N_4O_2S$ $[M+H]^+$: 391.1040, found : 391.1036.

Compound 15k: ethyl 1,3-di(thiazol-2-yl)-3,5,6,7-tetrahydropyrrolo [1,2-c]pyrimidine -4-carboxylate was prepared by the procedure starting with thiazole-2-carbaldehyde, ethyl 3-oxo-6-((tetrahydro-2H-pyran-2-yl)oxy)hexanoate and thiazole-2-carboximidamide hydrochloride. ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J*=3.2 Hz, 1H), 7.73 (d, *J*=3.2 Hz, 1H), 7.43 (d, *J*=3.2 Hz, 1H), 7.23 (d, *J*=3.2 Hz, 1H), 6.23 (s, 1H), 4.36 (m, 2H), 4.21 (q, *J*=7.04 Hz, 2H), 3.40 (m, 1H), 2.87-3.04 (m,

1H), 1.93-2.20 (m, 2H), 1.26 (t, *J*=7.2 Hz, 3H).

^{13}C NMR (101 MHz, CHLOROFORM-d) δ 174.0, 166.1, 164.3, 154.4, 146.9, 143.2, 142.7, 123.0, 118.7, 95.6, 60.0, 56.8, 51.7, 30.6, 22.5, 14.3. HRMS(EI): m/z calculated for $C_{16}H_{16}N_4O_2S_2$ $[M+H]^+$: 361.0793, found: 361.0788.

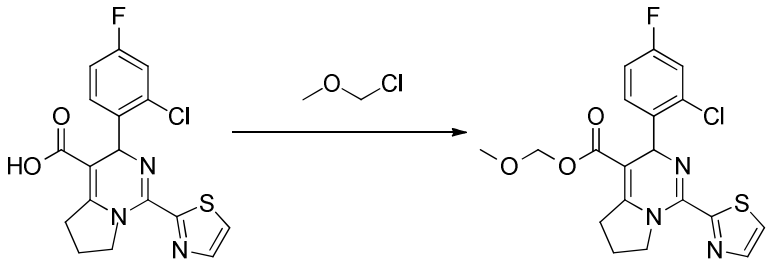
Compound 15l: ethyl 3-(2,5-dichlorothiophen-3-yl)-1-(thiazol-2-yl)-3,5,6,7-tetrahydropyrrolo[1,2-c]pyrimidine-4-carboxylate was prepared by the procedure starting with 2,5-dichlorothiophene-3-carbaldehyde, ethyl 3-oxo-6-((tetrahydro -2H-pyran-2-yl)oxy) hexanoate and thiazole-2-carboximidamide hydrochloride. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, *J*=2.0 Hz, 1H), 7.81-7.91 (m, 1H), 7.38 (d, *J*= 3.2 Hz, 1H), 7.17 (m, 1H), 6.26 (s, 1H), 4.36-4.46 (m, 1H), 4.24-4.36 (m, 1H), 4.07 (m, 2H), 3.29-3.42 (m, 1H), 3.06 (td, *J*=9.04, 18.07 Hz, 1H), 1.99-2.18 (m, 2H), 1.17 (t, *J*=7.2 Hz, 3H); HRMS(EI): m/z calculated for $C_{17}H_{15}Cl_2N_3O_2S_2$ $[M+H]^+$: 427.9983, found: 427.9981.

Compound 15m: ethyl 3-(1-methyl-1H-pyrazol-4-yl)-1-(thiazol-2-yl)-3,5,6,7-tetrahy dropyrrolo[1,2-c]pyrimidine-4-carboxylate was prepared by the procedure starting with 1-methyl-1H-pyrazole-4-carbaldehyde, ethyl 3-oxo-6-((tetrahydro-2H-pyran-2-yl)oxy) hexanoate and thiazole-2-carboximidamide hydrochloride. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83-7.91 (m, 1H), 7.44 (d, *J*=3.2 Hz, 1H), 7.40 (s, 1H), 7.28 (s, 1H), 5.82 (s, 1H), 4.15-4.42 (m, 4H), 3.85 (s, 3H), 3.26-3.37 (m, 1H), 2.86-2.99 (m, 1H), 2.12-2.22 (m, 1H), 1.92-2.07 (m, 1H), 1.30 (t, *J*=7.2 Hz, 3H); HRMS(EI): m/z calculated for $C_{17}H_{19}N_5O_2S$ $[M+H]^+$: 358.1259, found: 358.1259.

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.0, 162.1, 156.2, 154.4, 143.9, 143.2, 142.7, 132.7, 125.2, 123.0, 118.7, 95.6, 60.0, 56.8, 30.6, 22.5, 14.2. HRMS(EI): m/z calculated for $C_{16}H_{16}N_4O_2S_2$ $[M+H]^+$: 361.0793, found: 361.0788.

Example 6: Exemplification of General Synthesis compound **16b**.

Scheme 6: The synthetic route for compound **16b**



16b-1 16b

Step A. methoxymethyl 3-(2-chloro-4-fluorophenyl)-1-(thiazol-2-yl)-3,5,6,7-tetrahydropyrrolo[1,2-c]pyrimidine-4-carboxylate (16b): To a mixture of 3-(2-chloro-4-fluorophenyl)-1-(thiazol-2-yl)-3,5,6,7-tetrahydropyrrolo[1,2-c]pyrimidi ne-4-carboxylic acid (50 mg, 0.12 mmol) and TEA (48 mg, 0.48 mmol) in THF (3 mL) was added chloro(methoxy)methane (19 mg, 0.24 mmol). The resulting mixture was stirred at room temperature for 2 h. Then the mixture was washed with water and extracted with EtOAc. The organic layer was concentrated and purified by column to give methoxymethyl3-(2-chloro-4-fluorophenyl)-1-(thiazol-2-yl)-3,5,6,7-tetrahydro pyrrolo[1,2-c]pyrimidine-4-carboxylate (34 mg, 60.7%). ^{1}H NMR (400MHz, $CDCl_3$) δ 7.76 (d, J=3.2 Hz, 1H), 7.32 (d, J=3.2 Hz, 1H), 7.29 - 7.26 (m, 1H), 7.23 (dd, J=2.8, 8.4 Hz, 1H), 6.93 (m, 1H), 6.15 (s, 1H), 5.19 (d, J=6.0 Hz, 1H), 5.04 (d, *J=6.0* Hz, 1H), 4.43 - 4.32 (m, 1H), 4.28 - 4.18 (m, 1H), 3.41 (m, 1H), 3.06 (m, 1H), 2.20 - 2.08 (m, 1H), 2.06 - 1.93 (m, 1H); HRMS(EI): m/z calculated for $C_{19}H_{17}ClFN_3O_3S$ $[M+H]^+$: 422.0663, found: 422.0665.

^{13}C NMR (101 MHz, CHLOROFORM-d) δ 165.3, 163.8, 160.0(d, *J* = 250.5), 153.6, 143.8, 142.0, 139.0(d, *J* = 3.7), 129.5(d, *J* = 8.1), 122.2(d, *J* = 9.5), 121.7, 119.1(d, *J* = 24.2), 113.7(d, *J* = 20.5), 95.7, 58.7, 57.5, 55.4, 29.5, 21.6, 13.2.

Compound 16a: methyl 3-(2-chloro-4-fluorophenyl)-1-(thiazol-2-yl)-3,5,6,7-tetrahydropyrrolo[1,2-c]pyrimidine-4-carboxylate was prepared by the procedure starting with 3-(2-chloro-4-fluorophenyl)-1-(thiazol-2-yl)-3,5,6,7-tetrahy dropyrrolo[1,2-c]pyrimidine-4-carboxylic acid, and methanol. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J=3.2 Hz, 1H), 7.37 (d, J=3.2 Hz, 1H), 7.28-7.32 (m, 1H), 7.12 (dd, J=2.4, 8.0 Hz, 1H), 6.92 (m, 1H), 6.19 (s, 1H), 4.18 (s, 3H), 4.01-4.11 (m, 2H), 3.40 (m, 1H), 3.06 (m, 1H), 1.93-2.29 (m, 2H); HRMS(EI): m/z calculated for

$C_{18}H_{15}ClFN_3O_2S$ $[M+H]^+$: 392.0558, found: 392.0558.

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2, 164.1, 161.3(d, *J* = 250.5), 156.2, 143.9, 135.9, 133.2, 132.7, 132.0, 122.2(d, *J* = 9.5), 121.7, 119.1(d, *J* = 24.2), 113.7(d, *J* = 20.5), 95.7, 57.5, 52.3, 32.2, 23.2.

Compound 16c: 2-methoxyethyl 3-(2-chloro-4-fluorophenyl)-1-(thiazol-2-yl)-3,5,6,7-tetrahydropyrrolo[1,2-c]pyrimidine-4-carboxylate was prepared by the procedure starting with 3-(2-chloro-4-fluorophenyl)-1-(thiazol-2-yl)-3,5,6,7-tetrahy dropyrrolo[1,2-c]pyrimidine-4-carboxylic acid, and 2-methoxyethanol. ^1H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J=3.2 Hz, 1H), 7.36 (d, J=3.2 Hz, 1H), 7.32 (dd, J=2.4, 8.0 Hz, 1H), 7.28 (d, J=6.4 Hz, 1H), 6.96 (m, 1H), 6.17 (s, 1H), 4.39 (m, 1H), 4.31 - 4.21 (m, 1H), 4.19 - 4.10 (m, 2H), 3.52 - 3.46 (m, 2H), 3.46 - 3.37 (m, 1H), 3.31 - 3.24 (m, 3H), 3.08 (m, 1H), 2.23 - 2.11 (m, 1H), 2.10 - 2.00 (m, 1H); HRMS(EI): m/z calculated for $C_{20}H_{19}ClFN_3O_3S$ $[M+H]^+$: 436.0820, found: 436.0820.

^{13}C NMR (101 MHz, CHLOROFORM-d) δ 165.3, 163.8, 160.0(d, *J* = 250.5), 153.6, 143.8, 142.0, 139.0(d, *J* = 3.7), 129.5(d, *J* = 8.1), 122.2(d, *J* = 9.5), 121.7, 119.1(d, *J* = 24.2), 95.7, 68.3, 64.8, 59.0, 56.0, 54.2, 36.0, 32.0, 23.2.

Compound 16d: 2-(dimethylamino)ethyl 3-(2-chloro-4-fluorophenyl)-1- (thiazol-2-yl) -3,5,6,7-tetrahydropyrrolo[1,2-c]pyrimidine-4-carboxylate was prepared by the procedure starting with 3-(2-chloro-4-fluorophenyl)-1-(thiazol-2-yl) -3,5,6,7-tetrahy dropyrrolo[1,2-c]pyrimidine-4-carboxylic acid, and 2-(dimethylamino) ethanol. ^1H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J=3.2 Hz, 1H), 7.36 (d, J=3.2 Hz, 1H), 7.32 (dd, J=2.4, 8.4 Hz, 1H), 7.26 - 7.21 (m, 1H), 6.96 (m, 1H), 6.15 (s, 1H), 4.42 - 4.34 (m, 1H), 4.31 - 4.22 (m, 1H), 4.16 - 4.06 (m, 2H), 3.49 - 3.38 (m, 1H), 3.07 (td, J=9.2, 18.4 Hz, 1H), 2.52 - 2.41 (m, 2H), 2.17 (s, 7H), 2.11 - 2.01 (m, 1H); HRMS(EI): m/z calculated for $C_{21}H_{22}ClFN_4O_2S$ $[M+H]^+$: 449.1136, found: 449.1134.

^{13}C NMR (101 MHz, CHLOROFORM-d) δ 165.3, 163.8, 160.0(d, *J* = 250.5), 153.6, 143.8, 142.0, 139.0(d, *J* = 3.7), 129.5(d, *J* = 8.1), 122.2(d, *J* = 9.5), 121.7, 119.1(d, *J* = 24.2), 113.5, 95.7, 61.9, 61.3, 56.3, 54.5, 46.7, 32.0, 23.2.

Compound 16e: 2,2-difluoroethyl 3-(2-chloro-4-fluorophenyl)-1-(thiazol-2-yl)-3,5,6,7-tetrahydropyrrolo[1,2-c]pyrimidine-4-carboxylate was prepared by the

procedure starting with 3-(2-chloro-4-fluorophenyl)-1-(thiazol-2-yl)-3,5,6,7 -tetrahydropyrrolo[1,2-c]pyrimidine -4-carboxylic acid, and 2,2-difluoroethanol. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J=3.2 Hz, 1H), 7.37 (d, J=3.2 Hz, 1H), 7.32 (dd, J=2.4, 8.4 Hz, 1H), 7.28 - 7.24 (m, 1H), 6.97 (m, 1H), 6.19 - 6.14 (m, 1H), 5.99 - 5.66 (m, 1H), 4.47 - 4.38 (m, 1H), 4.34 - 4.25 (m, 1H), 4.20 (m, 2H), 3.39 (m, 1H), 3.08 (m, 1H), 2.25 - 2.13 (m, 1H), 2.13 - 2.02 (m, 1H); HRMS(EI): m/z calculated for $C_{19}H_{15}ClF_3N_3O_2S$ $[M+H]^+$: 442.0526, found: 442.0522.

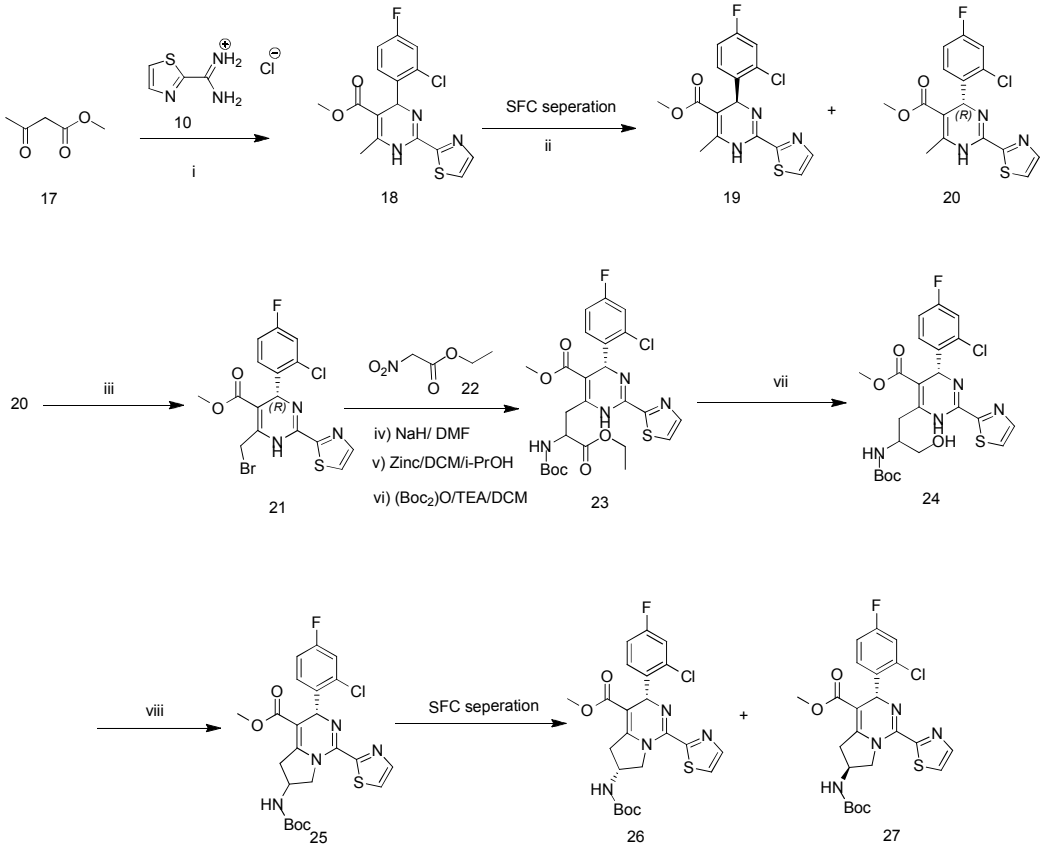
^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2, 164.1, 161.3(d, *J* = 250.5), 156.2, 154.3, 143.9, 135.9, 133.2, 132.7, 132.0, 122.2(d, *J* = 9.5), 121.3, 119.1(d, *J* = 24.2), 113.7(d, *J* = 20.5), 95.7, 73.0, 52.3, 32.2, 23.2.

