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Supporting Information

Ru-Catalyzed C-H Annulation: Accessing Quinazolinone-BCP

Hybrids from Stable Precursors

Yu-Yong Luan, Jin-Ye Li, Xue-Yuan Liu* and Yong-Min Liang*

State Key Laboratory of Applied Organic Chemistry, School of Chemistry and Chemical Engineering, Lanzhou University, Lanzhou 730000, P.R. China

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1. General Remarks

Unless otherwise noted, all of these reactions were carried out under an argon atmosphere. Solvent was freshly distilled prior to use unless otherwise noted. For column chromatography, silica gel (200-300 mesh) was employed. Analytical TLC was performed with silica gel GF 254 plates. Organic solutions were concentrated under reduced pressure using a rotary evaporator. Unless otherwise noted below, all other compounds have been reported in the literature or are commercially available. Commercial reagents were used without further purification. Extra dry toluene was obtained by distillation and for the [Ru(*p*-cymene)Cl₂]₂, we used the brand of LaaJoo.

Instrumentation. Deuterated solvents were purchased from Cambridge Isotope Laboratories. 1 H NMR spectra were recorded on Bruker AVANCE III 400, 600 and INOVA instruments with 400, 600 frequencies, and 13 C NMR spectra were recorded on Bruker AVANCE III 400 and 600 with 101 and 151 MHz frequencies. 19 F NMR spectra were recorded on a Bruker AVANCE III 400 spectrometer with a 19 F operating frequency of 376 MHz. Chemical shifts (δ) were reported in ppm relative to the residual solvent signal (CDCl₃ δ = 7.26 for 1 H NMR and δ = 77.0 for 13 C NMR). Chemical shifts (ppm) were recorded with tetramethyl silane (TMS) as the internal reference standard. Multiplicities are given as s (singlet), d (doublet), t (triplet), dd (doublet of doublets), m (multiplet). HRMS was obtained using a Q-TOF instrument equipped with an ESI source.

2 General Procedure

In an oven-dried 10 mL tube, [Ru(*p*-cymene)Cl₂]₂ (5 mol%, 6.1 mg), NaOAc (1.0 equiv., 16.4 mg), Ethyl benzimidate hydrochloride **1a** (0.2 mmol), methyl 3-(5-oxo-1,4,2-dioxazol-3-yl)bicyclo[1.1.1]pentane-1-carboxylate **2a** (0.3 mmol), and AgNTf₂ (30 mol%) were added and charged with argon more than three times (The tube was sealed with tipping plug). TBME (2 mL) was then added to the tube. The resulting vigorously stirred at 80 °C in an oil bath for 18 hours. After the reaction was completed, mixture added silica gel dry method sample. The residue was purified with chromatography column (petroleum ether/ ethyl acetate = 10:1-5:1) on silica gel or preparative TLC.

3. General Procedure for the Preparation of Starting Material

3.1 Synthesis of benzimidate hydrochloride¹

The procedure for the preparation of benzimidates was in line with the literature: AcCl (8 mmol, 0.57 mL) was added to a stirred solution of a nitrile (1 mmol) and an alcohol (12 mmol). The reaction flask was stoppered tightly and stirred at 25 °C. After the reaction was completed by TLC, the volatile was removed under reduced pressure to isolate the benzimidate hydrochloride. Alternatively, the reaction mixture was cooled to 0 °C and mixed slowly with saturated aqueous NaHCO₃ solution, until gas evolution had ceased. The product was extracted into Et₂O (3 × 5 mL) and the organic solution was washed with H_2O (1 × 5 mL) and NaCl (1 × 5 mL) and concentrated under reduced pressure to obtain the benzimidates. The benzimidate substrates were all known compounds.

3.2 Synthesis of alkyl carboxylic acid²

$$\label{eq:co2} \text{HO}_2\text{C} - \bigcirc \text{CO}_2\text{Me} \xrightarrow{\begin{array}{c} 1. \text{ Oxalyl chloride (1.2 eq.)} \\ \text{DMF, DCM} \\ \hline 2. \text{ RNH}_2 \text{ (1.1 eq.)} \\ \text{Et}_3\text{N (2.0 eq.)} \end{array}} \begin{array}{c} O \\ \text{RHN} \end{array} \\ \begin{array}{c} O \\ \text{RHN} \end{array}$$

To the solution of 3-(methoxycarbonyl)bicyclo[1.1.1]pentane-1-carboxylic acid (510 mg, 3.0 mmol, 1.0 equiv.) in dry DCM (10 mL) was added oxalyl chloride (457 mg, 3.6 mmol, 1.2 equiv.) and a catalytic amount of DMF at 0 °C. The resulting solution was stirred for 1.5 h and reaction was completed by concentrating solution under reduced pressure to give the crude acyl chloride. A solution of Et₃N (2.0 equiv.) and primary amine (3.3 mmol, 1.1 equiv.) in 10 mL THF was cooled to 0 °C. The crude acyl chloride was dissolved in 5.0 mL THF and dropwise added to the solution. The reaction mixture was stirred for 3 h at room temperature. Upon completion of the reaction, H₂O was added, the mixture was extracted with EtOAc (x 2). The combined organic layer was washed with brine (x 2), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure to afford S1 which did not require further purification.

To a mixture of S1 in MeOH (15 mL) was added a 4 N NaOH solution (2.0 mL). The reaction was stirred overnight at room temperature. After the reaction was completed, the mixture was concentrated, then the residue was treated with water (20 mL), adjusted to pH 1 using 1 N HCl. The mixture was filtered, then the solid was washed with deionized water and hexanes to give the desired compound.

$$\begin{array}{c} \text{ROH (1.1 eq.), EDCI (1.2 eq.)} \\ \text{HO}_2\text{C} & \xrightarrow{\hspace*{1cm} \text{DMAP (15 mol\%)} \hspace*{1cm}} \text{HO}_2\text{C} & \xrightarrow{\hspace*{1cm} \text{CO}_2\text{R}} \end{array}$$

To a round-bottom flask equipped with a stirring bar was charged with DMAP (37 mg, 0.3 mmol, 15 mol%), alkyl alcohol (2.2 mmol, 1.1 equiv.) and bicycle[1.1.1]pentane-1,3-dicarboxylic acid (312 mg, 2.0 mmol, 1.0 equiv.). DCM (10 mL) was added and the solution was cooled to 0 °C in an ice/water bath for 15 minutes, at which point EDCI (1.2 equiv.) was added in one portion. The ice bath was removed, and the reaction mixture was stirred overnight at room temperature. Upon completion, 1 N HCl was added, and the mixture was extracted with DCM (x 2). The organic layer was dried over anhydrous Na₂SO₄. The organic solution was concentrated under reduced pressure to give crude product and further purification was conducted by column chromatography (50:50–0:100, hexane/EtOAc).

3-((benzyloxy)carbonyl)bicyclo[1.1.1]pentane-1-carboxylic acid

 1 H NMR (400 MHz, Chloroform-*d*) δ 7.39 – 7.31 (m, 5H), 5.13 (s, 2H), 2.36 (s, 6H). 13 C { 1 H} NMR (101 MHz, Chloroform-*d*) δ 175.1, 169.0, 135.5, 128.6, 128.3, 128.1, 66.5, 52.8, 37.6, 37.5.

3-(((4-(prop-1-en-2-yl)cyclohex-1-en-1-yl)methoxy)carbonyl)bicyclo[1.1.1]pentane-1-carboxylic acid

¹H NMR (400 MHz, Chloroform-*d*) δ 5.74 (s, 1H), 4.72 (d, J = 7.6 Hz, 2H), 4.48 (s, 2H), 2.36 (s, 6H), 2.20 – 1.82 (m, 7H), 1.74 (s, 3H), 1.58 – 1.42 (m, 1H). ¹³C{¹H} NMR (101 MHz, Chloroform-*d*) δ 175.0, 169.1, 149.4, 132.2, 125.8, 108.8, 68.7, 52.8, 40.7, 37.7, 37.4, 30.4, 27.2, 26.2, 20.7.

3.3 Synthesis of dioxazolones³

Step 1. Synthesis of hydroxamic acids: 1,1'-Carbonyldiimidazole (CDI, 1.5 equiv.) was added to a mixture of carboxylic acid (1.0 equiv.) in dry tetrahydrofuran (THF, 1.0 M) at room temperature. The reaction mixture was stirred for 1-2 hours. Afterward, powdered hydroxylamine hydrochloride (2.0 equiv.) was added. The resulting mixture was stirred overnight. The reaction direct vacuum concentration. The resulting residue was purified by silica gel flash chromatography (DCM/Methanol = $50:1 \sim 20:1$) to give the hydroxamic acid.

Step 2. Synthesis of dioxazolone substrates: To a stirred solution of hydoxamic acid (1.0 equiv.) in freshly distilled dichloromethane, 1,1'-carbonyldiimidazole (1.0 equiv.) was added in one portion at room temperature. After being stirred for 10-30 minutes, the reaction mixture was quenched with 1 N HCl, and extracted with EtOAc. The combined organic phase was dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo. The resulting residue was purified quickly by short silica pad (PE/EA = 10:1 $\sim 5:1$) to give the desired dioxazolones glycogen anomeric.

3-(bicyclo[1.1.1]pentan-1-yl)-1,4,2-dioxazol-5-one

¹H NMR (400 MHz, Chloroform-d) δ 2.64 (s, 1H), 2.27 (s, 6H).

¹³C{¹H} NMR (101 MHz, Chloroform-*d*) δ 163.1, 154.1, 51.9, 34.9, 30.6.

3-(3-fluorobicyclo[1.1.1]pentan-1-yl)-1,4,2-dioxazol-5-one

¹H NMR (400 MHz, Chloroform-*d*) δ 2.56 (d, J = 2.2 Hz, 6H).

¹³C{¹H} NMR (101 MHz, Chloroform-*d*) δ 162.9 (d, J = 35.8 Hz), 153.6, 74.7 (d, J = 327.2 Hz), 56.1 (d, J = 22.7 Hz), 22.0 (d, J = 57.1 Hz).

N-(tert-butyl)-3-(5-oxo-1,4,2-dioxazol-3-yl)bicyclo[1.1.1]pentane-1-carboxamide

¹H NMR (400 MHz, Chloroform-*d*) δ 2.43 (s, 6H), 1.36 (s, 9H).

¹³C{¹H} NMR (101 MHz, Chloroform-*d*) δ 166.9, 163.1, 153.8, 52.6, 51.6, 42.2, 29.7, 28.6.