Compound 16f: 3-(2-chloro-4-fluorophenyl)-N-methoxy-1-(thiazol-2-yl)-3,5,6,7 -tetrahydropyrrolo[1,2-c]pyrimidine-4-carboxamide was prepared by the procedure starting with 3-(2-chloro-4-fluorophenyl)-1-(thiazol-2-yl)-3,5,6,7-tetrahydropyrrolo [1,2-c]pyrimidine-4-carboxylic acid, and O-methylhydroxylamine. ^{1}HNMR (400 MHz, MeOH-d_4) δ 7.91 (d, *J* = 2.4 Hz, 1H), 7.70 (d, *J* = 2.4 Hz, 1H), 7.58 - 7.43 (m, 1H), 7.38 (d, *J* = 8.4 Hz, 1H), 7.20 - 7.06 (m, 1H), 6.01 (s, 1H), 3.57 (s, 3H), 2.81 (s, 2H), 2.14 (s, 3H); HRMS(EI): m/z calculated for $C_{18}H_{16}ClFN_4O_2S$ $[M+H]^+$: 407.0667, found: 407.0667.

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.5, 164.2, 161.3(d, *J* = 250.5), 156.2, 154.3, 143.9, 135.9, 133.2, 132.7, 132.0, 121.5, 119.1(d, *J* = 24.2), 113.7(d, *J* = 20.5), 95.7, 61.1, 52.3, 32.2, 23.2.

Example 7: Exemplification of General Synthesis compound **26&27**

Scheme 7: The synthetic route for compound **26&27**



Step 1: Preparation of Methyl 4-(2-chloro-4-fluorophenyl)-6-methyl-2-(thiazol-2-yl) -1,4-dihydropyrimidine-5-carboxylate(18)

To a solution of thiazole-2-carboximidamide hydrochloride (2.06 g, 6.12 mmol), methyl 3-oxopentanoate (820 mg, 6.31 mmol), 2-chloro-4-fluorobenzaldehyde (1.0 g, 12.61 mmol), sodium acetate (1.58 g, 19.23 mmol) were dissolved in anhydrous EtOH (70 mL). The mixture reaction was refluxed for overnight under N_2 atmosphere. After the reaction was reacted completely, the mixture was cooled to room temperature and concentrated. The residue washed by H_2O (50 mL), extracted by DCM (50 mL x 3). The combined organic layer was evaporated to give a crude product. The crude product was purified by column chromatography on silica gel (Eluent: Petroleum ether: EtOAc from 10:1 to 5:1) to give the desired product **18** (580 mg, yield 24%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77-7.86 (m, 2H), 7.43-7.52 (m, 1H), 7.32-7.38 (m, 1H), 7.11-7.16 (m, 1H), 6.88-6.98 (m, 1H), 6.08-6.23 (m, 1H), 3.78 (s, 3H), 2.50-2.59 (m, 3H); HRMS(EI): m/z calculated for $C_{16}H_{13}ClFN_3O_2S$ $[M+H]^+$: 366.0441, found: 366.0443.

The enantiopure of **20** was obtained through SFC chiral separation of the stereomixtures (**18**) eluting with a mixed solvent of 85% supercritical CO_2/15% EtOH at 100 mL/min rate. The absolute stereochemistry of (−)-enantiomer **20** was determined by its rotation value as reported in patent US2014/343032 A1. Compound **20**: $[\alpha]_D^{20}$ +44.6 (c 0.175, MeOH). Compound **19**: $[\alpha]_D^{20}$ −55.0 (c 0.845, MeOH).

Step 2: Preparation of (R)-methyl 6-(bromomethyl)-4-(2-chloro-4-fluorophenyl)-2-(thiazol-2-yl)-1,4-dihydropyrimidine-5-carboxylate (21): To a solution of **compound 20** (580 mg, 1.53 mmol), NBS (298 mg, 1.68 mmol) and AIBN (50 mg, 0.31 mmol) in 50 mL CCl_4 was heated to reflux for 1 h at N_2 mosphere. After that time, remove the solvent in vaccumn. The residue was diluted with DCM (50 mL * 3) and washed with brine. The organic layer was dried with anhydrous sodium sulfate, filter and concentrate. The residue was purified by column chromatographyon silica gel (Eluent: Petroleum ether: EtOAc from 10:1 to 4:1) to give the desired product **21** (699 mg, yield 54 %). HRMS(EI): m/z calculated for $C_{16}H_{12}BrClFN_3O_2S$ $[M+H]^+$: 444.0556, found: 444.0542.

Step 3. (4R)-methyl 4-(2-chloro-4-fluorophenyl)-6-(3-ethoxy-2-nitro-3-oxopropyl) -2-(thiazol-2-yl)-1,4-dihydropyrimidine-5-carboxylate: To a mixture of ethyl 2-nitroacetate (1.59 g, 11.92 mmol) in DMF (30 mL) was added NaH (214.56 mg, 8.94 mmol) in one portion at r.t. under N2. The mixture was stirred at r.t. for 2 hrs. Then **compound 21** (3.00 g, 5.96 mmol) was added. The mixture was stirred at r.t. overnight. The aqueous phase was extracted with EtOAc (40 mL × 3). The combined organic phase was washed with saturated brine (20 mL × 2), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography to afford (4R)-methyl 4-(2-chloro-4-fluorophenyl)-6-(3-ethoxy -2-nitro-3-oxopropyl)-2-(thiazol-2-yl)-1,4-dihydropyrimidine-5-carboxylate (2.60 g, 78.55% yield). HRMS(EI): m/z calculated for $C_{20}H_{18}ClFN_4O_6S$ $[M+H]^+$: 497.0620, found: 497.0620.

Step 4. (4R)-methyl 6-(2-amino-3-ethoxy-3-oxopropyl)-4-(2-chloro

-4-fluorophenyl)-2-(thiazol-2-yl)-1,4-dihydropyrimidine-5-carboxylate: To a mixture of (4R)-methyl 4-(2-chloro-4-fluorophenyl)-6-(3-ethoxy-2-nitro -3-oxopropyl) -2-(thiazol-2-yl)-1,4-dihydropyrimidine-5-carboxylate (500.00 mg, 900.30 umol) in DCM (10 mL) and i-PrOH (100 mL) was added Zn (588.71 mg, 9.00 mmol) in one portion at r.t. under N_2. The mixture was stirred at r.t. for overnight. The mixture filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (Petroleum ether / EtOAc = 100 / 1, 1 / 20) to afford **(4R)-methyl 6-(2-amino-3-ethoxy-3-oxopropyl)-4-(2-chloro-4-fluorophenyl)-2-(thiazol-2-yl)-1, 4-dihydropyrimidine-5-carboxylate** (200.00 mg, 42.28% yield). HRMS(EI): m/z calculated for $C_{20}H_{20}ClFN_4O_4S$ $[M+H]^+$: 467.0876, found: 467.0876.

Step 5. (4R)-methyl 6-(2-((tert-butoxycarbonyl)amino)-3-ethoxy-3-oxopropyl)-4-(2-chloro-4-fluorophenyl)-2-(thiazol-2-yl)-1,4-dihydropyrimidine-5-carboxylate (23): To a mixture of (4R)-methyl 6-(2-amino-3-ethoxy-3-oxopropyl)-4-(2-chloro-4-fluorophenyl)-2-(thiazol-2-yl)-1,4-dihydropyrimidine-5-carboxylate (200.00 mg, 0.38 mmol) in DCM (20 mL) was added TEA (115.56 mg, 1.14 mmol) and Boc_2O(124.62 mg, 0.57 mmol) in one portion at r.t. under N_2. The mixture was stirred at r.t. overnight. The aqueous phase was extracted with DCM (20 mL × 3). The combined organic phase was washed with saturated brine (20 mL × 2), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (column height: 250 mm, diameter: 100 mm, 100-200 mesh silica gel, Petroleum ether / EtOAc = 50 / 1, 5 / 1) to afford **compound 23** (200.00 mg, 83.99% yield). HRMS(EI): m/z calculated for $C_{25}H_{28}ClFN_4O_6S$ $[M+H]^+$: 567.1402, found: 567.1402.

Step 6. (4R)-methyl 6-(2-((tert-butoxycarbonyl)amino)-3-hydroxypropyl) -4-(2-chloro-4-fluorophenyl)-2-(thiazol-2-yl)-1,4-dihydropyrimidine-5-carboxylate(24): To a mixture of **compound 23**(100.00 mg, 160 umol) in THF (10 mL) was added $NaBH_4$ (6.05 mg, 160 umol) in one portion at r.t. under N_2. The mixture was stirred at r.t. for 10 min. Then heated to 80 ^oC and stirred for 6 hours. The mixture was cooled to r.t. and concentrated in reduced pressure at 60 ^oC. The residue was poured into ice-water (w/w = 1/1) (150 mL) and stirred for 20 min. The aqueous

phase was extracted with EtOAc (40 Ml × 3). The combined organic phase was washed with saturated brine (20 mL × 2), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (column height: 250 mm, diameter: 100 mm, 100-200 mesh silica gel, Petroleum ether / EtOAc = 30 / 1 to 20 / 1) to afford **compound 24** (70.00 mg, 75.04% yield). HRMS(EI): m/z calculated for $C_{23}H_{26}ClFN_4O_5S$ $[M+H]^+$: 525.1296, found: 525.1296.

Step 7. (3R)-methyl 6-((tert-butoxycarbonyl)amino)-3-(2-chloro-4-fluorophenyl) -1-(thiazol-2-yl)-3,5,6,7-tetrahydropyrrolo[1,2-c]pyrimidine-4-carboxylate (25): To a mixture of **compound 24** (60.00 mg, 102.83 umol) in DCM (15 mL), was added MsCl (29.41 mg, 154.25 umol) in one portion at r.t. under N_2. The mixture was stirred at r.t. for 10 min. Then heated to 45 ^oC and stirred for 6 hours. The mixture was cooled to r.t. and concentrated in reduced pressure at 60 ^oC. The residue was poured into ice-water (w/w = 1/1) (150 mL) and stirred for 20 min. The aqueous phase was extracted with EtOAc (20 mL × 3). The combined organic phase was washed with saturated brine (10 mL × 2), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (column height: 250 mm, diameter: 100 mm, 100-200 mesh silica gel, Petroleum ether / EtOAc = 30 / 1, 5 / 1) to afford **compound 25** (30.00 mg, 51.59% yield). HRMS(EI): m/z calculated for $C_{23}H_{24}ClFN_4O_4S$ $[M+H]^+$: 507.1191, found: 507.1191.

Step 8. compound 26 and 27 was separated by SFC: Methyl(3R)-3-(2-bromo-4-fluoro-phenyl)-6-(tert-butoxycarbonylamino)-1-thiazol-2-y l-3,5,6,7-tetrahydropyrrolo[1,2-c]pyrimidine-4-carboxylate (30.00 mg, 53.06 umol) was separated by SFC to give (3R,6R)-methyl 3-(2-bromo-4-fluorophenyl) -6-((tert-butoxycarbonyl)amino)-1-(thiazol-2-yl)-3,5,6,7-tetrahydropyrrolo[1,2-c]pyri midine-4-carboxylate (5 mg) and (3R,6S)-methyl 3-(2-bromo-4-fluorophenyl) -6-((tert-butoxycarbonyl)amino)-1-(thiazol-2-yl)-3,5,6,7-tetrahydropyrrolo[1,2-c]pyri midine-4-carboxylate (10 mg) .

SFC method

Instrument: MG-II

Column: Chiralcel OJ 250×30 mm I.D., 5um
Mobile phase: Supercritical CO_2/MEOH(0.1%NH3H2O) = 75/25 at 60 mL/min

Column Temp: 38 ^oC

Nozzle Pressure: 100 Bar

Nozzle Temp: 60 ^oC

Evaporator Temp: 20 ^oC

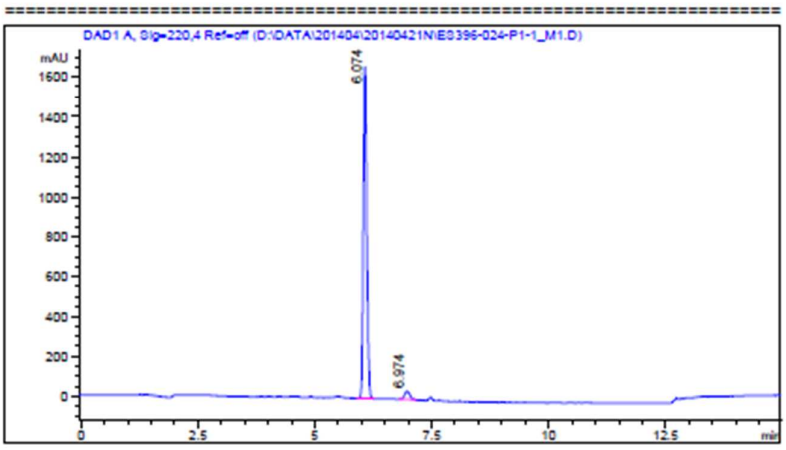
Trimmer Temp: 25 ^oC

Wavelength: 220 nm

26: (3R,6R)-methyl 6-((tert-butoxycarbonyl)amino)-3-(2-chloro-4-fluorophenyl) -1-(thiazol-2-yl)-3,5,6,7-tetrahydropyrrolo[1,2-c]pyrimidine-4-carboxylate (26):

^1H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J*=3.2 Hz, 1H), 7.37 (d, *J*=3.2 Hz, 1H), 7.31 (dd, *J*=2.8, 8.4 Hz, 1H), 7.24 - 7.20 (m, 1H), 6.97 (m, 1H), 6.15 (s, 1H), 4.74 (br. s., 1H), 4.46 (d, *J*=8.0 Hz, 1H), 4.35 - 4.29 (m, 1H), 3.85 (s, 3H), 3.58 (m, 1H), 3.08 (m, 2H), 1.46 (s, 9H); HRMS(EI): m/z calculated for $C_{23}H_{24}ClFN_4O_4S$ $[M+H]^+$: 507.1191, found: 507.1191; SFC: RT = 6.07 min.

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2, 164.1, 161.3(d, *J* = 250.5), 156.2, 155.2, 154.3, 143.9, 135.9, 133.2, 132.7, 132.0, 122.2(d, *J* = 9.5), 121.3, 119.1(d, *J* = 24.2), 95.7, 79.5, 70.3, 58.9, 52.3, 41.4, 28.4.



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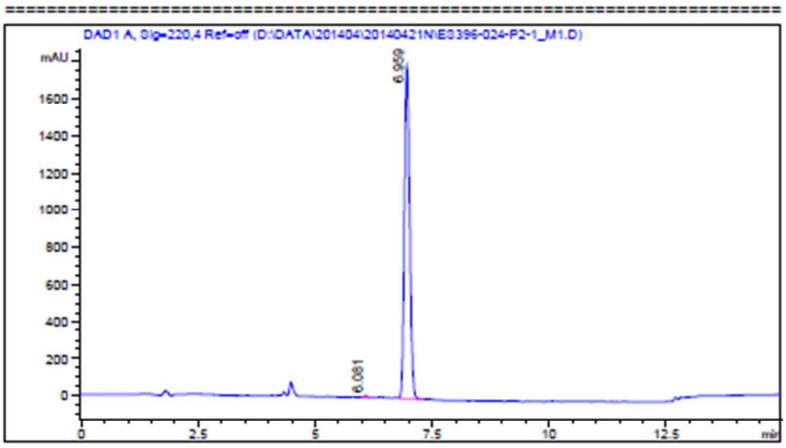
#	Meas. Ret. Time	Height	Height %	Width	Area	Area %
1	6.074	1.666e3	97.548	0.086	8.604e3	96.376
2	6.974	41.878	2.452	0.129	323.503	3.624

27: (3R,6S)-methyl 6-((tert-butoxycarbonyl)amino)-3-(2-chloro-4-fluorophenyl)-

1-(thiazol-2-yl)-3,5,6,7-tetrahydropyrrolo[1,2-c]pyrimidine-4-carboxylate:

^{1}H NMR (400MHz, $CDCl_3$) □δ: 7.80 (d, J=3.2 Hz, 1H), 7.37 (d, J=3.2 Hz, 1H), 7.35 - 7.27 (m, 2H), 6.99 (dt, J=2.4, 8.0 Hz, 1H), 6.16 (s, 1H), 4.77 (br. s., 1H), 4.42 (s, 2H), 3.85 (s, 3H), 3.42 - 3.27 (m, 2H), 1.51 - 1.41 (m, 9H); HRMS(EI): m/z calculated for $C_{23}H_{24}ClFN_4O_4S$ $[M+H]^+$: 507.1191, found: 507.1191; SFC: RT = 6.95 min.

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2, 164.1, 161.3(d, *J* = 250.5), 156.2, 155.2, 154.3, 143.9, 135.9, 133.2, 132.7, 132.0, 122.2(d, *J* = 9.5), 121.3, 119.1(d, *J* = 24.2), 95.7, 79.5, 70.3, 58.9, 52.3, 41.4, 28.4.

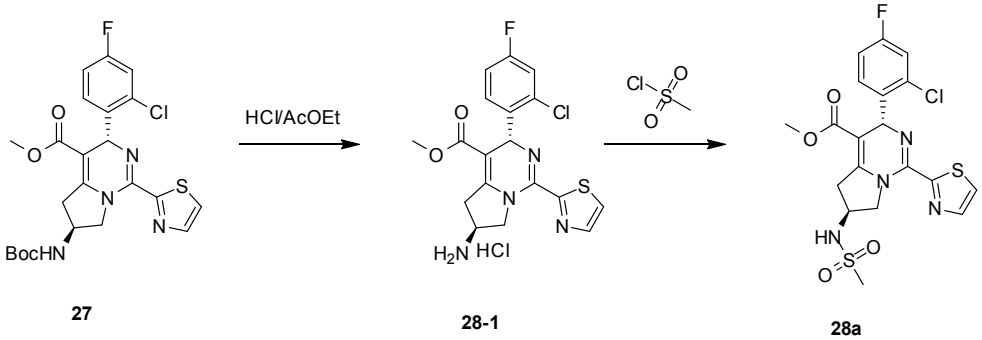


DAD1 A, Sig=220,4 Ref=off

#	Meas. Ret. Time	Height	Height %	Width	Area	Area %
1	6.081	8.128	0.451	0.078	40.210	0.283
2	6.959	1.793e3	99.549	0.124	1.419e4	99.717

Example 8: Exemplification of General Synthesis compound **28a**.

Scheme 8: The synthetic route for compound **28a**



27 28-1 28a

Step 1. (3R,6S)-methyl 6-amino-3-(2-chloro-4-fluorophenyl)-1-(thiazol-2-yl)-

3,5,6,7-tetrahydropyrrolo[1,2-c]pyrimidine-4-carboxylate(28-1): To a mixture of **27** (100.00 mg, 0.19 mmol) in AcOEt (3 mL) was added HCL/AcOEt (3 mL) in one portion at r.t. under N_2. The mixture was stirred at r.t. overnight. The mixture was concentrated in reduced pressure to give (3R,6S)-methyl 6-amino-3-(2-chloro-4 -fluorophenyl)-1-(thiazol-2-yl)-3,5,6,7-tetrahydropyrrolo[1,2-c]pyrimidine-4-carboxyl ate (80.00 mg, 84.04% yield), which was used to next step without any purification; HRMS(EI): m/z calculated for $C_{18}H_{16}ClFN_4O_2S$ $[M+H]^+$: 407.0667, found: 407.0663;

Step 2. (3R,6S)-methyl 3-(2-chloro-4-fluorophenyl)-6-(methylsulfonamido)-1-(thiazol-2-yl)-3,5,6,7-tetrahydropyrrolo[1,2-c]pyrimidine-4-carboxylate(28a): To a mixture of methyl (3R,6S)-6-amino-3-(2-chloro-4-fluoro-phenyl)-1-thiazol-2-yl-3,5,6,7-tetrahydropyrrolo[1,2-c]pyrimidine-4-carboxylate (100.00 mg, 245.78 umol, 1.00 Eq) and TEA (74.61 mg, 737.34 umol) in DCM (3 mL) was added MsC l (56.31 mg, 491.56 umol, 2.00 Eq) in one portion at 25°C under N_2. The mi xture was stirred at 25°C for 15 hours. LCMS showed the reaction was comple ted. The mixture was washed with water (10 mL) and stirred for 5 min. The a queous phase was extracted with DCM (10 mL*3). The combined organic pha se was washed with saturated brine (10 mL), dried with anhydrous Na_2SO_4, fi ltered and concentrated in vacuum. The residue was purified by preparative TL C (Petroleum ether/Ethyl acetate=1/1) to afford **28a (3R,6S)-methyl 3-(2-chlor o-4-fluorophenyl)-6-(methylsulfonamido)-1- (thiazol-2-yl)-3,5,6,7-tetrahydropyr rolo[1,2-c]pyrimidine-4-carboxylate** (15.00 mg, 30.93 umol, 12.58% yield, 100% purity) as pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) : 7.82 (d, J=3.2 Hz, 1H), 7.40 (d, J = 3.2 Hz, 1H), 7.23 (dd, J = 6.4, 8.4 Hz, 1H), 7.14 (dd, J = 2.4, 8.4 Hz, 1H), 6.93 (m, 1H), 6.16 (s, 1H), 4.81 (d, J=7.2 Hz, 1H), 4.60-4. 45 (m, 2H), 4.37-4.24 (m, 1H), 3.67(m, 1H), 3.61 (s, 3H), 3.16 (m, 1H), 3.07 (s, 3H). HRMS calculated for $C_{19}H_{18}ClFN_4O_4S_2$ $[M+H]^+$:485.0520, found: 485. 0520. ^{13}C NMR (101 MHz, CHLOROFORM-d) δ 169.4, 166.1, 164.8(d, *J* = 252.1), 157.0, 151.9, 150.8, 143.8(d, *J* = 3.7), 143.2(d, *J* = 8.1), 130.2(

d, *J* = 8.7), 123.0, 117.7(d, *J* = 23.2), 114.3(d, *J* = 21.7), 94.4, 58.7, 57. 5, 50.4, 29.5, 21.6, 13.2.

Compound 28b: (3R,6R)-methyl 3-(2-chloro-4-fluorophenyl)-6-(methyl sulfona mido)-1-(thiazol-2-yl)-3,5,6,7-tetrahydropyrrolo[1,2-c]pyrimidine-4-carboxylate:

^{1}H NMR (400 MHz, $CDCl_3$) δ : 7.84 (d, J=3.2 Hz, 1H), 7.41 (d, J=3.2 Hz, 1H), 7.33 (dd, J=6.0, 8.4 Hz, 1H), 7.16 (dd, J=2.4, 8.4 Hz, 1H), 6.98 (m, 1H), 6.20 (s, 1H), 4.72 (d, J=6.2 Hz, 1H), 4.57-4.65 (m, 1H), 4.45-4.54 (m, 1H), 4.29-4.40 (m, 1H), 4.08 (q, J=7.2 Hz, 2H), 3.47-3.56 (m, 1H), 3.32-3.43 (m, 1 H), 3.08 (s, 3H), 1.17 (t, J=7.2 Hz, 3H). LCMS m/z: 485.2 $[M+H]^+$; HRMS c alculated for $C_{19}H_{18}ClFN_4O_4S_2$ $[M+H]^+$:485.0520, found: 485.0520.

Compound 29a: (3R,6S)-ethyl 3-(2-chloro-4-fluorophenyl)-6-(methylsulfon am ido)-1-(thiazol-2-yl)-3,5,6,7-tetrahydropyrrolo[1,2-c]pyrimidine-4-carboxylate:

^{1}H NMR (400MHz, $CDCl_3$) δ : 7.84 (d, J=3.2 Hz, 1H), 7.41 (d, J=3.2 Hz, 1 H), 7.24-7.28 (m, 1H), 7.15 (dd, J=2.4, 8.4 Hz, 1H), 6.96 (dt, J=2.4, 8.0 Hz, 1H), 6.19 (s, 1H), 4.76 (d, J=7.2 Hz, 1H), 4.47-4.60 (m, 2H), 4.32 (s, 1H), 4. 07 (q, J=7.2 Hz, 2H), 3.68 (m, 1H), 3.19 (m, 1H), 3.09 (s, 3H), 1.15 (t, J=7. 2 Hz, 3H); HRMS calculated for $C_{20}H_{20}ClFN_4O_4S_2$ $[M+H]^+$: 499.0599, found: 499.0599.

Compound 29b: (3R,6R)-ethyl 3-(2-chloro-4-fluorophenyl)-6-(methylsulfon am ido)-1-(thiazol-2-yl)-3,5,6,7-tetrahydropyrrolo[1,2-c]pyrimidine-4-carboxylate:

^{1}H NMR (400 MHz, $CDCl_3$) δ : 7.84 (d, J=3.2 Hz, 1H), 7.41 (d, J=3.2 Hz, 1 H), 7.33 (dd, J=6.4, 8.4 Hz, 1H), 7.16 (dd, J=2.4, 8.4 Hz, 1H), 6.98 (dt, J=2. 4, 8.4 Hz, 1H), 6.20 (s, 1H), 4.72 (d, J=6.4 Hz, 1H), 4.57-4.65 (m, 1H), 4.45-4.54 (m, 1H), 4.29-4.40 (m, 1H), 4.08 (q, J=7.2 Hz, 2H), 3.47-3.56 (m, 1H), 3.32-3.43 (m, 1H), 3.08 (s, 3H), 1.17 (t, J=7.2 Hz, 3H). HRMS calculated for $C_{20}H_{20}ClFN_4O_4S_2$ $[M+H]^+$: 499.0599, found: 499.0599.

Compound 30: (3R,6S)-methyl 6-(methylsulfonamido)-1-(thiazol-2-yl)-3-(2,3,4-trifluorophenyl)-3,5,6,7-tetrahydropyrrolo[1,2-c]pyrimidine-4-carboxylate:

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.85 (d, *J*=3.2 Hz, 1H), 7.42 (d, *J*=3.2 Hz, 1 H), 6.98-7.06 (m, 1H), 6.87-6.95 (m, 1H), 5.98 (s, 1H), 4.92 (d, *J*=7.2 Hz, 1 H), 4.48-4.60 (m, 2H), 4.28 (sxt, *J*=6.93 Hz, 1H), 3.64 (s, 3H), 3.55-3.62 (m, 1H), 3.13 (m, 1H), 3.07 (s, 3H); HRMS calculated for $C_{19}H_{17}F_3N_4O_4S_2$ $[M+H]^+$: 487.0643, found: 487.0643.

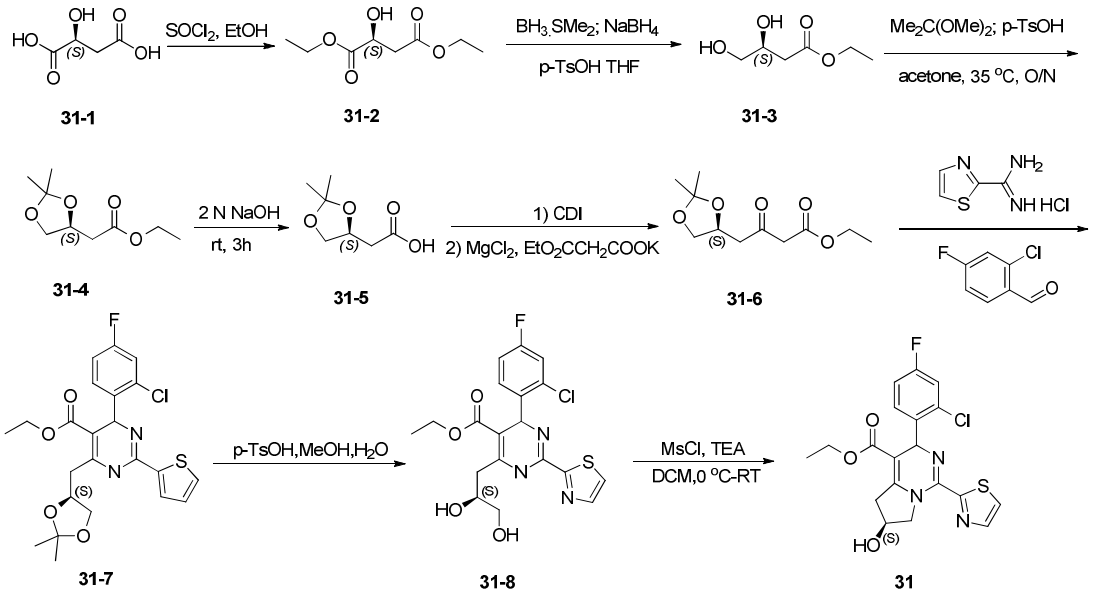
Compound 32: (3R,6S)-ethyl 3-(2-bromo-4-fluorophenyl)-6-(dimethylamino)-1-(thiazol-2-yl)-3,5,6,7-tetrahydropyrrolo[1,2-c]pyrimidine-4-carboxylate:

To a mixture of ethyl (3R, 6S)-6-amino-3-(2-bromo-4-fluoro-phenyl)-1-thiazol-2-yl-3,5,6,7-tetrahydropyrrolo[1,2-c]pyrimidine-4-carboxylate (80.00 mg, 0.17 mmol, 1.0 eq) in DCM (5 mL) , was added TEA(17 mg, 0.17 mmol, 1.0 eq), (HCHO)n (25 mg, 0.85 mmol, 5.00 Eq) and $NaBH(OAc)_3$ (109. mg, 0.51 m mol, 3.00 eq) in one portion at r.t. under N_2.The mixture was stirred at r.t. for 10 min. Then heated to 45 ^oC and stirred overnight .The mixture was cooled to r.t. and concentrated in reduced pressure at 60 ^oC. The residue was poured into ice-water (w/w = 1/1) (150 mL) and stirred for 20 min. The aqueous phase was extracted with EtOAc (20 mL*3). The combined organic phase was washed with saturated brine (10 mL*2), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatogr aphy to afford **32** (3R,6S)-ethyl 3-(2-bromo-4-fluorophenyl)-6-(dimethylamino)-1-(thiazol-2-yl)-3,5,6,7-tetrahydropyrrolo[1,2-c]pyrimidine-4-carboxylate (20.00 mg, 0.04 mmol, yield 23.58%).