3-(5-oxo-1,4,2-dioxazol-3-yl)-N-phenylbicyclo[1.1.1]pentane-1-carboxamide

¹H NMR (400 MHz, Chloroform-*d*) δ 7.52 (d, J = 7.9 Hz, 2H), 7.34 (t, J = 7.8 Hz, 2H), 7.15 (t, J = 7.4 Hz, 1H), 2.57 (s, 6H).

¹³C{¹H} NMR (101 MHz, Chloroform-*d*) δ 165.5, 162.8, 153.7, 136.8, 129.1, 125.0, 119.9, 52.8, 42.3, 30.1.

3-(3-benzoylbicyclo[1.1.1]pentan-1-yl)-1,4,2-dioxazol-5-one

 1 H NMR (400 MHz, Chloroform-d) δ 7.98 – 7.95 (m, 2H), 7.65 – 7.58 (m, 1H), 7.53 – 7.47 (m, 2H), 2.74 (s, 6H).

¹³C{¹H} NMR (101 MHz, Chloroform-*d*) δ 194.7, 163.0, 153.8, 135.6, 133.6, 128.8, 54.7, 46.0, 31.4.

benzyl 3-(5-oxo-1,4,2-dioxazol-3-yl)bicyclo[1.1.1]pentane-1-carboxylate

¹H NMR (400 MHz, Chloroform-*d*) δ 7.41 – 7.29 (m, 5H), 5.14 (s, 2H), 2.50 (s, 6H).

¹³C{¹H} NMR (101 MHz, Chloroform-*d*) δ 167.5, 162.8, 153.6, 135.2, 128.5, 128.4, 128.1, 66.7, 53.1, 39.8, 30.7.

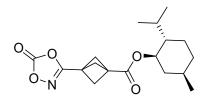
3,7-dimethyloct-6-en-1-yl 3-(5-oxo-1,4,2-dioxazol-3-yl)bicyclo[1.1.1]pentane-1-carboxylate

¹H NMR (400 MHz, Chloroform-*d*) δ 5.08 (t, J = 7.0 Hz, 1H), 4.23 – 3.99 (m, 2H), 2.49 (s, 6H), 2.06 – 1.93 (m, 2H), 1.68 (s, 4H), 1.61 (s, 3H), 1.55 – 1.41 (m, 2H), 1.38 – 1.29 (m, 1H), 1.24 – 1.15 (m, 1H), 0.92 (d, J = 6.5 Hz, 3H).

¹³C{¹H} NMR (101 MHz, Chloroform-*d*) δ 167.7, 162.8, 153.6, 131.2, 124.3, 63.6, 53.0, 39.9, 36.8, 35.1, 30.6, 29.4, 25.6, 25.2, 19.3, 17.5.

(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl yl)bicyclo[1.1.1]pentane-1-carboxylate

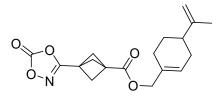
3-(5-oxo-1,4,2-dioxazol-3-



¹H NMR (400 MHz, Chloroform-*d*) δ 4.70 (td, J = 10.9, 4.4 Hz, 1H), 2.48 (s, 6H), 1.97 (d, J = 11.8 Hz, 1H), 1.82 – 1.37 (m, 6H), 1.15 – 0.82 (m, 8H), 0.76 (d, J = 7.0 Hz, 3H). ¹³C{¹H} NMR (101 MHz, Chloroform-*d*) δ 167.4, 163.0, 153.8, 75.3, 53.1, 46.9, 40.7, 40.2, 34.1, 31.3, 30.7, 26.7, 23.8, 22.0, 20.6, 16.7.

(4-(prop-1-en-2-yl)cyclohex-1-en-1-yl)methyl yl)bicyclo[1.1.1]pentane-1-carboxylate

3-(5-oxo-1,4,2-dioxazol-3-



¹H NMR (400 MHz, Chloroform-*d*) δ 5.76 (s, 1H), 4.73 (d, J = 10.0 Hz, 2H), 4.50 (s, 2H), 2.51 (s, 6H), 2.25 – 1.83 (m, 6H), 1.74 (t, J = 1.1 Hz, 3H), 1.56 – 1.43 (m, 1H). ¹³C{¹H} NMR (101 MHz, Chloroform-*d*) δ 167.6, 162.8, 153.7, 149.3, 132.0, 126.1, 108.8, 68.9, 53.1, 40.6, 39.9, 30.7, 30.3, 27.1, 26.2, 20.7.

3.4 Synthesis of Aryl-TT Salts

CI DCM, -40°C
$$\stackrel{S}{\longrightarrow}$$
 $\stackrel{S}{\longrightarrow}$ $\stackrel{S}{\longrightarrow}$

A 25 mL Schlenk tube was charged with thianthrene S-oxide (TTSO) (2.0 mmol), CH₂Cl₂ (10.0 mL), and clofibrate (2.0 mmol) under an argon atmosphere. The reaction mixture was cooled to -40 °C and stirred at this temperature. Trifluoromethanesulfonic anhydride (Tf₂O) (2.4 mmol) was added dropwise. The reaction mixture was stirred at -40 °C for 30 minutes, then allowed to warm to room temperature and stirred for an additional 12 hours. The reaction was neutralized using a saturated aqueous solution of NaHCO₃, followed by extraction with DCM. The combined organic layers were dried over Na₂SO₄ and concentrated to dryness under reduced pressure. The crude product⁴ was purified by crystallization from a DCM/Et₂O system.

A 50 mL schlenk tube was charged with thianthrene S-oxide (557 mg, 2.4 mmol, 1.2 equiv.), DCM (10 mL) and methyl 5-(2,5-dimethylphenoxy)-2,2 dimethylpentanoate (528 mg, 2 mmol, 1.0 equiv.) under a nitrogen atmosphere. The reaction mixture was then cooled to -40 °C and stirred at this temperature. Tf₂O (2.4 mmol, 1.2 equiv.) was added dropwise. The reaction mixture was stirred at -40 °C for 30 min, and then allowed to stir at room temperature for 12 h, neutralized by a saturated aqueous NaHCO₃ solution, and extracted with DCM. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated to dryness under reduced pressure. The crude product⁵ was purified by column chromatography on silica gel (eluents: DCM/MeOH = 30/0 to 30/1 (v/v)) to afford product as a brown solid (0.88 g, 68 %).

4. General procedure for scale-up preparation

In a nitrogen-filled glove box, an oven-dried 100 mL tube equipped with a magnetic stir bar was charged with $[Ru(p\text{-cymene})Cl_2]_2$ (5 mol%, 98 mg), NaOAc (1.0 equiv., 262.5 mg), ethyl benzimidate hydrochloride **1a** (3.2 mmol), methyl 3-(5-oxo-1,4,2-dioxazol-3-yl)bicyclo[1.1.1]pentane-1-carboxylate **2a** (4.8 mmol), and AgNTf₂ (30 mol%). TBME (32 mL) was then added to the tube. The reaction tube was removed from the glove box and stirred in an oil bath at 80 °C for 18 h. After completion of the reaction, the mixture was subjected to silica gel by the dry-loading method. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 10:1-5:1) or by preparative TLC.

5. General procedure for transformations of compound 3a

$$\begin{array}{c|c} \text{EtO} & & \text{EtO} \\ \hline & N & \\ \hline & N & \\ \hline & N & \\ \hline & CO_2\text{Me} & \\ \hline & THF, 0^{\circ}\text{C}, 2h & \\ \hline \end{array}$$

To a suspension of LiAlH₄ (10 mg, 0.24 mmol, 1.2 equiv.) in THF (3.0 mL) at 0 °C was added dropwise solution of **3a** (83.4 mg, 0.2 mmol, 1.0 equiv.) in THF (2.0 mL). The reaction mixture was stirred at 0 °C 2h and then quenched by careful addition of water (4.0 mL), NaOH (15%, 4.0 mL), and water (12 mL). The aluminium salts formed were removed by filtration through Celite, and the solution was dried over MgSO₄. The solvent was evaporated to give product **4** (48.6 mg, 90% yield) as a colorless oil.

$$\begin{array}{c|c} EtO & EtO \\ \hline \\ N & CO_2Me \end{array} \begin{array}{c} LiOH \\ \hline \\ MeOH, rt, overnight \end{array} \begin{array}{c} EtO \\ \hline \\ N & O \end{array}$$

To a 10 mL Schlenk tube charged with **3a** (59.6 mg, 0.2 mmol) was added MeOH (0.6 mL) and 0.6 mL 1 M LiOH aqueous solution. After stirring at room temperature for 4 h, the reaction mixture was quenched with 1 M HCl solution, extracted with EtOAc, washed with brine, dried over anhydrous Na₂SO₄ and purified by column chromatography (Petroleum ether/EtOAc = 5:1-2:1) on silica gel to afford 75% yield of acid **5** as green solid (45.5 mg, 80% yield).

6. Derivatization of Bioactive Molecules from 3d⁶

In an oven-dried 10 mL tube, thianthrenium salt (0.1 mmol, 1.0 equiv.), methyl 3-(7-bromo-4-ethoxyquinazolin-2-yl)bicyclo[1.1.1]pentane-1-carboxylate 3d (1.3 equiv.), $B_2(OH)_4$ (2.0 equiv.), K_3PO_4 (3.0 equiv.), SPhos (10 mol%) and SPhos-Pd-G3 (5.0 mol%) were added and charged with argon more than three times (The tube was sealed with tipping plug). MeOH (1 mL, c = 0.1 M). The Schlenk tube was stirred vigorously at 80 °C for 16 h in an oil bath. After the indicated time, the reaction mixture was allowed to cool to 23 °C. Then, the reaction vial was opened to air, and the resulting mixture was concentrated by rotary evaporation. The residue was purified by chromatography on silica gel eluting with hexanes/ethyl acetate (10:1 to 5:1, v/v) to afford the product.

7. X-ray Single Crystal Diffraction Data

Bond precision: C-C = 0.0020 A Wavelength= 1.54184

Cell: a = 9.0582(1) b = 11.4917(2) c = 16.1874(2)

alpha=102.344(1) beta=104.774(1) gamma=102.029(1)

Temperature: 296 K

r omperature.	27011	
	Calculated	Reported
Volume	1528.74(4)	1528.74(4)
Space group	P -1	P -1
Hall group	-P 1	-P 1
Moiety formula	C17 H18 N2 O3	2(C17 H18 N2 O3)
Sum formula	C17 H18 N2 O3	C34 H36 N4 O6
Mr	298.33	596.67
Dx,g cm ⁻³	1.296	1.296
Z	4	2
Mu (mm-1)	0.732	0.732
F000	632.0	632.0
F000'	633.96	
h,k,lmax	11,14,20	11,14,20
Nref	6419	6121
Tmin,Tmax	0.877,0.916	0.840,1.000
Tmin'	0.877	

Correction method= # Reported T Limits: Tmin=0.840 Tmax=1.000

AbsCorr = MULTI-SCAN

Data completeness= 0.954 Theta(max)= 76.186

R(reflections)= 0.0469(5351) wR2(reflections)= 0.1414(6121)

S = 1.072 Npar= 401

Thermal ellipsoids are shown at 50% probability

8. Plausible Catalytic Cycle

9. References

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10. Characterization Data

methyl 3-(4-ethoxyquinazolin-2-yl)bicyclo[1.1.1]pentane-1-carboxylate (3a)

Purified by flash chromatography (on silica gel, petroleum ether /ethyl acetate = 10:1-5:1) White solid; 47.7 mg, 80% yield.