^{1}H NMR (400MHz, $CDCl_3$) δ: 7.81 (d, J=3.2 Hz, 1H), 7.36 (d, J=3.2 Hz, 1H), 7.31 (dd, J=2.4, 8.4 Hz, 1H), 7.26 - 7.23 (m, 1H), 6.96 (m, 1H), 6.14 (s, 1 H), 4.55 (m, 1H), 4.14 - 4.06 (m, 1H), 4.05 - 3.97 (m, 2H), 3.63 (m, 1H), 3. 05 - 2.89 (m, 2H), 2.34 (s, 6H), 1.14 (t, J=7.2 Hz, 3H); HRMS calculated for $C_{21}H_{22}BrFN_4O_2S$ $[M+H]^+$: 493.0631, found: 493.0631.

Example 7: Exemplification of General Synthesis compound **31.**

Scheme 7: The synthetic route for compound **31**



Step 1. (S)-diethyl 2-hydroxysuccinate(31-2): To a solution of (S)-2-hydroxysuccinic acid (80 g, 600 mmol) in EtOH (500 mL) was added $SOCl_2$ (100 mL, 1.5 mol) at 0 °C, then stirred at 0 °C for 20 min. The resulting solution was warmed to 35 °C and stirred overnight. After the reaction was completed, the solvent was removed in vacuo and the residue was portioned between EtOAc and Sat. $NaHCO_3$. The aqueous was extracted with EtOAc, washed with brine, dried and concentrated in vacuo. Purified by column chromatograph to give the desired compound (113 g, yield 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.47 (q, J=4.8 Hz, 1H), 4.26 (dq, J=2.4, 7.2 Hz, 2H), 4.16 (q, J=7.2 Hz, 2H), 3.28 (d, J=4.8 Hz, 1H), 2.72-2.89 (m, 2H), 1.20-1.34 (m, 6H).

Step 2. (S)-ethyl 3,4-dihydroxybutanoate(31-3): To a solution of (S)-diethyl 2-hydroxysuccinate (30 g, 158 mmol) in dry THF (400 mL) was added dropwise $BH_3.Me_2S$ (16.5 mL, 165 mmol) at room temperature for 1 h. The solution was stirred at room temperature until the evolution of H_2 ceased. Then the flask was cooled to ice-bath and stirred was continued for 30 min. To the solution was added $NaBH_4$ (300

mg, 8 mmol) in one portion (exothermic) under vigorous stirring at this temperature for 30 min, and then stirred at room temperature for overnight. To the reaction mixture was added EtOH (80 mL) and p-TsOH (450 mg, 4 mmol). The mixture was stirred another 30 min at room temperature, followed by concentration to give a colorless gum, which purified by column chromatograph (Petroleum ether -EtOAc= 1:1) to give the desired compound (13.6 g, yield 60%).

Step 3. (S)-ethyl 2-(2,2-dimethyl-1,3-dioxolan-4-yl)acetate(31-4): To a solution of (S)-ethyl 3,4-dihydroxybutanoate (15 g, 100 mmol) in acetone (200 mL) was added 2,2-dimethoxypronae (21 g, 200 mmol) and p-TsOH (350 mg, 2 mmol). The reaction was stirred at 30 °C for overnight. The solvent was removed and the residue was purified by column chromatograph to give the desired compound (12 g, yield 64%).^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.48 (q, *J*=6.4 Hz, 1H), 4.09-4.24 (m, 3H), 3.66 (dd, *J*=6.0, 8.4 Hz, 1H), 2.72 (m, 1H), 2.52 (m, 1H), 1.42 (s, 3H), 1.37 (s, 3H), 1.27 (t, *J*=7.2 Hz, 3H).

Step 4. (S)-2-(2,2-dimethyl-1,3-dioxolan-4-yl)acetic acid(31-5): To an ice-cooled aqueous 2N NaOH solution (32.9 mL, 65.88 mmol) was added (S)-ethyl 2-(2,2-dimethyl-1,3-dioxolan-4-yl)acetate (6.20 g, 32.94 mmol) with stirring. The bath was removed and the resultant mixture was stirred at room temperature for 3 h. The mixture was extracted with DCM (3 × 50 mL) and the organic extracts were discarded. The water layer was mixed with EtOAc and cooled in an ice bath. To this mixture an aqueous $NaHSO_4$ solution (2 N) was added. The mixture was vigorously stirred for 15 min. The organic layer was separated and the water layer was additionally extracted with EtOAc (2 × 50 mL). The combined organic extracts were dried over Na_2SO_4, filtered and evaporated to give (S)-2-(2,2-dimethyl-1,3-dioxolan-4-yl)acetic acid (4.2 g, yield :79.5 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.49 (q, *J*=6.4 Hz, 1H), 4.18 (dd, *J*=6.0, 8.0 Hz, 1H), 3.68 (dd, *J*=6.0, 8.4 Hz, 1H), 2.70-2.80 (m, 1H), 2.54-2.64 (m, 1H), 1.44 (s, 3H), 1.37 (s, 3H).

Step 5.: (S)-ethyl 4-(2,2-dimethyl-1,3-dioxolan-4-yl)-3-oxobutanoate(31-6): To a solution of (S)-2-(2,2-dimethyl-1,3-dioxolan-4-yl)acetic acid (1.00 g, 6.24 mmol) in THF(17 mL) was added CDI (1.21 g, 7.49 mmol) in one portion. The suspension was

stirred under a stream of N_2 for 1 h, then a bollon full of N_2 was placed on the flask. The solution was stirred at room temperature for 3 h before a mixture of $MgCl_2$ (594 mg, 6.24 mmol), potassium 3-ethoxy-3-oxopropanoate (2.12 g, 12.48 mmol) and TEA (1.26 g, 12.49 mmol) were added under N_2. The mixture was stirred at room temperature overnight. Then the mixture was acidified with 1.0 N HCl to pH = 5, extracted with EtOAc, washed with sat. NaCl, dried over Na_2SO_4, filtered and evaporated. The crude product was purified by silica column chromatography (hexane:EtOAc=5:1) to give (S)-ethyl 4-(2,2-dimethyl-1,3-dioxolan-4-yl)-3-oxobutanoate (336 g, yield :23.3 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.48 (q, *J*=6.40 Hz, 1H), 4.16-4.25 (m, 3H), 3.57 (dd, *J*=6.8, 8.4 Hz, 1H), 3.49 (s, 2H), 3.00 (m, 1H), 2.75 (m, 1H), 1.39-1.44 (m, 3H), 1.33-1.38 (m, 3H), 1.27-1.32 (m, 3H).

Step 6: ethyl 4-(2-chloro-4-fluorophenyl)-6-(((S)-2,2-dimethyl-1,3-dioxolan -4-yl)methyl)-2-(thiophen-2-yl)-1,4-dihydropyrimidine-5-carboxylate(31-7): To a solution of 2-chloro-4-fluorobenzaldehyde (438 mg, 2.76 mmol) in EtOH (25 mL) was added (S)-ethyl 4-(2,2-dimethyl-1,3-dioxolan-4-yl)-3-oxobutanoate (636 mg, 2.76 mmol), thiazole-2- carboximidamide hydrochloride (542 mg, 3.31 mmol) and sodium acetate (566 g, 6.91 mmol). The mixture was stirred at 85 ^{o}C overnight under N_2 atmosphere. Then the mixture was concentrated in vacuum to give crude product. The crude product was purified by silica column chromatography (hexane : EtOAc = 3:1) to give ethyl 4-(2-chloro-4-fluorophenyl) -6-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl) methyl)-2-(thiophen-2-yl)-1,4-dihydropyrimidine-5-carboxylate (720 mg, yield: 54.1 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.77 (br. s., 1H), 7.82 (br. s., 1H), 7.37-7.48 (m, 2H), 7.13 (d, *J*=8.4 Hz, 1H), 6.94 (d, *J*=7.2 Hz, 1H), 6.22 (s, 1H), 4.42-4.56 (m, 1H), 4.19 (t, *J*=7.2 Hz, 1H), 3.98-4.08 (m, 2H), 3.78 (t, *J*=7.2 Hz, 1H), 3.61 (m, 1H), 3.04 (m, 1H), 1.47-1.57 (m, 3H), 1.38-1.44 (m, 3H), 1.13 (t, *J*=7.03 Hz, 3H). HRMS(EI): m/z calculated for $C_{23}H_{24}ClFN_2O_4S$ $[M+H]^+$: 479.1129, found: 479.1129.

Step 7.: ethyl 4-(2-chloro-4-fluorophenyl)-6-((S)-2,3-dihydroxypropyl) -2-(thiazol-2-yl) -1,4-dihydropyrimidine-5-carboxylate(31-8): To a solution of ethyl 4-(2-chloro-4-fluorophenyl)-6-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-2-(thiophen-2-yl)-1,4-dihydropyrimidine-5- carboxylate (340 mg, 0.71 mmol) in MeOH

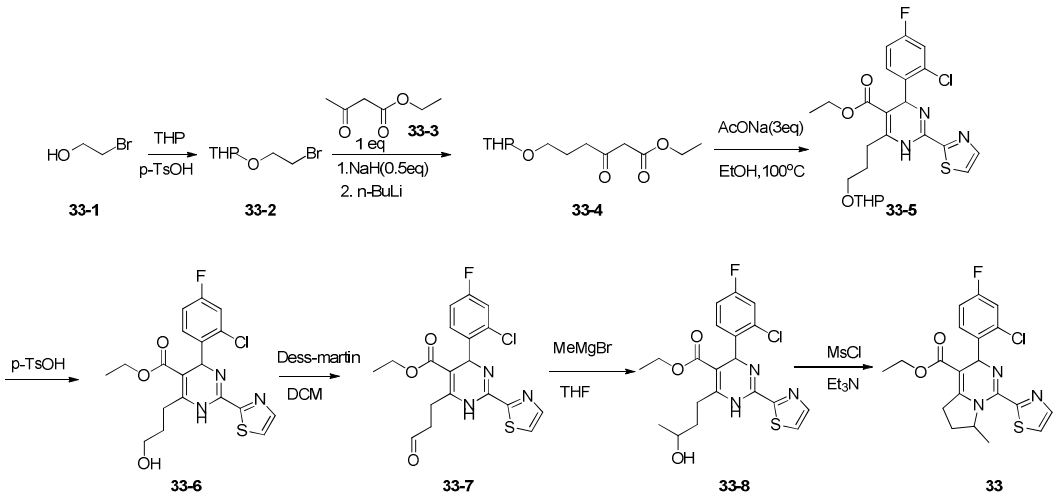
(6.8 mL) was added 4-methylbenzenesulfonic acid hydrate (81 mg, 0.43 mmol) and H_2O (2.0 mL). The mixture was stirred at 65 ^oC overnight. Then the mixture was neutralized with TEA and concentrated to remove MeOH. The mixture was extracted with EtOAc, dried over Na_2SO_4, filtered and evaporated. The crude product was purified by silica column chromatography (DCM : MeOH = 20 : 1) to give ethyl 4-(2-chloro-4-fluorophenyl)-6-((S)-2,3-dihydroxypropyl)-2-(thiazol-2-yl)-1,4-dihydro pyrimidine-5-carboxylate (214 mg, yield: 68.6 %).

^1H NMR (400 MHz, $CDCl_3$) δ: 7.80-7.90 (m, 1H), 7.56 (br. s., 1H), 7.42 (dd, *J*=6.2, 8.4 Hz, 1H), 7.16 (d, *J*=7.2 Hz, 1H), 6.90-7.05 (m, 1H), 6.08-6.25 (m, 1H), 4.66 (br. s., 1H), 4.17-4.29 (m, 1H), 4.07 (d, *J*=7.2 Hz, 2H), 3.71 (br. s., 2H), 3.30-3.53 (m, 1H), 2.88-3.26 (m, 2H), 1.06-1.19 (m, 3H); HRMS(EI): m/z calculated for $C_{19}H_{19}ClFN_3O_4S$ $[M+H]^+$: 440.0769, found: 440.0769.

Step 8.: (*6S*)-ethyl 3-(2-chloro-4-fluorophenyl)-6-hydroxy-1-(thiazol-2-yl) -3,5,6,7 -tetrahydropyrrolo[1,2-c]pyrimidine-4-carboxylate(31): To a solution of ethyl 4-(2-chloro-4-fluorophenyl)-6-((S)-2,3-dihydroxypropyl)-2-(thiazol-2-yl)-1,4-dihydro pyrimidine-5 -carboxylate (199 mg, 0.45 mmol) in dry DCM (5 ml) was added TEA (69 mg, 0.68 mmol) and MsCl (52 mg, 0.45 mmol) at 0 ^oC. After stirring at 0 ^oC for 1.5 h, the mixture was allowed to stir at room temperature for 18 h. The reaction mixture was extracted with DCM, dried over Na_2SO_4, filtered and concentrated. The crude product was purified by silica column chromatography (hexane : EtOAc = 1:1) and pre-HPLC to give (*6S*)-ethyl 3-(2-chloro-4-fluorophenyl)-6-hydroxy-1 -(thiazol-2-yl)-3,5,6,7-tetrahydropyrrolo[1,2-c]- pyrimidine-4-carboxylate (3 mg). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.82 (d, *J*=3.2 Hz, 1H), 7.38 (d, *J*=3.2 Hz, 1H), 7.28-7.32 (m, 1H), 7.12 (dd, *J*=2.4, 8.4 Hz, 1H), 6.92 (m, 1H), 6.21 (s, 1H), 4.59-4.72 (m, 2H), 4.29 (m, 1H), 4.03 (m, 2H), 3.38-3.50 (m, 1H), 3.25-3.37 (m, 1H), 1.12 (t, *J*=7.2 Hz, 3H); HRMS(EI): m/z calculated for $C_{19}H_{17}ClFN_3O_3S$ $[M+H]^+$: 422.0663, found: 422.0663.

Example 8: Exemplification of General Synthesis compound **33**

Scheme 8: The synthetic route for compound **33**



step 1: Preparation of 2-(2-bromoethoxy)tetrahydro-2H-pyran(33-2): To a solution of ***1*** (12.5 g, 0.1 mol) in DCM (30 mL) was added THP (12.6 g, 0.15 mol) and p-TsOH(250 mg ,1.3 mmol) . The mixture reaction was stirred overnight at room temperature. Then the reaction was evaporated and purified by chromatography to give the compound 2-(2-bromoethoxy)tetrahydro-2H-pyran**.** ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.68 (t, *J*=3.2 Hz, 1H), 4.03 (m, 1H), 3.90 (m, 1H), 3.73-3.82 (m, 1H), 3.45-3.58 (m, 3H), 1.80-1.91 (m, 1H), 1.70-1.79 (m, 1H), 1.51-1.63 (m, 4H); HRMS(EI): m/z calculated for $C_7H_{13}BrO_2$ $[M+H]^+$: 209.0099, found: 209.0099.

step 2 Preparation of ethyl 3-oxo-6-((tetrahydro-2H-pyran-2-yl) oxy)hexanoate (33-4): To the stirred suspension of sodium hydride (400 mg) in THF (30 mL) were added the solution of ethyl 3-oxobutanoate (936 mg, 7.2 mmol) in THF (10mL) at -40^{o}C .The mixture was stirred at -20 ^{o}C for 30 minutes. The reaction mixture became clear. Then 4 mL n-BuLi (2.5 M in n-hexane) was added and the reaction mixture was stirred at 0 ^{o}C for 15 minutes. Then 2-(2-bromoethoxy)tetrahydro-2H-pyran (1 g, 4.8 mmol), dissolved in THF (10 mL). The reaction mixture was stirred at 0 ^{o}C for two hours and then at room temperature overnight. 100 mL saturated NH_4Cl solution was added and the mixture extracted with 100mL ethyl acetate. The organic layers were evaporated in vacuo and purified by chromatography to give the ethyl 3-oxo-6-((tetrahydro-2H -pyran-2-yl)oxy)hexanoate (700 mg, 56%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.50-4.61 (m, 1H), 4.20 (q, *J*=7.2 Hz, 2H), 3.69-3.89 (m, 2H), 3.32-3.57 (m, 4H), 2.58-2.75 (m, 2H), 1.91 (q, *J*=6.4 Hz, 2H), 1.75-1.84 (m, 1H),

1.63-1.75 (m, 2H), 1.51-1.57 (m, 3H), 1.23-1.33 (m, 3H); HRMS(EI): m/z calculated for $C_{13}H_{22}O_5$ $[M+H]^+$: 259.1467, found: 259.1467.

step 3 Preparation of ethyl 4-(2-chloro-4-fluorophenyl)-2-(pyridin-2-yl)-6-(3-((tetrahydro-2H-pyran-2-yl)oxy)propyl)-1,4-dihydropyrimidine-5-carboxylate(33-5): To a solution of ethyl 3-oxo-6-((tetrahydro-2H-pyran-2-yl)oxy)hexanoate (700 mg, 2.7 mmol) in EtOH (20 mL) was added 2-chloro-4-fluorobenzaldehyde (545 mg,2.7 mmol), thiazole-2-carboximidamide hydrochloride (880 mg, 5.4 mmol) and AcONa (664 mg, 8.1 mmol). The resulting mixture was stirred at 100 □ overnight. The mixture was evaporated and extracted with ethyl acetate three times. The residue was purified by chromatography to give the ethyl 4-(2-chloro-4-fluorophenyl)-2-(pyridin-2-yl)-6-(3-((tetrahydro-2H-pyran-2-yl)oxy)propyl)-1,4-dihydropyrimidine-5-carboxylate (500 mg, 61%).

step 4 Preparation of ethyl 4-(2-chloro-4-fluorophenyl)-6-(3-oxopropyl)-2-(pyridin-2-yl)-1,4-dihydropyrimidine-5-carboxylate(33-6): To a solution of ethyl 4-(2-chloro-4-fluorophenyl)-6-(3-((tetrahydro-2H-pyran-2-yl)oxy)propyl)-2-(thiazol-2-yl)-1,4-dihydropyrimidine-5-carboxylate (103 mg, 0.2 mmol) in EtOH (10mL) was added p-TsOH (114 mg, 0.6 mmol). The resulting mixture was stirred for 30min. The mixture was added $NaHCO_3$ to adjust pH=8 and extracted with ethyl acetate three times. The residue was purified by chromatography to give the ethyl 4-(2-chloro-4-fluorophenyl)-6-(3-hydroxypropyl)-2-(thiazol-2-yl)-1,4-dihydropyrimidine-5-carboxylate (100mg, 85%). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.28 (br. s., 1H), 8.57-8.67 (m, 1H), 8.03 (d, J=8.0 Hz, 1H), 7.89 (dd, J=1.6, 7.6 Hz, 1H), 7.49-7.58 (m, 1H), 7.28-7.42 (m, 2H), 7.09-7.21 (m, 1H), 6.12 (s, 1H), 3.95-4.07 (m, 2H), 3.56 (q, J=6.02 Hz, 2H), 2.80-3.02 (m, 2H), 1.78-1.94 (m, 2H), 1.01-1.14 (m, 3H); HRMS(EI): m/z calculated for $C_{19}H_{19}ClFN_3O_3S$ $[M+H]^+$: 424.0820, found:424.0820.

step 5 Preparation of ethyl 4-(2-chloro-4-fluorophenyl)-6-(3-oxopropyl)-2-(thiazol-2-yl)-1,4-dihydropyrimidine-5-carboxylate(33-7): To a solution of ethyl 4-(2-bromo-4-fluorophenyl)-6-(3-hydroxypropyl)-2-(thiazol-2-yl)-1,4-dihydropyrimidine-5-carboxylate (93.4 mg, 0.2 mmol) in DCM (10 mL) was added Dess-Martin reagent (142.2 mg, 0.3 mmol). The resulting mixture was stirred for 1 hour. The

mixture was added $NaHCO_3$ and saturated $Na_2S_2O_3$ solution ,then extracted with ethyl acetate for three times. The residue was purified by chromatography to give the ethyl 4-(2-chloro-4-fluorophenyl)-6-(3-oxopropyl)-2-(thiazol-2-yl)-1,4-dihydropyrimidine-5-carboxylate (70mg, 85%); HRMS(EI): m/z calculated for $C_{19}H_{17}ClFN_3O_3S$ $[M+H]^+$: 422.0663, found:422.0663.

step 6 Preparation of ethyl 4-(2-chloro-4-fluorophenyl)-6-(3-hydroxybutyl) -2-(thiazol-2-yl)-1,4-dihydropyrimidine-5-carboxylate(33-8): To a solution of ethyl 4-(2-chloro-4-fluorophenyl)-6-(3-oxopropyl)-2-(thiazol-2-yl)-1,4-dihydropyrimidine-5-carboxylate (74 mg, 0.16 mmol) in THF (10 mL) was added MeMgBr (0.16 mL, 0.48 mmol). The resulting mixture was stirred for 3 hours. The mixture was added NH_4Cl (aq.) and ,then extracted with ethyl acetate for three times. The residue was purified by chromatography to give the ethyl 4-(2-chloro-4-fluorophenyl)-6-(3-hydroxybutyl)-2-(thiazol-2-yl)-1,4-dihydropyrimidine-5-carboxylate (55mg, 80%); HRMS(EI): m/z calculated for $C_{20}H_{21}ClFN_3O_3S$ $[M+H]^+$: 438.0976, found:438.0976.

step 7 Preparation of ethyl 3-(2-chloro-4-fluorophenyl)-7-methyl-1-(thiazol-2-yl)-3,5,6,7-tetrahydropyrrolo[1,2-c]pyrimidine-4-carboxylate(33): To a solution of ethyl 4-(2-chloro-4-fluorophenyl)-6-(3-hydroxybutyl)-2-(thiazol-2-yl)-1,4-dihydropyrimidine-5-carboxylate (62 mg, 0.13 mmol) in DCM (10 mL) was added MsCl (74.1 mg, 0.39 mmol) and Et3N(65.7 mg, 0.65 mmol). The resulting mixture was stirred for 3 hours. The mixture was added water and extracted with ethyl acetate for three times. The residue was purified by chromatography to give the ethyl 4-(2-chloro-4-fluorophenyl)-6-(3-hydroxybutyl)-2-(thiazol-2-yl)-1,4-dihydropyrimidine-5-carboxylate (20mg, 37%). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.82 (d, J=3.2 Hz, 1H), 7.37 (d, J=3.2 Hz, 1H), 7.33 (m, 1H), 7.21 (m, 1H), 6.97 (m, 1H), 6.17 (s, 1H), 5.52-5.66 (m, 1H), 3.99-4.11 (m, 2H), 3.32-3.44 (m, 1H), 3.15-3.29 (m, 1H), 2.27 (m, 1H), 1.79 (m, 1H), 1.13-1.20 (m, 6H); HRMS(EI): m/z calculated for $C_{20}H_{19}ClFN_3O_2S$ $[M+H]^+$: 419.0871, found:419.0871

^{13}C NMR (101 MHz, CHLOROFORM-d) δ 167.2, 164.1, 161.3(d, *J* = 250.5), 153.6, 143.8, 142.0, 139.0(d, *J* = 3.7), 129.5(d, *J* = 8.1), 122.2(d, *J*

= 9.5), 121.7, 119.1(d, *J* = 24.2), 94.4, 77.9, 57.5, 50.4, 43.4, 31.5, 29.5, 19.2, 14.2.

2. X-ray Single Crystal Structure of (*3R,6S*)-30

General information

The single crystal X-ray diffraction experiment was performed on a Bruker SMART system equipped with an APEX2 CCD camera. Data were collected at 296 K with graphite-monochromated Cu Kα radiation (l = 1.54178 A). The data was collected and processed using Saint. The structure was solved using direct methods that generated non-hydrogen atoms. All hydrogen atoms were placed in geometrically idealized positions and constrained to ride on their parent atoms . Refinement was achieved with the use of SHELX-TL.

The absolute stereochemistry of (*3R,6S*)-**30** was confirmed by a single crystal X-ray study

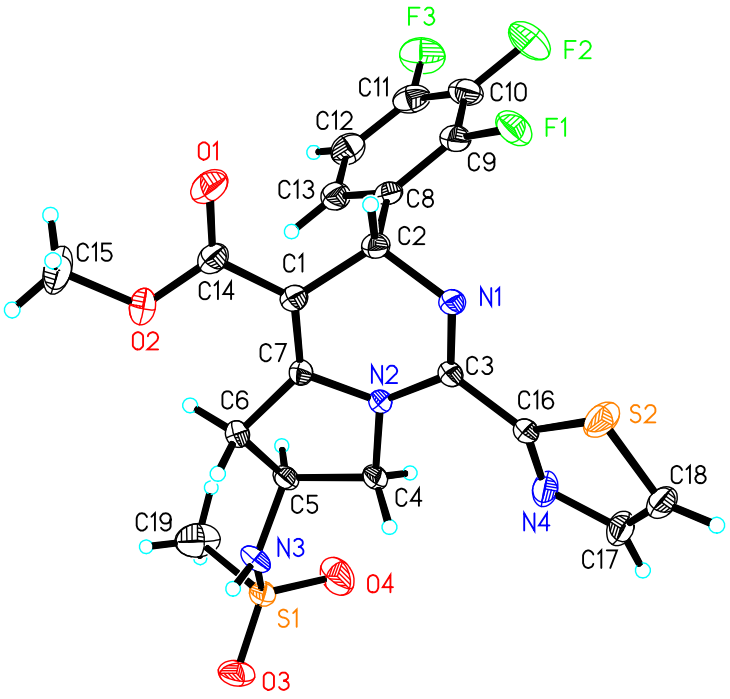


Fig 1: The absolute stereochemistry of (*3R,6S*)-**30**

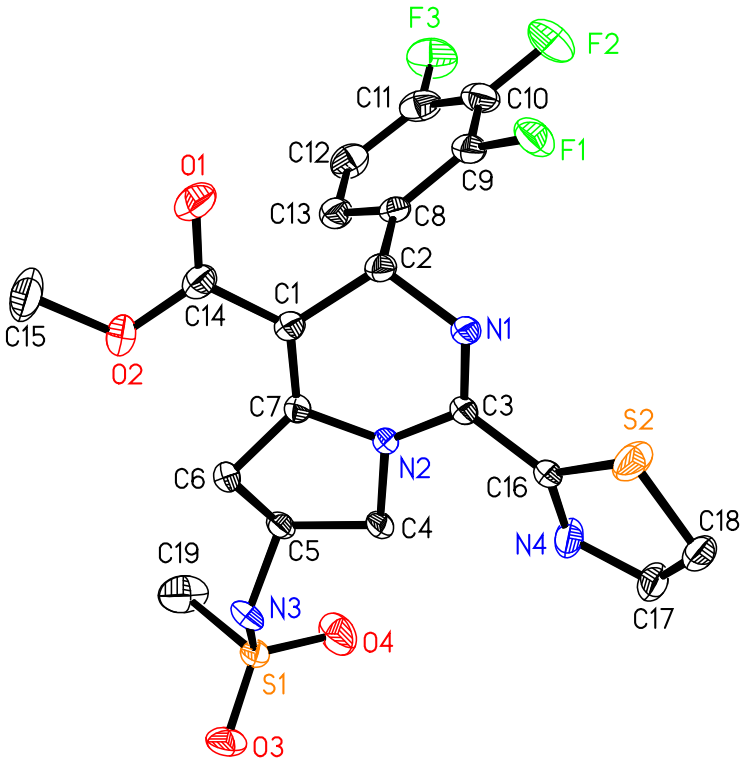


Fig 2: The absolute stereochemistry of (*3R,6S*)-**30**

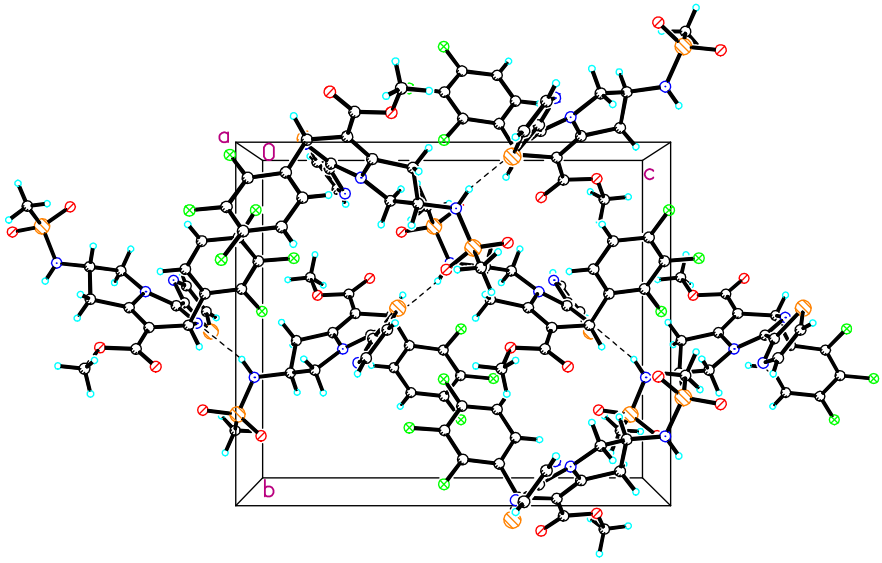


Fig 3: The absolute stereochemistry of (*3R,6S*)-**30**

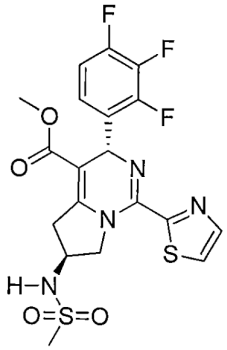


Table 1. Crystal data and structure refinement for **30**.