¹H NMR (400 MHz, Chloroform-*d*) δ 8.13 (d, J = 8.2 Hz, 1H), 7.90 (d, J = 8.4 Hz, 1H), 7.80 – 7.72 (m, 1H), 7.51 – 7.43 (m, 1H), 4.64 (q, J = 7.1 Hz, 2H), 3.74 (s, 3H), 2.51 (s, 6H), 1.50 (t, J = 7.1 Hz, 3H).

¹³C{¹H} NMR (101 MHz, Chloroform-*d*) δ 170.9, 166.6, 162.4, 151.2, 133.2, 127.4, 126.3, 123.4, 115.2, 62.8, 53.2, 51.6, 43.0, 37.3, 14.3.

HRMS (ESI-TOF) m/z: [M+H]⁺ Calcd for C₁₇H₁₉N₂O₃ 299.1390; Found 299.1389.

methyl 3-(4-ethoxy-7-fluoroquinazolin-2-yl)bicyclo[1.1.1]pentane-1-carboxylate (3b)

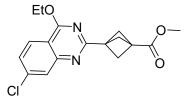
Purified by flash chromatography (on silica gel, petroleum ether /ethyl acetate = 10:1-5:1) White solid; 44.9 mg, 71% yield.

¹H NMR (400 MHz, Chloroform-*d*) δ 8.13 (dd, J = 9.0, 6.1 Hz, 1H), 7.52 (dd, J = 10.0, 2.5 Hz, 1H), 7.26 – 7.19 (m, 1H), 4.63 (q, J = 7.1 Hz, 2H), 3.74 (s, 3H), 2.50 (s, 6H), 1.50 (t, J = 7.1 Hz, 3H).

¹³C {¹H} NMR (101 MHz, Chloroform-*d*) δ 170.8, 166.4, 165.6 (d, J = 253.5 Hz), 163.8, 153.1 (d, J = 13.5 Hz), 126.1 (d, J = 10.5 Hz), 116.1 (d, J = 24.7 Hz), 112.1 (d, J = 1.4 Hz), 111.7 (d, J = 21.0 Hz), 62.9, 53.2, 51.7, 42.9, 37.3, 14.2.

¹⁹F NMR (376 MHz, Chloroform-d) δ -104.0.

HRMS (ESI-TOF) m/z: [M+H]⁺ Calcd for C₁₇H₁₈FN₂O₃ 317.1296; Found 317.1295.



methyl 3-(7-chloro-4-ethoxyquinazolin-2-yl)bicyclo[1.1.1]pentane-1-carboxylate (3c)

Purified by flash chromatography (on silica gel, petroleum ether /ethyl acetate = 10:1-5:1) White solid; 48.5 mg, 73% yield.

 1 H NMR (400 MHz, Chloroform-d) δ 8.04 (d, J = 8.7 Hz, 1H), 7.90 (d, J = 2.0 Hz, 1H), 7.42 (dd, J = 8.7, 2.0 Hz, 1H), 4.63 (q, J = 7.1 Hz, 2H), 3.74 (s, 3H), 2.49 (s, 6H), 1.50 (t, J = 7.1 Hz, 3H).

¹³C{¹H} NMR (101 MHz, Chloroform-*d*) δ 170.7, 166.5, 163.7, 152.0, 139.4, 127.2, 126.7, 124.9, 113.6, 63.0, 53.2, 51.7, 42.9, 37.3, 14.2.

HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{17}H_{18}ClN_2O_3$ 333.1000; Found 333.0999.

methyl 3-(7-bromo-4-ethoxyquinazolin-2-yl)bicyclo[1.1.1]pentane-1-carboxylate (3d)

Purified by flash chromatography (on silica gel, petroleum ether /ethyl acetate = 10:1-5:1) White solid; 53.4 mg, 71% yield.

¹H NMR (400 MHz, Chloroform-*d*) δ 8.09 (d, J = 1.9 Hz, 1H), 7.97 (d, J = 8.7 Hz, 1H), 7.57 (dd, J = 8.7, 1.9 Hz, 1H), 4.63 (q, J = 7.1 Hz, 2H), 3.74 (s, 3H), 2.49 (s, 6H), 1.50 (t, J = 7.1 Hz, 3H).

¹³C{¹H} NMR (101 MHz, Chloroform-*d*) δ 170.7, 166.6, 163.6, 152.1, 130.0, 129.8, 127.9, 124.8, 113.9, 63.1, 53.2, 51.7, 42.9, 37.3, 14.2.

HRMS (ESI-TOF) m/z: [M+H]⁺ Calcd for C₁₇H₁₈BrN₂O₃ 377.0495; Found 377.0493.

methyl 4-ethoxy-2-(3-(methoxycarbonyl)bicyclo[1.1.1]pentan-1-yl)quinazoline-7-carboxylate (3e)

Purified by flash chromatography (on silica gel, petroleum ether /ethyl acetate = 10:1-5:1) White solid; 24.9 mg, 35% yield.

¹H NMR (400 MHz, Chloroform-d) δ 8.61 (d, J = 1.6 Hz, 1H), 8.17 (d, J = 8.5 Hz, 1H), 8.08 (dd, J = 8.5, 1.6 Hz, 1H), 4.66 (q, J = 7.1 Hz, 2H), 3.98 (s, 3H), 3.74 (s, 3H), 2.51 (s, 6H), 1.52 (t, J = 7.1 Hz, 3H).

¹³C{¹H} NMR (101 MHz, Chloroform-*d*) δ 170.7, 166.6, 166.2, 163.3, 150.9, 134.4, 129.7, 126.0, 123.8, 117.7, 63.2, 53.2, 52.5, 51.7, 42.9, 37.3, 14.2.

HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{19}H_{21}N_2O_5$ 357.1445; Found 357.1447.

$$F_3C$$

methyl 3-(4-ethoxy-7-(trifluoromethyl)quinazolin-2-yl)bicyclo[1.1.1]pentane-1-carboxylate (3f)

Purified by flash chromatography (on silica gel, petroleum ether /ethyl acetate = 10:1-5:1) Colourless liquid; 41.0 mg, 56% yield.

¹H NMR (400 MHz, Chloroform-*d*) δ 8.27 – 8.20 (m, 2H), 7.67 (dd, J = 8.6, 1.8 Hz, 1H), 4.67 (q, J = 7.1 Hz, 2H), 3.75 (s, 3H), 2.51 (s, 6H), 1.53 (t, J = 7.1 Hz, 3H).

¹³C{¹H} NMR (101 MHz, Chloroform-*d*) δ 170.7, 166.5, 163.9, 150.7, 134.9 (q, J = 32.6 Hz), 125.2 (q, J = 4.2 Hz), 124.8, 122.1 (q, J = 3.2 Hz), 117.0, 63.4, 53.2, 51.7, 42.9, 37.4, 14.2.

¹⁹F NMR (376 MHz, Chloroform-*d*) δ -63.2.

HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{18}H_{18}F_3N_2O_3$ 367.1264; Found 367.1265.

$$F_3C$$
 N
 O
 O

methyl 3-(4-ethoxy-6-(trifluoromethyl)quinazolin-2-yl)bicyclo[1.1.1]pentane-1-carboxylate (3g)

Purified by flash chromatography (on silica gel, petroleum ether /ethyl acetate = 10:1-5:1) White solid; 47.6 mg, 65% yield.

¹H NMR (400 MHz, Chloroform-*d*) δ 8.4 (s, 1H), 8.2 – 7.7 (m, 2H), 4.7 (q, J = 7.1 Hz, 2H), 3.7 (s, 3H), 2.5 (s, 6H), 1.5 (t, J = 7.0 Hz, 3H).

¹³C{¹H} NMR (101 MHz, Chloroform-*d*) δ 170.7, 167.0, 164.7, 152.8, 129.1 (q, J = 3.1 Hz), 128.6, 128.2 (q, J = 33.2 Hz), 123.7 (d, J = 272.5 Hz), 121.7 (q, J = 4.3 Hz), 114.6, 63.5, 53.3, 51.7, 43.0, 37.4, 14.2.

¹⁹F NMR (376 MHz, Chloroform-d) δ -62.3.

HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{18}H_{18}F_3N_2O_3$ 367.1264; Found 367.1262.

methyl 3-(4-ethoxy-7-methylquinazolin-2-yl)bicyclo[1.1.1]pentane-1-carboxylate (3h)

Purified by flash chromatography (on silica gel, petroleum ether /ethyl acetate = 10:1-5:1) White solid; 44.3 mg, 71% yield.

¹H NMR (400 MHz, Chloroform-*d*) δ 8.00 (d, J = 8.3 Hz, 1H), 7.72 – 7.67 (m, 1H), 7.30 (dd, J = 8.3, 1.6 Hz, 1H), 4.62 (q, J = 7.1 Hz, 2H), 3.73 (s, 3H), 2.50 (s, 6H), 1.49 (t, J = 7.1 Hz, 3H).

¹³C{¹H} NMR (101 MHz, Chloroform-*d*) δ 170.9, 166.5, 162.5, 151.5, 144.0, 128.2, 126.6, 123.0, 113.0, 62.6, 53.1, 51.6, 42.9, 37.2, 22.0, 14.3.

HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{18}H_{21}N_2O_3$ 313.1547; Found 313.1544.

methyl 3-(4-ethoxy-6-methylquinazolin-2-yl)bicyclo[1.1.1]pentane-1-carboxylate (3i)

Purified by flash chromatography (on silica gel, petroleum ether /ethyl acetate = 10:1-5:1) White solid; 49.9 mg, 80% yield.

¹H NMR (400 MHz, Chloroform-*d*) δ 7.89 (d, J = 2.0 Hz, 1H), 7.79 (d, J = 8.5 Hz, 1H), 7.59 (dd, J = 8.6, 2.1 Hz, 1H), 4.62 (q, J = 7.1 Hz, 2H), 3.73 (s, 3H), 2.50 (s, 6H), 1.50 (t, J = 7.1 Hz, 3H).

¹³C{¹H} NMR (101 MHz, Chloroform-*d*) δ 170.9, 166.2, 161.5, 149.6, 136.3, 135.2, 127.1, 122.3, 115.0, 62.6, 53.2, 51.6, 42.9, 37.3, 21.5, 14.3.

HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{18}H_{21}N_2O_3$ 313.1547; Found 313.1546.

methyl 3-(4-ethoxy-7-methoxyquinazolin-2-yl)bicyclo[1.1.1]pentane-1-carboxylate (3j)

Purified by flash chromatography (on silica gel, petroleum ether /ethyl acetate = 10:1-5:1) White solid; 31.5 mg, 48% yield.

 1 H NMR (400 MHz, Chloroform-d) δ 8.00 (d, J = 9.0 Hz, 1H), 7.23 (d, J = 2.4 Hz, 1H), 7.08 (dd, J = 9.0, 2.5 Hz, 1H), 4.61 (q, J = 7.1 Hz, 2H), 3.92 (s, 3H), 3.73 (s, 3H), 2.50 (s, 6H), 1.48 (t, J = 7.1 Hz, 3H).

¹³C{¹H} NMR (101 MHz, Chloroform-*d*) δ 170.9, 166.3, 163.7, 163.2, 153.7, 124.7, 118.6, 109.5, 106.1, 62.5, 55.6, 53.2, 51.7, 42.9, 37.2, 14.3.

HRMS (ESI-TOF) m/z: [M+H]⁺Calcd for C₁₈H₂₁N₂O₄ 329.1496; Found 329.1495.

methyl 3-(7-(benzyloxy)-4-ethoxyquinazolin-2-yl)bicyclo[1.1.1]pentane-1-carboxylate (3k)

Purified by flash chromatography (on silica gel, petroleum ether /ethyl acetate = 10:1-5:1) White solid; 33.9 mg, 42% yield.

¹H NMR (400 MHz, Chloroform-*d*) δ 8.02 (d, J = 9.0 Hz, 1H), 7.47 – 7.43 (m, 2H), 7.42 – 7.39 (m, 2H), 7.37 – 7.30 (m, 2H), 7.17 (dd, J = 9.0, 2.5 Hz, 1H), 5.17 (s, 2H), 4.61 (q, J = 7.1 Hz, 2H), 3.73 (s, 3H), 2.49 (s, 6H), 1.48 (t, J = 7.1 Hz, 3H).

¹³C{¹H} NMR (101 MHz, Chloroform-*d*) δ 170.9, 166.3, 163.2, 162.8, 153.6, 136.1, 128.6, 128.2, 127.6, 124.8, 118.9, 109.7, 107.2, 70.2, 62.6, 53.2, 51.6, 42.9, 37.3, 14.3. **HRMS** (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{24}H_{25}N_2O_4$ 405.1809; Found 405.1808.

methyl 3-(4-ethoxy-7-phenylquinazolin-2-yl)bicyclo[1.1.1]pentane-1-carboxylate (3l)

Purified by flash chromatography (on silica gel, petroleum ether /ethyl acetate = 10:1-5:1) White solid; 53.9 mg, 72% yield.

¹H NMR (400 MHz, Chloroform-*d*) δ 8.16 (d, J = 8.5 Hz, 1H), 8.13 (d, J = 1.7 Hz, 1H), 7.76 – 7.68 (m, 3H), 7.47 (t, J = 7.4 Hz, 2H), 7.40 (t, J = 7.3 Hz, 1H), 4.65 (q, J = 7.1 Hz, 2H), 3.74 (s, 3H), 2.53 (s, 6H), 1.51 (t, J = 7.1 Hz, 3H).

¹³C{¹H} NMR (101 MHz, Chloroform-*d*) δ 170.8, 166.6, 162.9, 151.7, 146.0, 139.8, 128.9, 128.2, 127.4, 125.7, 125.1, 123.8, 114.1, 62.8, 53.2, 51.6, 43.0, 37.3, 14.3.

HRMS (ESI-TOF) m/z: [M+H]⁺Calcd for C₂₃H₂₃N₂O₃ 375.1703; Found 375.1700.

methyl 3-(4-ethoxybenzo[g]quinazolin-2-yl)bicyclo[1.1.1]pentane-1-carboxylate (3m)

Purified by flash chromatography (on silica gel, petroleum ether /ethyl acetate = 10:1-5:1) White solid; 55.7 mg, 80% yield.

¹H NMR (400 MHz, Chloroform-*d*) δ 8.71 (s, 1H), 8.43 (s, 1H), 8.00 (dd, J = 11.7, 8.4 Hz, 2H), 7.57 – 7.52 (m, 1H), 7.51 – 7.45 (m, 1H), 4.70 (q, J = 7.1 Hz, 2H), 3.74 (s, 3H), 2.55 (s, 6H), 1.56 (t, J = 7.1 Hz, 3H).

¹³C{¹H} NMR (101 MHz, Chloroform-*d*) δ 170.9, 167.3, 161.7, 146.2, 136.2, 131.4, 129.0, 128.1, 127.7, 125.9, 125.0, 123.8, 114.5, 63.0, 53.2, 51.6, 43.1, 37.4, 14.3.

HRMS (ESI-TOF) m/z: [M+H]⁺Calcd for C₂₁H₂₁N₂O₃ 349.1547; Found 349.1543.

methyl 3-(4-ethoxythieno[3,2-d]pyrimidin-2-yl)bicyclo[1.1.1]pentane-1-carboxylate (3n)

Purified by flash chromatography (on silica gel, petroleum ether /ethyl acetate = 10:1-5:1) White solid; 45.6 mg, 75% yield.

¹H NMR (400 MHz, Chloroform-*d*) δ 7.81 (d, J = 5.4 Hz, 1H), 7.48 (d, J = 5.4 Hz, 1H), 4.64 (q, J = 7.1 Hz, 2H), 3.73 (s, 3H), 2.49 (s, 6H), 1.48 (t, J = 7.1 Hz, 3H).

¹³C{¹H} NMR (101 MHz, Chloroform-*d*) δ 170.8, 164.1, 163.1, 162.3, 133.7, 124.4, 116.0, 62.8, 53.3, 51.7, 42.6, 37.3, 14.4.

HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{15}H_{17}N_2O_3S$ 305.0954; Found 305.0956.

methyl 3-(4-methoxyquinazolin-2-yl)bicyclo[1.1.1]pentane-1-carboxylate (30)

Purified by flash chromatography (on silica gel, petroleum ether /ethyl acetate = 10:1-5:1) White solid; 38.6 mg, 68% yield.

¹H NMR (400 MHz, Chloroform-*d*) δ 8.11 (d, J = 9.0 Hz, 1H), 7.91 (d, J = 8.4 Hz, 1H), 7.81 – 7.75 (m, 1H), 7.54 – 7.45 (m, 1H), 4.16 (s, 3H), 3.74 (s, 3H), 2.52 (s, 6H). ¹³C{¹H} NMR (101 MHz, Chloroform-*d*) δ 170.8, 167.0, 162.4, 151.2, 133.3, 127.4, 126.4, 123.3, 115.1, 53.9, 53.2, 51.7, 43.0, 37.3.

HRMS (ESI-TOF) m/z: [M+H]⁺Calcd for C₁₆H₁₇N₂O₃ 285.1234; Found 285.1235.

$$N$$
 $O-$

methyl 3-(4-isopropoxyquinazolin-2-yl)bicyclo[1.1.1]pentane-1-carboxylate (3p)

Purified by flash chromatography (on silica gel, petroleum ether /ethyl acetate = 10:1-5:1) Colourless liquid; 39.3 mg, 63% yield.

¹H NMR (400 MHz, Chloroform-*d*) δ 8.11 (d, J = 8.1 Hz, 1H), 7.89 (d, J = 8.4 Hz, 1H), 7.82 – 7.69 (m, 1H), 7.53 – 7.42 (m, 1H), 5.69 – 5.56 (m, 1H), 3.74 (s, 3H), 2.51 (s, 6H), 1.47 (d, J = 6.3 Hz, 6H).

¹³C{¹H} NMR (101 MHz, Chloroform-*d*) δ 170.9, 166.2, 162.4, 151.3, 133.2, 127.3, 126.2, 123.5, 115.5, 70.0, 53.2, 51.6, 43.0, 37.3, 21.7.

HRMS (ESI-TOF) m/z: [M+H]⁺Calcd for C₁₈H₂₁N₂O₃ 313.1547; Found 313.1544.

2-(bicyclo[1.1.1]pentan-1-yl)-4-ethoxyquinazoline (3q)

Purified by flash chromatography (on silica gel, petroleum ether /ethyl acetate = 10:1-5:1) Colourless liquid; 28.8 mg, 60% yield.

 1 H NMR (400 MHz, Chloroform-*d*) δ 8.15 – 8.05 (m, 1H), 7.98 – 7.88 (m, 1H), 7.80 – 7.72 (m, 1H), 7.51 – 7.42 (m, 1H), 4.64 (q, J = 7.1 Hz, 2H), 2.56 (s, 1H), 2.27 (s, 6H), 1.50 (t, J = 7.1 Hz, 3H).

¹³C{¹H} NMR (101 MHz, Chloroform-*d*) δ 166.5, 163.5, 151.3, 133.1, 127.4, 126.0, 123.3, 115.1, 62.6, 51.9, 48.2, 27.2, 14.3.

HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{15}H_{17}N_2O$ 241.1335; Found 241.1334.

4-ethoxy-2-(3-fluorobicyclo[1.1.1]pentan-1-yl)quinazoline (3r)

Purified by flash chromatography (on silica gel, petroleum ether /ethyl acetate = 10:1-5:1) White solid; 32.0 mg, 62% yield.

¹H NMR (400 MHz, Chloroform-*d*) δ 8.15 – 8.10 (m, 1H), 7.88 (d, J = 8.2 Hz, 1H), 7.82 – 7.74 (m, 1H), 7.52 – 7.46 (m, 1H), 4.63 (q, J = 7.1 Hz, 2H), 2.54 (d, J = 2.6 Hz, 6H), 1.50 (t, J = 7.1 Hz, 3H).

 13 C{ 1 H} NMR (101 MHz, Chloroform-*d*) δ 166.5, 161.5 (d, J = 34.6 Hz), 151.3, 133.3, 127.3, 126.4, 123.4, 115.1, 76.2 (d, J = 326.3 Hz), 62.8, 55.8, 55.6, 33.1 (d, J = 47.2 Hz), 14.3.

¹⁹F NMR (565 MHz, Chloroform-d) δ -150.2.