Identification code	WXFL20050436
Empirical formula	C19 H17 F3 N4 O4 S2
Formula weight	486.49
Temperature	296(2) K
Wavelength	1.54178 A
Crystal system, space group	Orthorhombic, P 21 21 21
Unit cell dimensions	a = 10.726(2) A alpha = 90 deg.
	b = 12.757(3) A beta = 90 deg.
	c = 15.265(3) A gamma = 90 deg.
Volume	2088.6(7) A^3
Z, Calculated density	4, 1.547 Mg/m^3
Absorption coefficient	2.884 mm^-1
F(000)	1000
Crystal size	0.26 x 0.18 x 0.15 mm
Theta range for data collection	4.52 to 67.30 deg.
Limiting indices	-12<=h<=12, -15<=k<=14, -18<=l<=17
Reflections collected / unique	14148 / 3621 [R(int) = 0.0277]
Completeness to theta = 67.30	98.6 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7529 and 0.4407
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3621 / 0 / 290
Goodness-of-fit on F^2	1.103
Final R indices [I>2sigma(I)]	R1 = 0.0293, wR2 = 0.0791
R indices (all data)	R1 = 0.0295, wR2 = 0.0793
Absolute structure parameter	0.057(14)
Extinction coefficient	0.0033(3)
Largest diff. peak and hole	0.214 and -0.236 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for **30**.

	x	y	z	U(eq)
S(1)	7419(1)	2868(1)	5480(1)	37(1)
S(2)	5021(1)	-390(1)	1361(1)	58(1)
F(1)	8836(1)	285(1)	-219(1)	57(1)
F(2)	9899(2)	1869(2)	-1073(1)	80(1)
F(3)	11391(2)	3243(1)	-228(1)	76(1)
O(1)	11175(2)	-1295(2)	2211(1)	60(1)
O(2)	10927(2)	-749(1)	3594(1)	52(1)
O(3)	6850(2)	2709(1)	6315(1)	55(1)
O(4)	6789(2)	3484(2)	4841(1)	76(1)
N(1)	7746(1)	-85(1)	1500(1)	33(1)
N(2)	7728(1)	878(1)	2811(1)	30(1)
N(3)	7690(2)	1746(1)	5070(1)	38(1)
N(4)	5072(2)	1228(2)	2341(1)	52(1)
C(1)	9490(2)	-188(1)	2543(1)	33(1)
C(2)	9117(2)	-126(1)	1593(1)	33(1)
C(3)	7154(2)	445(2)	2077(1)	31(1)
C(4)	7123(2)	1511(2)	3498(1)	33(1)
C(5)	8164(2)	1629(2)	4174(1)	32(1)
C(6)	8970(2)	652(2)	4062(1)	35(1)
C(7)	8814(2)	401(2)	3107(1)	30(1)
C(8)	9715(2)	819(2)	1135(1)	34(1)
C(9)	9540(2)	959(2)	244(1)	40(1)
C(10)	10089(2)	1777(2)	-208(1)	49(1)
C(11)	10841(2)	2463(2)	226(2)	51(1)
C(12)	11050(2)	2355(2)	1109(2)	50(1)
C(13)	10481(2)	1540(2)	1556(1)	41(1)
C(14)	10602(2)	-796(2)	2751(1)	39(1)
C(15)	12022(3)	-1329(3)	3838(2)	76(1)
C(16)	5788(2)	523(2)	1991(1)	34(1)
C(17)	3857(2)	1049(2)	2106(2)	59(1)
C(18)	3648(2)	224(2)	1590(2)	57(1)
C(19)	8896(3)	3442(3)	5647(2)	79(1)
H(3B)	7555	1195	5380	46
H(2A)	9414	-763	1301	39
H(4C)	6408	1150	3744	39
H(4D)	6860	2187	3274	39
H(5A)	8663	2247	4026	38
H(6A)	9835	796	4203	42
H(6B)	8673	82	4427	42

H(12A)	11567	2822	1403	60
H(13A)	10615	1474	2155	49
H(15A)	12172	-1246	4454	114
H(15B)	12726	-1071	3515	114
H(15C)	11900	-2058	3708	114
H(17A)	3213	1480	2297	71
H(18A)	2870	16	1385	69
H(19A)	8793	4128	5896	118
H(19B)	9323	3498	5097	118
H(19C)	9374	3013	6040	118

Table 3. Bond lengths [A] and angles [deg] for **30**.

S(1)-O(4)	1.4236(19)	C(3)-C(16)	1.475(3)
S(1)-O(3)	1.4269(16)	C(4)-C(5)	1.528(3)
S(1)-N(3)	1.5891(16)	C(4)-H(4C)	0.9700
S(1)-C(19)	1.763(3)	C(4)-H(4D)	0.9700
S(2)-C(18)	1.704(2)	C(5)-C(6)	1.526(3)
S(2)-C(16)	1.7202(19)	C(5)-H(5A)	0.9800
F(1)-C(9)	1.345(2)	C(6)-C(7)	1.501(2)
F(2)-C(10)	1.342(3)	C(6)-H(6A)	0.9700
F(3)-C(11)	1.348(3)	C(6)-H(6B)	0.9700
O(1)-C(14)	1.209(3)	C(8)-C(9)	1.385(3)
O(2)-C(14)	1.335(3)	C(8)-C(13)	1.390(3)
O(2)-C(15)	1.438(3)	C(9)-C(10)	1.383(3)
N(1)-C(3)	1.279(2)	C(10)-C(11)	1.362(4)
N(1)-C(2)	1.479(2)	C(11)-C(12)	1.373(4)
N(2)-C(7)	1.390(2)	C(12)-C(13)	1.385(3)
N(2)-C(3)	1.392(2)	C(12)-H(12A)	0.9300
N(2)-C(4)	1.475(2)	C(13)-H(13A)	0.9300
N(3)-C(5)	1.466(2)	C(15)-H(15A)	0.9600
N(3)-H(3B)	0.8600	C(15)-H(15B)	0.9600
N(4)-C(16)	1.298(3)	C(15)-H(15C)	0.9600
N(4)-C(17)	1.370(3)	C(17)-C(18)	1.334(4)
C(1)-C(7)	1.353(3)	C(17)-H(17A)	0.9300
C(1)-C(14)	1.458(3)	C(18)-H(18A)	0.9300
C(1)-C(2)	1.505(3)	C(19)-H(19A)	0.9600
C(2)-C(8)	1.534(3)	C(19)-H(19B)	0.9600
C(2)-H(2A)	0.9800	C(19)-H(19C)	0.9600
O(4)-S(1)-O(3)	119.18(12)	O(3)-S(1)-C(19)	108.30(13)
O(4)-S(1)-N(3)	108.24(11)	N(3)-S(1)-C(19)	105.50(13)
O(3)-S(1)-N(3)	107.59(9)	C(18)-S(2)-C(16)	89.25(10)
O(4)-S(1)-C(19)	107.24(17)	C(14)-O(2)-C(15)	116.1(2)

C(3)-N(1)-C(2)	116.48(15)
C(7)-N(2)-C(3)	117.31(15)
C(7)-N(2)-C(4)	112.13(14)
C(3)-N(2)-C(4)	126.48(14)
C(5)-N(3)-S(1)	121.54(13)
C(5)-N(3)-H(3B)	119.2
S(1)-N(3)-H(3B)	119.2
C(16)-N(4)-C(17)	109.80(19)
C(7)-C(1)-C(14)	126.44(17)
C(7)-C(1)-C(2)	116.24(16)
C(14)-C(1)-C(2)	117.08(16)
N(1)-C(2)-C(1)	111.01(15)
N(1)-C(2)-C(8)	110.17(15)
C(1)-C(2)-C(8)	111.67(15)
N(1)-C(2)-H(2A)	107.9
C(1)-C(2)-H(2A)	107.9
C(8)-C(2)-H(2A)	107.9
N(1)-C(3)-N(2)	122.95(16)
N(1)-C(3)-C(16)	117.85(16)
N(2)-C(3)-C(16)	119.01(15)
N(2)-C(4)-C(5)	102.29(14)
N(2)-C(4)-H(4C)	111.3
C(5)-C(4)-H(4C)	111.3
N(2)-C(4)-H(4D)	111.3
C(5)-C(4)-H(4D)	111.3
H(4C)-C(4)-H(4D)	109.2
N(3)-C(5)-C(6)	112.63(14)
N(3)-C(5)-C(4)	112.72(15)
C(6)-C(5)-C(4)	104.91(14)
N(3)-C(5)-H(5A)	108.8
C(6)-C(5)-H(5A)	108.8
C(4)-C(5)-H(5A)	108.8
C(7)-C(6)-C(5)	102.73(14)
C(7)-C(6)-H(6A)	111.2
C(5)-C(6)-H(6A)	111.2
C(7)-C(6)-H(6B)	111.2
C(5)-C(6)-H(6B)	111.2
H(6A)-C(6)-H(6B)	109.1
C(1)-C(7)-N(2)	118.94(16)
C(1)-C(7)-C(6)	132.60(17)
N(2)-C(7)-C(6)	108.44(15)
C(9)-C(8)-C(13)	116.61(19)
C(9)-C(8)-C(2)	119.52(17)
C(13)-C(8)-C(2)	123.82(17)
F(1)-C(9)-C(10)	117.36(19)
F(1)-C(9)-C(8)	120.65(19)
C(10)-C(9)-C(8)	122.0(2)
F(2)-C(10)-C(11)	120.8(2)
F(2)-C(10)-C(9)	119.5(2)
C(11)-C(10)-C(9)	119.7(2)
F(3)-C(11)-C(10)	118.9(2)
F(3)-C(11)-C(12)	120.5(2)
C(10)-C(11)-C(12)	120.6(2)
C(11)-C(12)-C(13)	119.2(2)
C(11)-C(12)-H(12A)	120.4
C(13)-C(12)-H(12A)	120.4
C(12)-C(13)-C(8)	122.0(2)
C(12)-C(13)-H(13A)	119.0
C(8)-C(13)-H(13A)	119.0
O(1)-C(14)-O(2)	123.21(19)
O(1)-C(14)-C(1)	123.2(2)
O(2)-C(14)-C(1)	113.60(17)
O(2)-C(15)-H(15A)	109.5
O(2)-C(15)-H(15B)	109.5
H(15A)-C(15)-H(15B)	109.5
O(2)-C(15)-H(15C)	109.5
H(15A)-C(15)-H(15C)	109.5
H(15B)-C(15)-H(15C)	109.5
N(4)-C(16)-C(3)	126.68(18)
N(4)-C(16)-S(2)	114.66(15)
C(3)-C(16)-S(2)	118.66(14)
C(18)-C(17)-N(4)	116.5(2)
C(18)-C(17)-H(17A)	121.7
N(4)-C(17)-H(17A)	121.7
C(17)-C(18)-S(2)	109.78(17)
C(17)-C(18)-H(18A)	125.1
S(2)-C(18)-H(18A)	125.1
S(1)-C(19)-H(19A)	109.5
S(1)-C(19)-H(19B)	109.5
H(19A)-C(19)-H(19B)	109.5
S(1)-C(19)-H(19C)	109.5
H(19A)-C(19)-H(19C)	109.5
H(19B)-C(19)-H(19C)	109.5

Table 4. Torsion angles [deg] for **30**.

O(4)-S(1)-N(3)-C(5)	44.0(2)
O(3)-S(1)-N(3)-C(5)	174.05(15)
C(19)-S(1)-N(3)-C(5)	-70.5(2)
C(3)-N(1)-C(2)-C(1)	37.4(2)
C(3)-N(1)-C(2)-C(8)	-86.78(19)
C(7)-C(1)-C(2)-N(1)	-39.2(2)
C(14)-C(1)-C(2)-N(1)	146.14(17)
C(7)-C(1)-C(2)-C(8)	84.20(19)
C(14)-C(1)-C(2)-C(8)	-90.5(2)
C(2)-N(1)-C(3)-N(2)	-6.5(3)
C(2)-N(1)-C(3)-C(16)	178.55(17)
C(7)-N(2)-C(3)-N(1)	-25.6(3)
C(4)-N(2)-C(3)-N(1)	179.00(17)
C(7)-N(2)-C(3)-C(16)	149.33(17)
C(4)-N(2)-C(3)-C(16)	-6.1(3)
C(7)-N(2)-C(4)-C(5)	16.15(19)
C(3)-N(2)-C(4)-C(5)	172.62(17)
S(1)-N(3)-C(5)-C(6)	150.10(15)
S(1)-N(3)-C(5)-C(4)	-91.42(19)
N(2)-C(4)-C(5)-N(3)	-151.23(15)
N(2)-C(4)-C(5)-C(6)	-28.32(18)
N(3)-C(5)-C(6)-C(7)	153.14(15)
C(4)-C(5)-C(6)-C(7)	30.18(18)
C(14)-C(1)-C(7)-N(2)	-175.89(17)
C(2)-C(1)-C(7)-N(2)	10.0(2)
C(14)-C(1)-C(7)-C(6)	2.3(3)
C(2)-C(1)-C(7)-C(6)	-171.84(19)
C(3)-N(2)-C(7)-C(1)	22.7(2)
C(4)-N(2)-C(7)-C(1)	-178.47(16)
C(3)-N(2)-C(7)-C(6)	-155.87(16)
C(4)-N(2)-C(7)-C(6)	3.0(2)
C(5)-C(6)-C(7)-C(1)	160.9(2)
C(5)-C(6)-C(7)-N(2)	-20.79(19)
N(1)-C(2)-C(8)-C(9)	-60.3(2)
C(1)-C(2)-C(8)-C(9)	175.83(17)
N(1)-C(2)-C(8)-C(13)	122.31(19)
C(1)-C(2)-C(8)-C(13)	-1.5(2)
C(13)-C(8)-C(9)-F(1)	178.54(17)
C(2)-C(8)-C(9)-F(1)	1.0(3)
C(13)-C(8)-C(9)-C(10)	-0.4(3)
C(2)-C(8)-C(9)-C(10)	-177.92(18)
F(1)-C(9)-C(10)-F(2)	0.3(3)