HRMS (ESI-TOF) m/z: [M+H]⁺Calcd for C₁₅H₁₆FN₂O 259.1241; Found 259.1242.

(3-(4-ethoxyquinazolin-2-yl)bicyclo[1.1.1]pentan-1-yl)(phenyl)methanone (3s)

Purified by flash chromatography (on silica gel, petroleum ether /ethyl acetate = 10:1-5:1) Colourless liquid; 58.5 mg, 85% yield.

¹H NMR (400 MHz, Chloroform-*d*) δ 8.15 (dd, J = 8.2, 1.4 Hz, 1H), 8.12 – 8.07 (m, 2H), 7.92 (d, J = 8.4 Hz, 1H), 7.83 – 7.76 (m, 1H), 7.63 – 7.54 (m, 1H), 7.53 – 7.43 (m, 3H), 4.67 (q, J = 7.1 Hz, 2H), 2.75 (s, 6H), 1.52 (t, J = 7.1 Hz, 3H).

¹³C{¹H} NMR (101 MHz, Chloroform-*d*) δ 197.9, 166.7, 162.6, 151.3, 136.6, 133.3, 132.9, 128.9, 128.5, 127.4, 126.3, 123.4, 115.3, 62.8, 54.9, 43.6, 43.6, 14.3.

HRMS (ESI-TOF) m/z: [M+H]⁺Calcd for C₂₂H₂₁N₂O₂ 345.1598; Found 345.1596.

benzyl 3-(4-ethoxyquinazolin-2-yl)bicyclo[1.1.1]pentane-1-carboxylate (3t)

Purified by flash chromatography (on silica gel, petroleum ether /ethyl acetate = 10:1-5:1) Colourless liquid; 44.9 mg, 60% yield.

¹H NMR (400 MHz, Chloroform-*d*) δ 8.12 (d, J = 8.1 Hz, 1H), 7.90 (d, J = 8.4 Hz, 1H), 7.81 – 7.73 (m, 1H), 7.48 (t, J = 7.5 Hz, 1H), 7.43 – 7.30 (m, 5H), 5.18 (s, 2H), 4.63 (q, J = 7.1 Hz, 2H), 2.53 (s, 6H), 1.49 (t, J = 7.1 Hz, 3H).

¹³C{¹H} NMR (101 MHz, Chloroform-*d*) δ 170.3, 166.6, 162.4, 151.2, 136.0, 133.3, 128.5, 128.1, 127.9, 127.4, 126.3, 123.4, 115.2, 66.1, 62.8, 53.2, 43.0, 37.4, 14.3.

HRMS (ESI-TOF) m/z: [M+H]+Calcd for C₂₃H₂₃N₂O₃ 375.1703; Found 375.1701.

3-(4-ethoxyquinazolin-2-yl)-N-phenylbicyclo[1.1.1]pentane-1-carboxamide (3u)

Purified by flash chromatography (on silica gel, petroleum ether /ethyl acetate = 10:1-5:1) White solid; 32.3 mg, 45% yield.

¹H NMR (600 MHz, Chloroform-*d*) δ 8.14 (dd, J = 8.2, 1.4 Hz, 1H), 7.91 (d, J = 8.4 Hz, 1H), 7.82 – 7.76 (m, 1H), 7.59 (d, J = 7.9 Hz, 2H), 7.54 – 7.49 (m, 1H), 7.39 (s, 1H), 7.34 (t, J = 7.8 Hz, 2H), 7.12 (t, J = 7.4 Hz, 1H), 4.65 (q, J = 7.1 Hz, 2H), 2.56 (s, 6H), 1.51 (t, J = 7.1 Hz, 3H).

¹³C{¹H} NMR (101 MHz, Chloroform-*d*) δ 168.4, 166.7, 162.3, 151.2, 137.6, 133.4, 129.0, 127.3, 126.4, 124.3, 123.4, 119.6, 115.3, 62.8, 52.8, 41.9, 39.8, 14.3.

HRMS (ESI-TOF) m/z: [M+H]⁺ Calcd for C₂₂H₂₂N₃O₂ 360.1707; Found 360.1708.

N-(*tert*-butyl)-3-(4-ethoxyquinazolin-2-yl)bicyclo[1.1.1]pentane-1-carboxamide (3v)

Purified by flash chromatography (on silica gel, petroleum ether /ethyl acetate = 10:1-5:1) White solid; 47.5 mg, 70% yield.

¹H NMR (400 MHz, Chloroform-*d*) δ 8.14 – 8.11 (m, 1H), 7.90 (d, J = 8.2 Hz, 1H), 7.80 – 7.74 (m, 1H), 7.51 – 7.46 (m, 1H), 4.63 (q, J = 7.1 Hz, 2H), 2.42 (s, 6H), 1.50 (t, J = 7.1 Hz, 3H), 1.39 (s, 9H).

¹³C{¹H} NMR (101 MHz, Chloroform-*d*) δ 169.8, 166.6, 162.6, 151.2, 133.2, 127.3, 126.2, 123.3, 115.2, 62.7, 52.5, 51.1, 41.5, 39.6, 28.7, 14.3.

HRMS (ESI-TOF) m/z: [M+H]⁺ Calcd for C₂₀H₂₆N₃O₂ 340.2020; Found 340.2017.

(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl yl)bicyclo[1.1.1]pentane-1-carboxylate (3w)

3-(4-ethoxyquinazolin-2-

Purified by flash chromatography (on silica gel, petroleum ether /ethyl acetate = 10:1-5:1) Colourless liquid; 69.3 mg, 82% yield.

¹H NMR (400 MHz, Chloroform-*d*) δ 8.12 (d, J = 8.1 Hz, 1H), 7.90 (d, J = 8.4 Hz, 1H), 7.82 – 7.72 (m, 1H), 7.48 (t, J = 7.6 Hz, 1H), 4.71 (td, J = 10.9, 4.4 Hz, 1H), 4.64 (q, J = 7.1 Hz, 2H), 2.49 (s, 6H), 2.10 – 1.99 (m, 1H), 1.96 – 1.81 (m, 1H), 1.75 – 1.63 (m, 2H), 1.55 – 1.39 (m, 5H), 1.13 – 0.99 (m, 2H), 0.97 – 0.88 (m, 7H), 0.80 (d, J = 7.0 Hz, 3H).

¹³C{¹H} NMR (101 MHz, Chloroform-*d*) δ 170.1, 166.6, 162.6, 151.3, 133.2, 127.4, 126.3, 123.4, 115.2, 74.3, 62.7, 53.1, 47.0, 42.9, 40.8, 37.6, 34.3, 31.4, 26.7, 23.9, 22.0, 20.6, 16.8, 14.3.

HRMS (ESI-TOF) m/z: [M+H]⁺ Calcd for C₂₆H₃₅N₂O₃ 423.2642; Found 423.2641.

3,7-dimethyloct-6-en-1-yl 3-(4-ethoxyquinazolin-2-yl)bicyclo[1.1.1]pentane-1-carboxylate (3x)

Purified by flash chromatography (on silica gel, petroleum ether /ethyl acetate = 10:1-5:1) Colourless liquid; 67.6 mg, 80% yield.

¹H NMR (400 MHz, Chloroform-*d*) δ 8.12 (dd, J = 8.2, 1.4 Hz, 1H), 7.92 – 7.87 (m, 1H), 7.82 – 7.73 (m, 1H), 7.52 – 7.44 (m, 1H), 5.10 (t, J = 7.1 Hz, 1H), 4.64 (q, J = 7.1 Hz, 2H), 4.22 – 4.13 (m, 2H), 2.50 (s, 6H), 2.06 – 1.93 (m, 3H), 1.75 – 1.66 (m, 4H), 1.62 – 1.56 (m, 4H), 1.50 (t, J = 7.1 Hz, 4H), 1.40 – 1.32 (m, 1H), 1.27 – 1.17 (m, 1H), 0.94 (d, J = 6.5 Hz, 3H).

¹³C{¹H} NMR (101 MHz, Chloroform-*d*) δ 170.6, 166.6, 162.5, 151.2, 133.2, 131.3, 127.4, 126.3, 124.5, 123.4, 115.2, 63.1, 62.7, 53.1, 42.9, 37.4, 37.0, 35.3, 29.6, 25.7, 25.4, 19.5, 17.6, 14.3.

HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{26}H_{35}N_2O_3$ 423.2642; Found 423.2639.

(4-(prop-1-en-2-yl)cyclohex-1-en-1-yl)methyl yl)bicyclo[1.1.1]pentane-1-carboxylate (3y)

3-(4-ethoxyquinazolin-2-

Purified by flash chromatography (on silica gel, petroleum ether /ethyl acetate = 10:1-5:1) Colourless liquid; 65.2 mg, 78% yield.

 1 H NMR (400 MHz, Chloroform-d) δ 8.12 (d, J = 8.1 Hz, 1H), 7.90 (d, J = 8.4 Hz, 1H), 7.81 – 7.73 (m, 1H), 7.53 – 7.44 (m, 1H), 5.77 (s, 1H), 4.76 – 4.71 (m, 2H), 4.64 (q, J = 7.1 Hz, 2H), 4.53 (s, 2H), 2.52 (s, 6H), 2.22 – 1.84 (m, 7H), 1.75 (s, 3H), 1.50 (t, J = 7.1 Hz, 3H).

¹³C{¹H} NMR (101 MHz, Chloroform-*d*) δ 170.4, 166.6, 162.5, 151.2, 149.6, 133.2, 132.5, 127.4, 126.3, 125.2, 123.4, 115.2, 108.7, 68.2, 62.7, 53.2, 43.0, 40.8, 37.4, 30.4, 27.3, 26.2, 20.7, 14.3.

HRMS (ESI-TOF) m/z: [M+H]⁺Calcd for C₂₆H₃₁N₂O₃ 419.2329; Found 419.2328.

(3-(4-ethoxyquinazolin-2-yl)bicyclo[1.1.1]pentan-1-yl)methanol (4)

Purified by flash chromatography (on silica gel, petroleum ether /ethyl acetate = 10:1-5:1) Colourless liquid; 48.6 mg, 90% yield.

¹H NMR (400 MHz, Chloroform-*d*) δ 8.12 (dd, J = 8.1, 1.5 Hz, 1H), 7.96 – 7.85 (m, 1H), 7.79 – 7.73 (m, 1H), 7.50 – 7.43 (m, 1H), 4.64 (q, J = 7.1 Hz, 2H), 3.76 (s, 2H), 2.18 (s, 6H), 1.50 (t, J = 7.1 Hz, 3H).

¹³C{¹H}NMR (101 MHz, Chloroform-*d*) δ 166.6, 163.5, 151.2, 133.1, 127.3, 126.1, 123.3, 115.1, 63.2, 62.7, 50.5, 43.4, 39.6, 14.3.

HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{19}N_2O_2$ 271.1441; Found 271.1438.

3-(4-ethoxyquinazolin-2-yl)bicyclo[1.1.1]pentane-1-carboxylic acid (5)

Purified by flash chromatography (on silica gel, petroleum ether /ethyl acetate = 10:1-5:1) White solid; 45.5 mg, 80% yield.

¹H NMR (600 MHz, DMSO-*d6*) δ 8.13 – 8.06 (m, 1H), 7.94 - 7.82 (m, 2H), 7.64 - 7.59 (m, 1H), 4.62 (q, J = 7.1 Hz, 2H), 2.36 (s, 6H), 1.46 (t, J = 7.1 Hz, 3H).

¹³C{¹H} NMR (151 MHz, DMSO-*d*6) δ 171.3, 166.1, 161.9, 150.6, 134.0, 127.1, 127.0, 123.1, 114.4, 62.7, 52.5, 42.4, 37.2, 14.1.

HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{17}N_2O_3$ 285.1234; Found 285.1231.

methyl 3-(7-(5-chloro-2-((1-ethoxy-2-methyl-1-oxopropan-2-yl)oxy)phenyl)-4-ethoxyquinazolin-2-yl)bicyclo[1.1.1]pentane-1-carboxylate (6)

Purified by flash chromatography (on silica gel, petroleum ether /ethyl acetate = 10:1-5:1) Colourless liquid; 43.1 mg, 40% yield.

 1 H NMR (400 MHz, Chloroform-d) δ 8.11 (d, J = 8.5 Hz, 1H), 7.97 (d, J = 1.6 Hz, 1H), 7.77 (dd, J = 8.5, 1.7 Hz, 1H), 7.43 (d, J = 2.6 Hz, 1H), 7.23 (dd, J = 8.8, 2.7 Hz, 1H), 6.87 (d, J = 8.8 Hz, 1H), 4.66 (q, J = 7.1 Hz, 2H), 4.22 (q, J = 7.1 Hz, 2H), 3.74 (s, 3H), 2.51 (s, 6H), 1.52 (t, J = 7.1 Hz, 3H), 1.38 (s, 6H), 1.25 (t, J = 7.1 Hz, 3H).

¹³C{¹H} NMR (101 MHz, Chloroform-*d*) δ 173.9, 170.9, 166.6, 162.7, 151.4, 151.3, 143.3, 134.7, 130.9, 128.7, 128.6, 127.7, 127.5, 122.4, 119.9, 114.1, 80.6, 62.8, 61.5, 53.2, 51.7, 43.0, 37.3, 29.7, 25.2, 14.3, 14.1.

HRMS (ESI-TOF) m/z: [M+H]⁺ Calcd for C₂₉H₃₂ClN₂O₆ 539.1943; Found 539.1942.

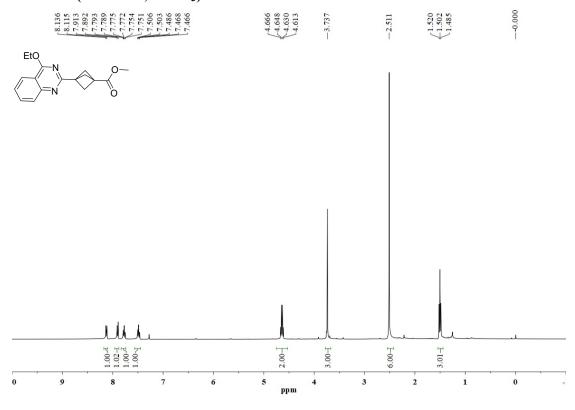
methyl 3-(4-ethoxy-7-((8R,9S,13S,14S)-3-methoxy-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-4-yl)quinazolin-2-yl)bicyclo[1.1.1]pentane-1-carboxylate (7)

Purified by flash chromatography (on silica gel, petroleum ether /ethyl acetate = 10:1-5:1) Colourless liquid; 52.2 mg, 45% yield.

¹H NMR (400 MHz, Chloroform-*d*) δ 8.10 (d, J = 8.5 Hz, 1H), 8.02 (d, J = 1.2 Hz, 1H), 7.70 (dd, J = 8.5, 1.7 Hz, 1H), 7.34 (s, 1H), 6.75 (s, 1H), 4.65 (q, J = 7.1 Hz, 2H), 3.79 (s, 3H), 3.74 (s, 3H), 3.08 – 2.94 (m, 2H), 2.51 (s, 6H), 2.47 – 2.26 (m, 3H), 2.22 – 2.01 (m, 3H), 1.99 – 1.93 (m, 1H), 1.68 – 1.60 (m, 4H), 1.57 – 1.43 (m, 7H), 0.93 (s, 3H). ¹³C{¹H} NMR (101 MHz, Chloroform-*d*) δ 171.0, 166.5, 162.5, 154.5, 151.4, 144.3, 138.0, 132.3, 128.6, 128.2, 127.3, 127.1, 122.5, 113.7, 111.7, 62.7, 55.6, 53.2, 51.7, 50.4, 48.0, 43.9, 43.0, 38.4, 37.3, 35.8, 31.5, 29.7, 26.5, 26.0, 21.6, 14.3, 13.8. **HRMS** (ESI-TOF) m/z: [M+H]⁺Calcd for C₃₆H₄₁N₂O₅ 581.3010; Found 581.3009.

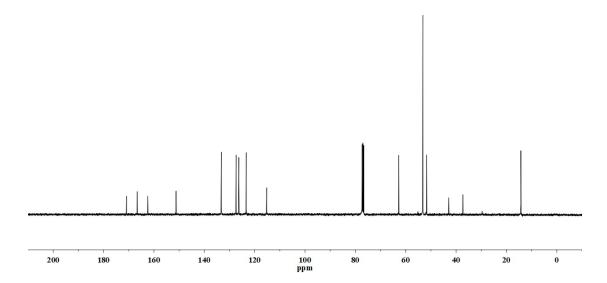
11. NMR Spectra of Products

^{1}H NMR (400 MHz, CDCl₃) of 3a

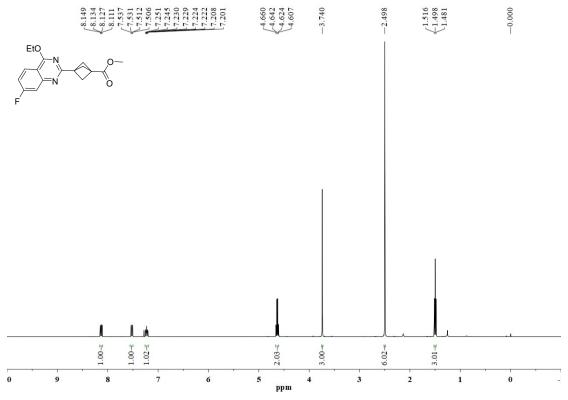


$^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl₃) of 3a

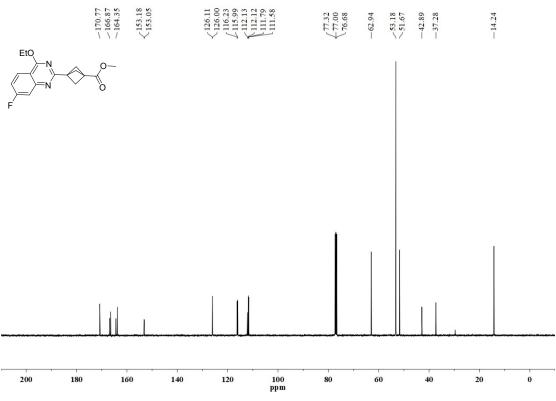




¹H NMR (400 MHz, CDCl₃) of 3b

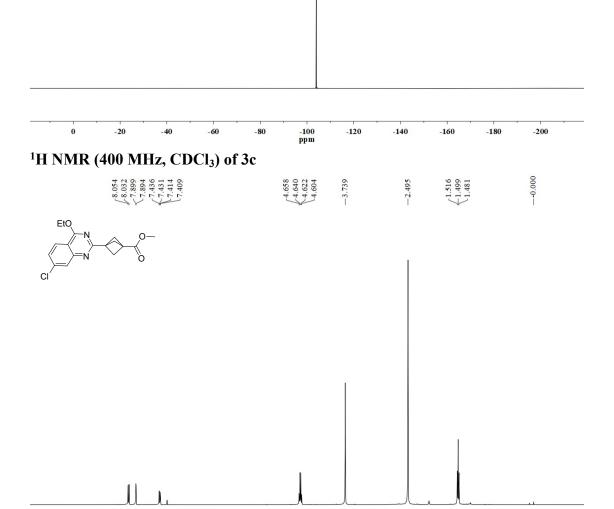


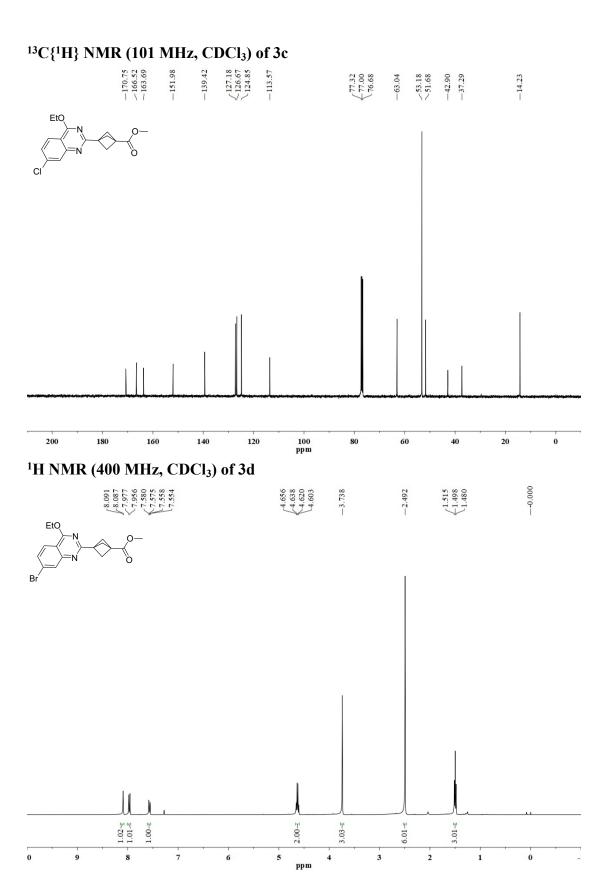
$^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl₃) of 3b