C(8)-C(9)-C(10)-F(2)	179.2(2)
F(1)-C(9)-C(10)-C(11)	-178.0(2)
C(8)-C(9)-C(10)-C(11)	0.9(3)
F(2)-C(10)-C(11)-F(3)	0.3(3)
C(9)-C(10)-C(11)-F(3)	178.5(2)
F(2)-C(10)-C(11)-C(12)	-178.8(2)
C(9)-C(10)-C(11)-C(12)	-0.5(3)
F(3)-C(11)-C(12)-C(13)	-179.4(2)
C(10)-C(11)-C(12)-C(13)	-0.3(3)
C(11)-C(12)-C(13)-C(8)	0.9(3)
C(9)-C(8)-C(13)-C(12)	-0.5(3)
C(2)-C(8)-C(13)-C(12)	176.91(19)
C(15)-O(2)-C(14)-O(1)	0.4(3)
C(15)-O(2)-C(14)-C(1)	-179.6(2)
C(7)-C(1)-C(14)-O(1)	-178.9(2)
C(2)-C(1)-C(14)-O(1)	-4.8(3)
C(7)-C(1)-C(14)-O(2)	1.1(3)
C(2)-C(1)-C(14)-O(2)	175.17(17)
C(17)-N(4)-C(16)-C(3)	179.4(2)
C(17)-N(4)-C(16)-S(2)	0.0(3)
N(1)-C(3)-C(16)-N(4)	-159.6(2)
N(2)-C(3)-C(16)-N(4)	25.2(3)
N(1)-C(3)-C(16)-S(2)	19.8(2)
N(2)-C(3)-C(16)-S(2)	-155.39(14)
C(18)-S(2)-C(16)-N(4)	-0.09(19)
C(18)-S(2)-C(16)-C(3)	-179.56(17)
C(16)-N(4)-C(17)-C(18)	0.1(4)
N(4)-C(17)-C(18)-S(2)	-0.2(3)
C(16)-S(2)-C(18)-C(17)	0.2(2)

Table 5. Hydrogen bonds for **30** [A and deg.].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(3)-H(3B)...N(1)#1	0.86	2.24	3.078(2)	163.7

Symmetry transformations used to generate equivalent atoms:
#1 -x+3/2,-y,z+1/2

3. Biological Assays:

Method of Cell-Based Assay

HepG2.2.15 cells, an HBV producing cell line, were seeded at 4×10^4 cells/well in 96-well plates in Dulbecco's minimal essential medium/F12 medium [DMEM-F12] (plus 2% fetal bovine serum, 100 IU/ml penicillin per ml, 100 μg/ml streptomycin, and 1% non-essential

amino acid) and cultured overnight at 37°C and 5% CO_2. Next day, compounds were added to the cell culture. Three days later, cells were replenished with fresh medium. After another 3 days, cell supernatants were collected for HBV DNA quantification. HBV DNA in cell culture supernatants was extracted with QIAamp 96 DNA Blood Kit and determined by a real-time PCR.

Method of Capsid Quenching assay

Purified C150 dimer was desalted and labeled with BoDIPY-FL *N*-(2-aminoethyl) maleimide (Invitrogen B-10250) according to a previously described protocol. Compounds were 3-fold serially diluted and tested at 8 concentrations, in duplicate. Labelled C150 protein (C150Bo) was incubated with the compounds at room temperature for 15 min. Then NaCl (final concentration 150 mM) were added to initiate assembly reaction. 1 M and 0 M of NaCl were used as 100% and 0% assembly controls, respectively. The final concentration of C150Bo was 2 μM. The assembly reaction mixtures were incubated at room temperature in dark for 1 h. Then fluorescence signal (485Ex/535Em) were read. EC_{50} values was calculated using the Graphpad Prism software.

4. Method of HDI Study

In-life experiment

Female BALB/c mice, 6-8 weeks old, specific pathogen free, were administered with pAAV2-HBV1.3mer plasmid DNA by hydrodynamic injection through a tail vein. Mice were orally dosed with vehicle or compounds for 7 days, twice a day. The first dose was performed at 1 hr before HDI. On Days 1, 3 and 5 post HDI, all mice were submandibularly bled for plasma preparation. On Day 7, all mice were euthanized by CO_2 inhalation, bled for plasma preparation via cardiac puncture, and thereafter liver samples were harvested.

***In vitro* analysis**

Quantification of HBV DNA in plasma by real-time PCR

DNA in plasma was isolated with the QIAamp 96 DNA Blood Kit according to the manual and quantified by real-time PCR. To eliminate the influence of input HBV plasmid DNA, two sets of primers and probes were used in the real-time PCR. One set of primers and probe targeting HBV sequences which detect newly synthesized HBV DNA and input HBV plasmid

DNA. Another set of primers and probe targeting the pAAV2 plasmid backbone sequences can only detect the input plasmid DNA. Quantity of replicated HBV DNA was calculated by subtracting DNA quantity determined by the HBV primers by DNA quantity determined by the plasmid primers.

Determination of total HBV DNA level in liver by real-time PCR

Isolation of total DNA from liver

In brief, liver tissue were homogenized with the Qiagen Tissue Lyser followed by digestion with proteinase K. The aqueous phase was transferred to new tubes followed by RNase A treatment, and extracted with phenol: chloroform: Isoamyl alcohol twice. DNA was precipitated with isopropanol and dissolved in ddH_2O.

Quantification of total HBV DNA in liver by real-time PCR

The concentrations of the extracted liver DNA were determined using a Nanodrop (Thermo) and then adjusted to10 ng/μL. 10 μl of the DNA was applied to real-time PCR.

5. Mouse PK studies:

Female Balb/c mice (SLAC Laboratory Animal Co. Ltd. (Shanghai, China)) were used to evaluate pharmacokinetics (PK) of the compound post single oral gavage or intravenous bolus injection. IACUC proposal number was R20140106-Mouse-A. Animals(n=3 per time point, total 6 animals were used in the study, 3 animals per group) were fasted overnight before dosing and food was returned 4 hours post dosing. Formulation of intravenous dosing was prepared in saline for **GLS4** or 50%PEG400 in water for **28a** as solution. Oral formulation for each of the compound was prepared in 0.5% HEC as a suspension. Blood samples were collected via submandibular vein or other appropriate vein up to 24 hours post dosing, with EDTA-K2 as anticoagulant. Sampling schedule was 0.0833, 0.25,0.5, 1, 2, 4, 6, 8 and 24 hours post intravenous dosing, and 0.25,0.5, 1, 2, 4, 6, 8 and 24 hours post oral dosing. The blood samples were processed for plasma by centrifugation at approximately 4□, 3000g within half an hour of collection.The collected plasma samples were then stored at -80 □until sample analysis. LC-MS/MS was applied for sample analysis.

LC-MS/MS method for GLS4 (API4000 Q TRAP): Plasma samples were by protein

precipitation extraction with acetonitrile containing internal standard (Dexamethasone, $[M+H]^+$ m/z 393.0/373.1) at volume ratio of 1:20 before LC-MS/MS injection.The compound was eluted with a binary solvent system on column of XSELECT CSH^{TM} XP C18 (2.1×50mm, 2.5 μm) using positive mode of electrospray ionization source (ESI+). The flow rate was 0.6 mL/min. The transition (precursor to daughter, Q1/Q3) detected was $[M+H]^+$ m/z 509.1/421.9 for GLS4with retention time at 0.8 minute for GLS4. Peak area ratio of GLS4/Dexamethasone(IS) was applied in the calculation. Linear calibration curve was fitted with 1 / X^2 linear regression analysis. The calibration curve was in linear from concentration at 1 to 3000 ng/mL (Correlation coefficient = 0.9967) with lower limit of quantification at 1 ng/mL.

LC-MS/MS method for 28a (API4000 Q TRAP): Plasma samples were by protein precipitation extraction with acetonitrile containing internal standard (Diclofenac, $[M+H]^+$ m/z 296.0/214.0) at volume ratio of 1:15 before LC-MS/MS injection.The compound was eluted with a binary solvent system on column of XSELECT CSH^{TM} XP C18 (2.1×50mm, 2.5 μm) using positive mode of electrospray ionization source (ESI+). The flow rate was 0.6 mL/min. The transition (precursor to daughter, Q1/Q3) detected was $[M+H]^+$ m/z 485.1/220.1 for 28a with retention time at 1.37 minute. Peak area ratio of 28a/ Diclofenac (IS) was applied in the calculation. Linear calibration curve was fitted with 1 / X^2 linear regression analysis. The calibration curve was in linear from concentration at 1 to 3000 nM (Correlation coefficient = 0.9962) with lower limit of quantification at 1 nM.

Plasma concentration versus time data were analyzed by non-compartmental approaches using the Phoenix WinNonlin 6.3 software program. Data was presented as below tables. Time- Plasma concentration profiles were presented as followings.

Table 6: Individual and mean plasma concentration (nM) post 1 mg/kg intravenous dosing of GLS4 to female Balb/c mice

Time (h)	M1	M2	M3	Mean IV		SD	CV (%)
0.0833	1110	1159	1037	**1102**	±	**61.4**	**5.57**
0.250	407	524	557	**496**	±	**78.8**	**15.9**
0.500	147	264	250	**220**	±	**63.9**	**29.0**
1.00	73.8	119	113	**102**	±	**24.5**	**24.1**
2.00	44.9	63.6	50.4	**53.0**	±	**9.61**	**18.1**

4.00	22.2	28.3	27.4	**26.0**	±	**3.29**	**12.7**
6.00	5.81	5.81	5.02	**5.55**	±	**0.456**	**8.22**
8.00	4.35	4.37	4.43	**4.38**	±	**0.0416**	**0.950**
24.0	BQL	BQL	BQL	**ND**	±	**ND**	**ND**

Table 7: Individual and mean plasma concentration (nM) post 10 mg/kg oral gavage dosing of GLS4 to female Balb/c mice

Time (h)	M4	M5	M6	Mean IV		SD	CV (%)
0.250	650	864	640	**718**	±	**127**	**17.6**
0.500	528	569	301	**466**	±	**144**	**31.0**
1.00	293	211	167	**224**	±	**63.9**	**28.6**
2.00	122	153	113	**129**	±	**21.0**	**16.2**
4.00	60.6	55.7	39.8	**52.0**	±	**10.9**	**20.9**
6.00	10.8	13.5	10.4	**11.6**	±	**1.69**	**14.6**
8.00	4.00	4.67	6.00	**4.89**		**1.02**	**20.8**
24.0	BQL	BQL	BQL	**ND**	±	**ND**	**ND**

Table 8: Individual and mean PK parameters post 1 mg/kg intravenous dosing of GLS4 to female Balb/c mice

PK Parameters	M1	M2	M3	Mean IV		SD	CV (%)
No. points used for $T_{1/2}$	4	4	3	**ND**	±	**--**	**--**
C_0 (nM)	1833	1723	1415	**1657**	±	**217**	**13.1**
$T_{1/2}$ (hr)	1.66	1.44	1.52*	**1.54**	±	**0.111**	**7.22**
Vd_{ss} (L/kg)	4.71	3.61	3.91	**4.07**	±	**0.569**	**14.0**
Cl (mL/min/kg)	63.0	49.7	53.8	**55.5**	±	**6.81**	**12.3**
T_{last} (hr)	8	8	8	**8**	±	**--**	**--**
$AUC_{0\text{-}last}$ (nM.hr)	511	652	601	**588**	±	**71.3**	**12.1**
$AUC_{0\text{-}inf}$ (nM.hr)	521	661	611	**598**	±	**70.6**	**11.8**
$MRT_{0\text{-}last}$ (hr)	1.06	1.09	1.07	**1.07**	±	**0.0139**	**1.30**
$MRT_{0\text{-}inf}$ (hr)	1.25	1.21	1.21	**1.22**	±	**0.0201**	**1.65**
$AUC_{0\text{-}inf}/AUC_{0\text{-}last}$ (%)	102	101	102	**102**	±	**0.328**	**0.323**

*The adjusted linear regression coefficient of the concentration value on the terminal phase is less than 0.9, t(1/2) might not be accurately estimated.

Table 9: Individual and mean PK parameters post 10 mg/kg oral gavage dosing of GLS4 to female Balb/c mice

PK Parameters	M4	M5	M6	Mean PO		SD	CV (%)
No. points used for $T_{1/2}$	3	3	4	**ND**	±	**--**	**--**
C_{max} (nM)	650	864	640	**718**	±	**127**	**17.6**
T_{max} (hr)	0.250	0.250	0.250	**0.250**	±	**0.0**	**0.0**
$T_{1/2}$ (hr)	1.02	1.12	1.37	**1.17**	±	**0.178**	**15.3**
T_{last} (hr)	8	8	8	**8**	±	**--**	**--**
$AUC_{0\text{-}last}$ (nM.hr)	870	914	644	**809**	±	**145**	**17.9**
$AUC_{0\text{-}inf}$ (nM.hr)	875	922	656	**818**	±	**142**	**17.3**

$MRT_{0\text{-}last}$ (hr)	1.58	1.56	1.65	**1.60**	±	**0.0463**	**2.90**
$MRT_{0\text{-}inf}$ (hr)	1.63	1.63	1.80	**1.69**	±	**0.0981**	**5.82**
$AUC_{0\text{-}inf}/AUC_{0\text{-}last}$ (%)	101	101	102	**101**	±	**0.630**	**0.623**
F (%)[a]	--	--	--	**13.7**	±	**--**	**--**

a:F (%) was calculated with $AUC_{0\text{-}inf}$ and nominal dose.