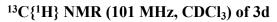


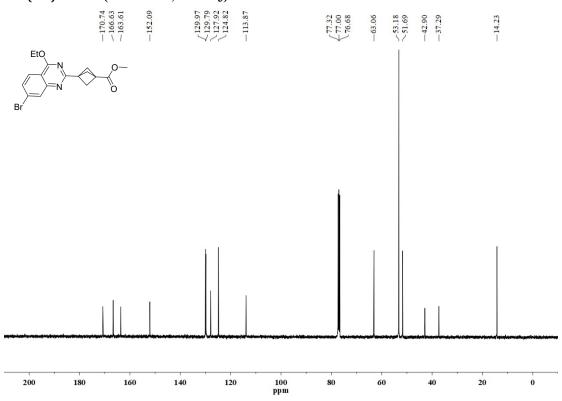




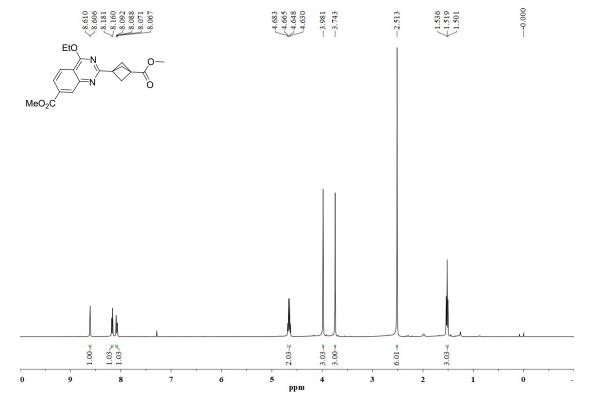




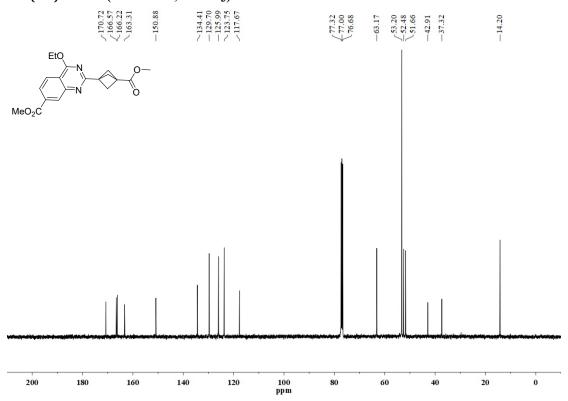




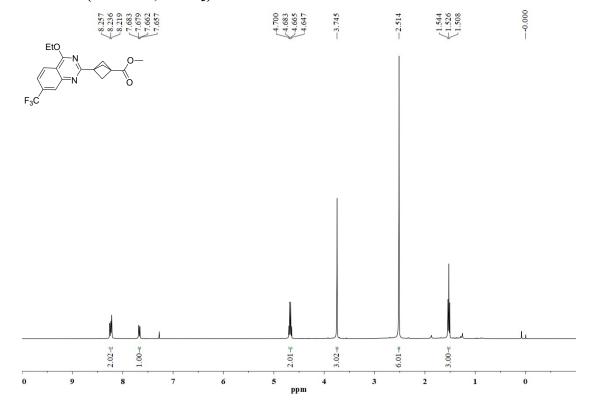
¹H NMR (400 MHz, CDCl₃) of 3e



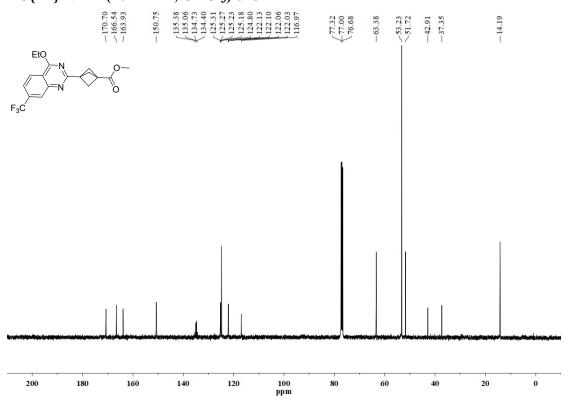




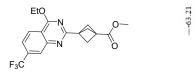
¹H NMR (400 MHz, CDCl₃) of 3f

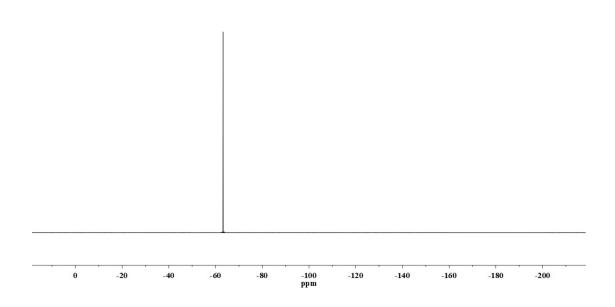


$^{13}\mathrm{C}\{^{1}\mathrm{H}\}$ NMR (101 MHz, CDCl₃) of 3f

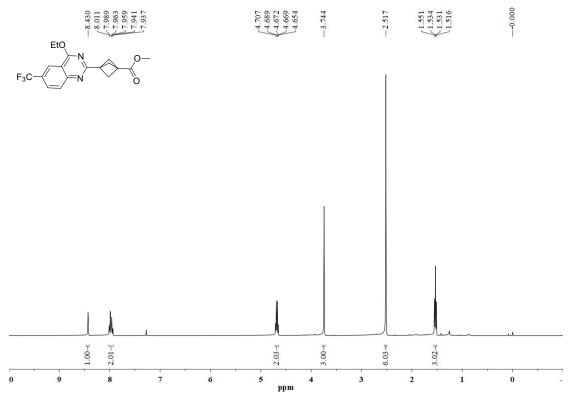


$^{19}\mathrm{F}\ \mathrm{NMR}\ (376\ \mathrm{MHz},\ \mathrm{CDCl_3})\ \mathrm{of}\ 3\mathrm{f}$