Table 10: Individual and mean plasma concentration (nM) post 1 mg/kg intravenous dosing of 28a to female Balb/c mice

Time (h)	M1	M2	M3	Mean IV		SD	CV (%)
0.0833	1371	1276	1297	**1315**	±	**49.9**	**3.80**
0.250	942	959	864	**922**	±	**50.7**	**5.50**
0.500	825	755	647	**742**	±	**89.7**	**12.1**
1.00	571	454	476	**500**	±	**62.2**	**12.4**
2.00	377	254	214	**282**	±	**84.9**	**30.2**
4.00	90.1	96.1	77.1	**87.8**	±	**9.71**	**11.1**
6.00	33.0	25.4	25.0	**27.8**	±	**4.51**	**16.2**
8.00	8.35	6.97	6.08	**7.13**	±	**1.14**	**16.0**
24.0	BQL	BQL	BQL	**ND**	±	**ND**	**ND**

Table 11: Individual and mean plasma concentration (nM) post 10 mg/kg oral gavage dosing of 28a to female Balb/c mice

Time (h)	M4	M5	M6	Mean IV		SD	CV (%)
0.250	3856	4454	3031	**3780**	±	**715**	**18.9**
0.500	4495	3093	5073	**4220**	±	**1018**	**24.1**
1.00	3114	2846	3670	**3210**	±	**420**	**13.1**
2.00	1615	1600	2289	**1835**	±	**394**	**21.4**
4.00	602	582	821	**668**	±	**133**	**19.8**
6.00	155	107	291	**184**	±	**95.4**	**51.8**
8.00	31.3	23.9	62.7	**39.3**	±	**20.6**	**52.4**
24.0	BQL	BQL	BQL	**ND**	±	**ND**	**ND**

Table 12: Individual and mean PK parameters post 1 mg/kg intravenous dosing of 28a to female Balb/c mice

PK Parameters	M1	M2	M3	Mean IV		SD	CV (%)
No. points used for $T_{1/2}$	3.00	3.00	3.00	**3.00**	±	**--**	**--**
C_0 (nM)	1654	1472	1589	**1571**	±	**92.3**	**5.87**
$T_{1/2}$ (hr)	1.17	1.06	1.09	**1.10**	±	**0.0556**	**5.03**
Vd_{ss} (L/kg)	1.74	2.00	2.10	**1.95**	±	**0.184**	**9.46**
Cl (mL/min/kg)	17.9	21.2	23.1	**20.7**	±	**2.59**	**12.5**
T_{last} (hr)	8.00	8.00	8.00	**8.00**	±	**--**	**--**
$AUC_{0\text{-}last}$ (nM.hr)	1900	1612	1479	**1664**	±	**215**	**12.9**
$AUC_{0\text{-}inf}$ (nM.hr)	1914	1623	1488	**1675**	±	**217**	**13.0**
$MRT_{0\text{-}last}$ (hr)	1.56	1.52	1.46	**1.51**	±	**0.0475**	**3.14**
$MRT_{0\text{-}inf}$ (hr)	1.62	1.57	1.52	**1.57**	±	**0.0510**	**3.25**

$AUC_{0\text{-}inf}/AUC_{0\text{-}last}$ (%)	101	101	101	**101**	±	**0.0500**	**0.0496**

Table 13: Individual and mean PK parameters post 10 mg/kg oral gavage dosing of 28a to female Balb/c mice

PK Parameters	M4	M5	M6	Mean PO		SD	CV (%)
No. points used for $T_{1/2}$	3.00	3.00	3.00	**3.00**	±	**--**	**--**
C_{max} (nM)	4495	4454	5073	**4674**	±	**346**	**7.41**
T_{max} (hr)	0.500	0.250	0.500	**0.417**	±	**0.144**	**34.6**
$T_{1/2}$ (hr)	0.938	0.868	1.08	**0.961**	±	**0.107**	**11.1**
T_{last} (hr)	8.00	8.00	8.00	**8.00**	±	**--**	**--**
$AUC_{0\text{-}last}$ (nM.hr)	8557	7822	10667	**9015**	±	**1477**	**16.4**
$AUC_{0\text{-}inf}$ (nM.hr)	8599	7852	10764	**9072**	±	**1513**	**16.7**
$MRT_{0\text{-}last}$ (hr)	1.78	1.77	2.01	**1.85**	±	**0.136**	**7.32**
$MRT_{0\text{-}inf}$ (hr)	1.82	1.80	2.08	**1.90**	±	**0.156**	**8.24**
$AUC_{0\text{-}inf}/AUC_{0\text{-}last}$ (%)	100	100	101	**101**	±	**0.280**	**0.278**
F (%)[a]	--	--	--	**54.2**	±		

a:F (%) was calculated with $AUC_{0\text{-}inf}$ and nominal dose.

Figure 4: Time-mean plasma concentration profile post 1 mg/kg intravenous dosing of GLS4 to female Balb/c mice

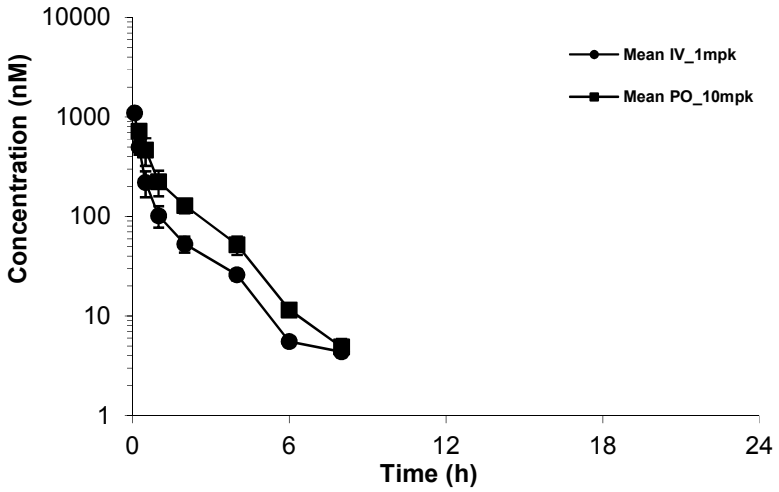
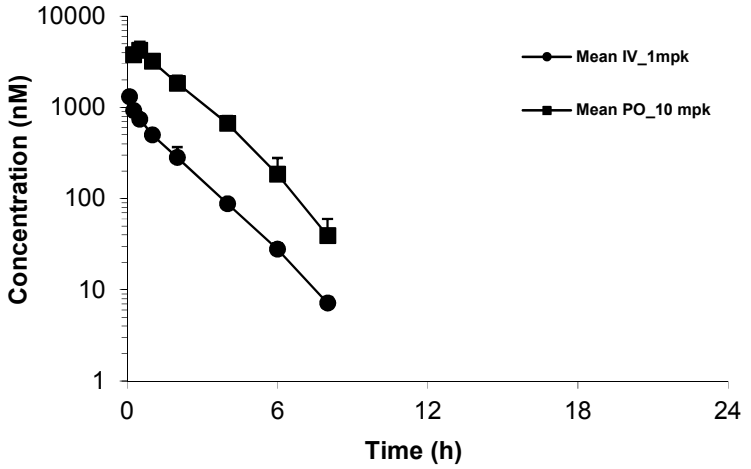


Figure 5: Time-mean plasma concentration profile post 1 mg/kg intravenous dosing of 28a to female Balb/c mice



Mouse liver distribution studies:

Female Balb/c mice (SLAC Laboratory Animal Co. Ltd. (Shanghai, China)) were used to evaluate liver distribution of the compound post single oral gavage.IACUC proposal number was R20140106-Mouse-A. Animals were fasted overnight before dosing and food was returned 4 hours post dosing. Oral formulation for each of the compound was prepared in 0.5% HEC as a suspension. Blood and liver samples were collected at 0.25, 1 and 4 hours post dosing, with EDTA-K2 as anticoagulant for blood samples. The blood samples were processed for plasma by centrifugation at approximately 4□, 3000g within half an hour of collection.The collected liver samples were homogenized with 4 volumes of ice-cold buffer (15mM PBS buffer(pH 7.4):MeOH= 2:1) on wet ice. The collected plasma samples and homogenized liver samples were then stored at -80 □until sample analysis. LC-MS/MS was applied for sample analysis.

LC-MS/MS method for GLS4 (API4000 Q TRAP): Plasma and liver homogenate samples were by protein precipitation extraction with acetonitrile containing internal standard (Dexamethasone, $[M+H]^+$ m/z 393.0/373.1) at volume ratio of 1:9 before LC-MS/MS injection.The compound was eluted with a binary solvent system on column of ACE 5 phenyl (2.1×100 mm, 5 μm) using positive mode of electrospray ionization source (ESI+). The flow rate was 0.45 mL/min. The transition (precursor to daughter, Q1/Q3) detected was $[M+H]^+$ m/z 509.1/100.2 for GLS4 with retention time at 2.11 minute. Peak area ratio of GLS4/Dexamethasone (IS) was applied in the calculation. Linear calibration curve was fitted

with 1 / X2 linear regression analysis. The calibration curve was in linear from concentration at 1 to 3000 nM (Correlation coefficient above 0.99 for both plasma and liver matrices) with lower limit of quantification at 1 nM.

LC-MS/MS method for 28a (API4000 Q TRAP): Plasma and liver homogenate samples were by protein precipitation extraction with acetonitrile containing internal standard (Diclofenac, $[M+H]^+$ m/z 296.0/214.0) at volume ratio of 1:9 for liver samples and 1:15 for plasma samples before LC-MS/MS injection.The compound was eluted with a binary solvent system on column of XSELECT CSHTM XP C18 (2.1×50mm, 2.5 μm) using positive mode of electrospray ionization source (ESI+). The flow rate was 0.6 mL/min. The transition (precursor to daughter, Q1/Q3) detected was $[M+H]^+$ m/z 485.0/220.2 for 28a with retention time at 1.72 minute. Peak area ratio of 28a/ Diclofenac (IS) was applied in the calculation. Linear calibration curve was fitted with 1 / X2 linear regression analysis. The calibration curve was in linear from concentration at 2.5 to 5000 nM for plasma and 25 to 5000 nM for liver homogenate samples (Correlation coefficient above 0.99 for both plasma and liver matrices) with lower limit of quantification at 2.5 nM for plasma and 25 nM for liver homogenate sample.

Plasma concentration or liver concentration versus time data were analyzed by non-compartmental approaches using the Phoenix WinNonlin 6.3 software program. $AUC_{0\text{-last}}$ with liver to plasma AUC ratio was reported. Data results were presented as below tables.

Table 14: Individual, mean plasma concentration (nM) and $AUC_{0\text{-last}}$post *10 mg/kg* oral dosing of GLS4 to female Balb/c mice

	PO Time (h)	M1+3n	M2+3n	M3+3n	Mean PO		SD	CV (%)
*n=0	0.250	274	303	174	**250**	±	**67.8**	**27.1**
n=1	1.00	65.1	42.3	81.3	**62.9**	±	**19.6**	**31.1**
n=2	4.00	22.0	12.2	12.6	**15.6**	±	**5.56**	**35.6**
	$AUC_{0\text{-4hr}}$ (nM.h)				**235**			

*n is the number to be calculated for the animal number in the study, for example if n=0, M1+3n is for animal number of M1

Table 15: Individual, mean plasma concentration (nM) and $AUC_{0\text{-last}}$ post *10 mg/kg* oral dosing of GLS4 to female Balb/c mice

	PO Time (h)	M1+3n	M2+3n	M3+3n	Mean PO		SD	CV (%)
*n=0	0.250	3795	4283	2661	**3580**	±	**832**	**23.2**

n=1	1.00	380	224	627	**410**	±	**204**	**49.6**
n=2	4.00	148	35.4	59.0	**80.8**	±	**59.4**	**73.5**
	AUC_{0-4hr} (nM.h)				**2153**			

*n is the number to be calculated for the animal number in the study, for example if n=0, M1+3n is for animal number of M1

Table 16: Individual, mean plasma concentration (nM) and AUC_{0-last} post *2 mg/kg* oral dosing of 28a to female Balb/c mice

	PO Time (h)	M1+3n	M2+3n	M3+3n	Mean PO		SD	CV (%)
*n=0	0.250	930	630	722	**761**	±	**154**	**20.2**
n=1	1.00	582	336	500	**473**	±	**125**	**26.5**
n=2	4.00	272	91.7	131	**165**	±	**94.8**	**57.5**
	AUC_{0-4hr} (nM.h)				**1427**			

*n is the number to be calculated for the animal number in the study, for example if n=0, M1+3n is for animal number of M1

Table 17: Individual, mean plasma concentration (nM) and AUC_{0-last} post *2 mg/kg* oral dosing of 28a to female Balb/c mice

	PO Time (h)	M1+3n	M2+3n	M3+3n	Mean PO		SD	CV (%)
*n=0	0.250	9560	10880	13880	**11440**	±	**2214**	**19.4**
n=1	1.00	4640	4280	4200	**4373**	±	**234**	**5.36**
n=2	4.00	2420	752	1076	**1416**	±	**884**	**62.5**
	AUC_{0-4hr} (nM.h)				**14809**			

*n is the number to be calculated for the animal number in the study, for example if n=0, M1+3n is for animal number of M1

CYP inhibition (%)

Compound was incubated at 7 concentrations from 0.05 to 50 μM with human liver microsomes with protein concentration at 0.253 mg/mL.α-Naphthoflavone, Sulfaphenazole, (+)-N-3-benzylnirvanol, Quinidine and Ketoconazole were used as positive control. The mixture of test compound or positive control were pre-warmed with human liver microsomes at 37 ℃ for 10 min. Phenacetin, Diclofenac, S-mephenytoin, Dextromethorphan and Midazolam were prepared in a mixture used as substrate of CYP1A2, 2C9, 2C19, 2D6 and 3A4, respectively.After addition of 5-in-1 substrates solution and cofactor NADPH, the mixture were incubated for another 10 min.The samples were finally quenched with stop solution containing internal standard and centrifuged at 4000 rpm (Centrifuge, 5810R Eppendorf) atroom temperature for 20 minutes. Then supernatant was diluted with purified

water with an appropriate ratio, which was shaken at 1000 rpm (Titer plate shaker, Thermo) for 10 minutes to mix well and for LC-MS/MS injection. The formation of the metabolite Acetaminophen, 4'-hydroxy diclofenac, 4'-hydroxy mephenytoin, Dextrorphan and 1'-hydroxy midazolam were determined by LC-MS/MS and IC50 values were calculated. SigmaPlot (V.11) was used to plot the mean CYP Activity (% VC) versus the test compound concentrations with non-linear regression analysis. IC50 values were determined using 3- or 4- parameter logistic equation. IC50 values were reported as "> 50 μM" when % inhibition at highest concentration (50 μM) was less than 50%.

Equation for three parameters logistic sigmoidal curve	**Equation for four parameters logistic sigmoidal curve**
$y = \frac{max}{1+\left(\frac{x}{IC_{50}}\right)^{-hillslope}}$	$y = min+\frac{max-min}{1+\left(\frac{x}{IC_{50}}\right)^{-hillslope}}$

The max represents the maximal enzyme activity and min is the minimal enzyme activity. x represents the concentrations of test compound and y is the enzyme activity at x. Hillslope is the slope factor and IC_{50} is the concentration to achieve the half maximal inhibition. Four parameters equation will be used when min is between ±10%, otherwise three parameters equation will be used.

6. Molecular modeling of dihydropyrimidine analogues in HBV capsid

The 3D coordinate of HBV capsid was downloaded from PDB website. The hydrogen atoms, missed atoms and residues, protonation states were prepared by protein preparation wizard tool. A grid in a rectangular box of maximum distance 30 angstrom to ligand was generated for docking. The dihydropyrimidine analogues, however, were firstly prepared by ligand preparation tool. The 2D structures were converted to 3D, followed by hydrogen addition, protonation and tautomerization prediction. An extensive conformational search for each compound was performed to obtain the global minimum and 10 diverse conformations for docking. Each conformation was then docked into the generated grid using Glide module, followed by conformation energy calculation. The strain energy, which is energy difference between the active conformation and global minimum, was then obtained. The pose with higher docking score and lower strain energy was selected as the final binding pose. All the calculations were performed by Schrodinger suite 2017-1.