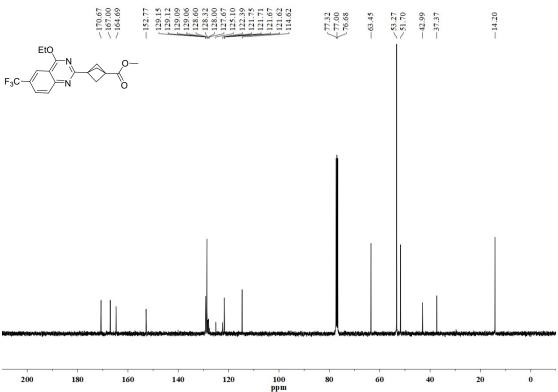




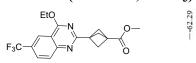
¹H NMR (400 MHz, CDCl₃) of 3g

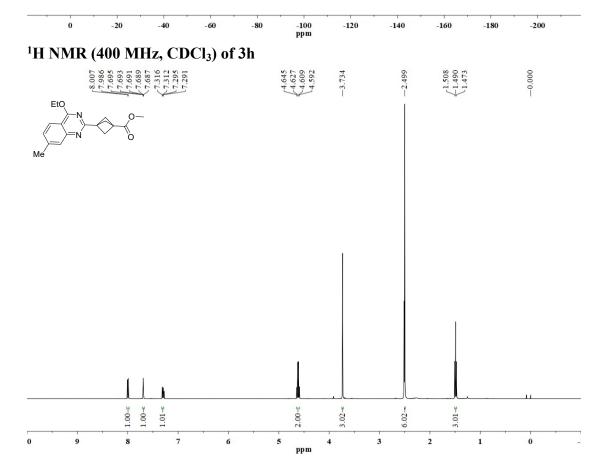


$^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl₃) of 3g

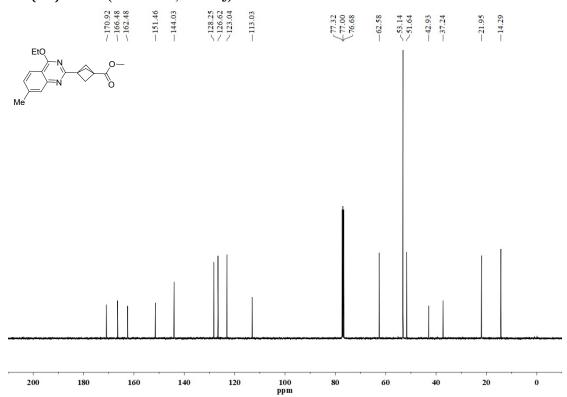




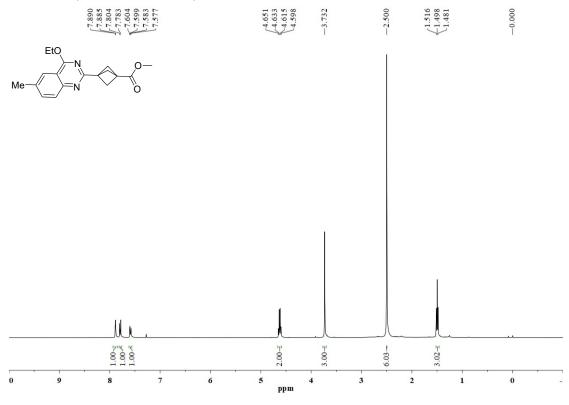




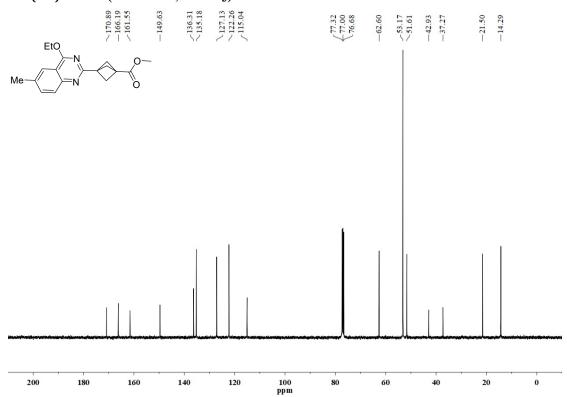




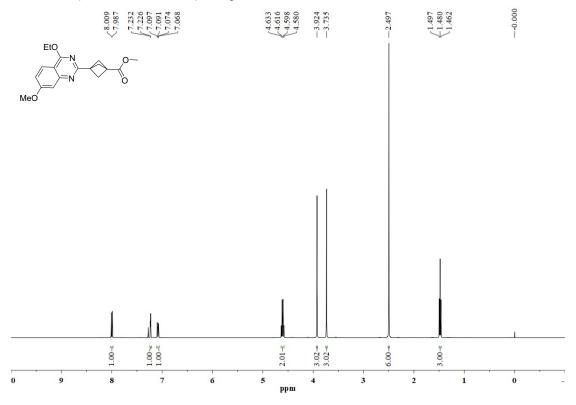
^{1}H NMR (400 MHz, CDCl₃) of 3i



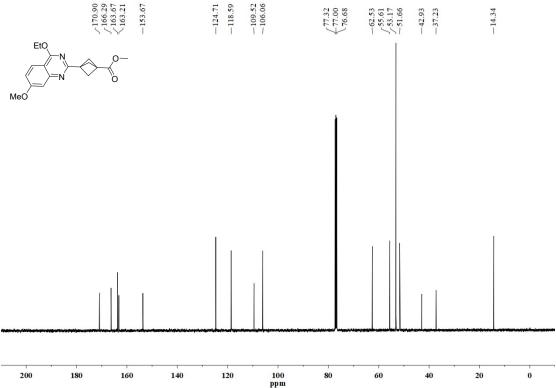




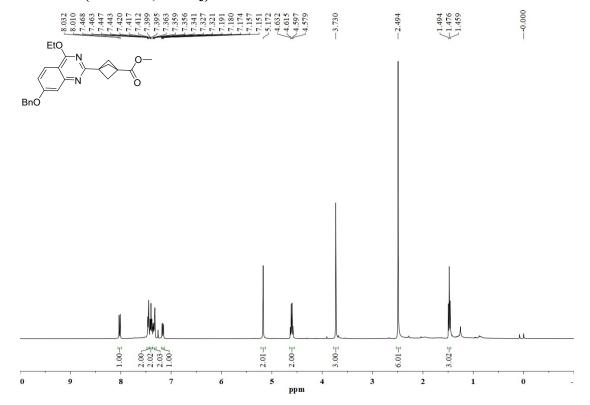
¹H NMR (400 MHz, CDCl₃) of 3j





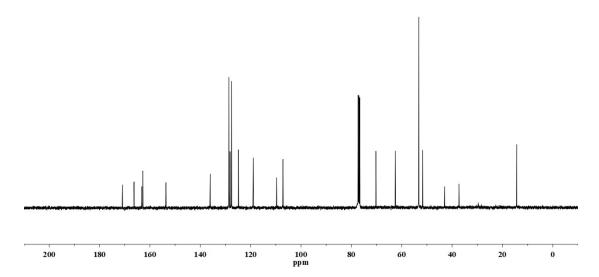


¹H NMR (400 MHz, CDCl₃) of 3k

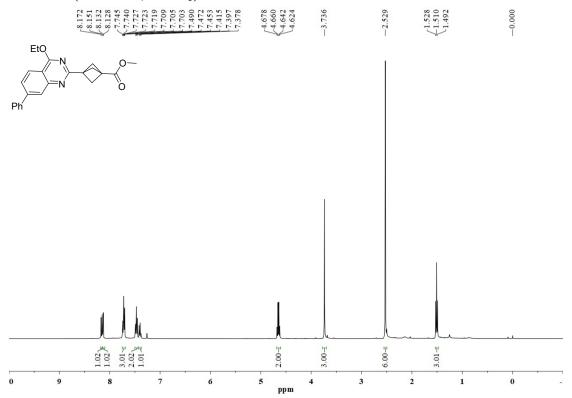


$^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl₃) of 3k

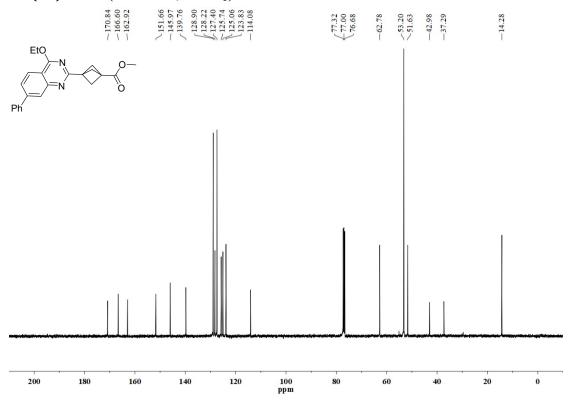




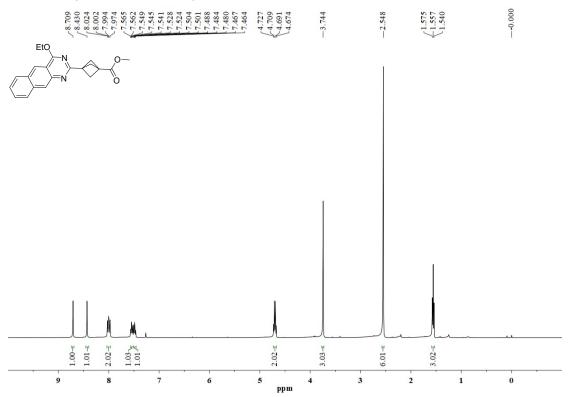
^{1}H NMR (400 MHz, CDCl₃) of 3l



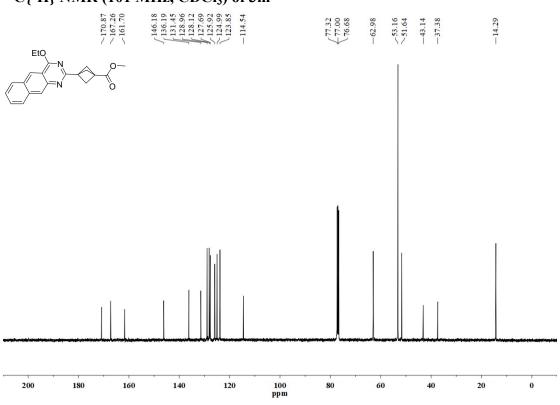




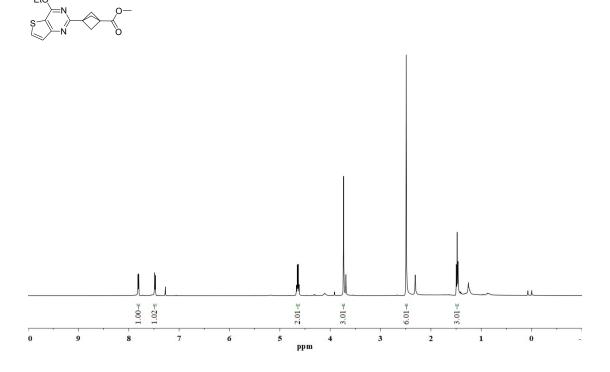
¹H NMR (400 MHz, CDCl₃) of 3m







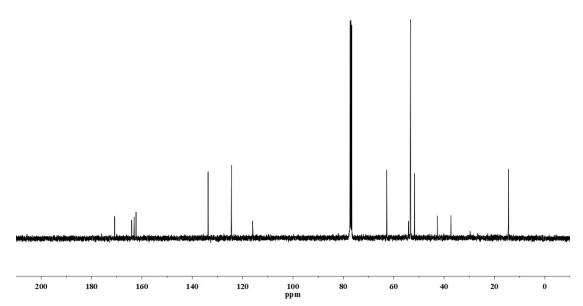
¹H NMR (400 MHz, CDCl₃) of 3n



4.669 4.651 4.634 4.616

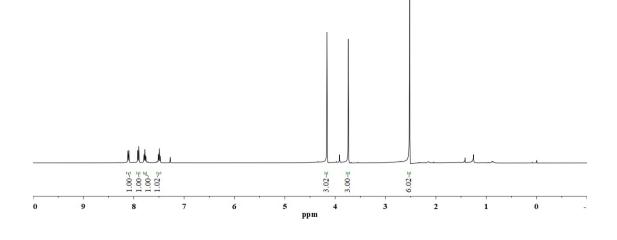






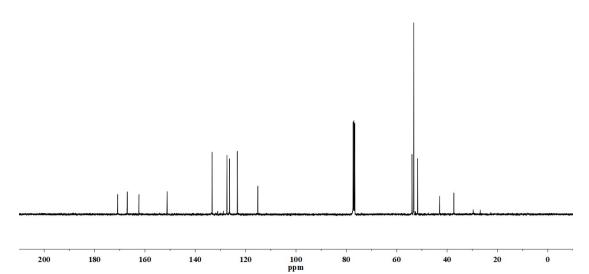
¹H NMR (400 MHz, CDCl₃) of 30



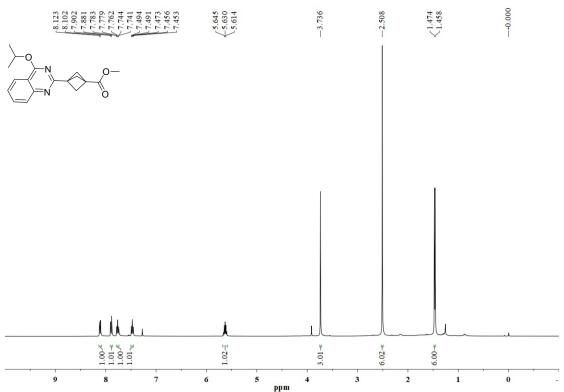


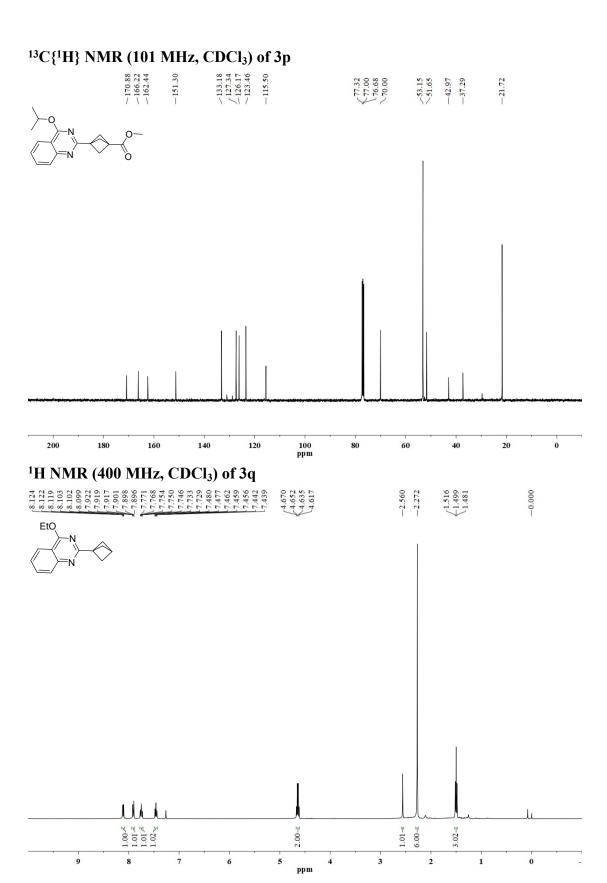


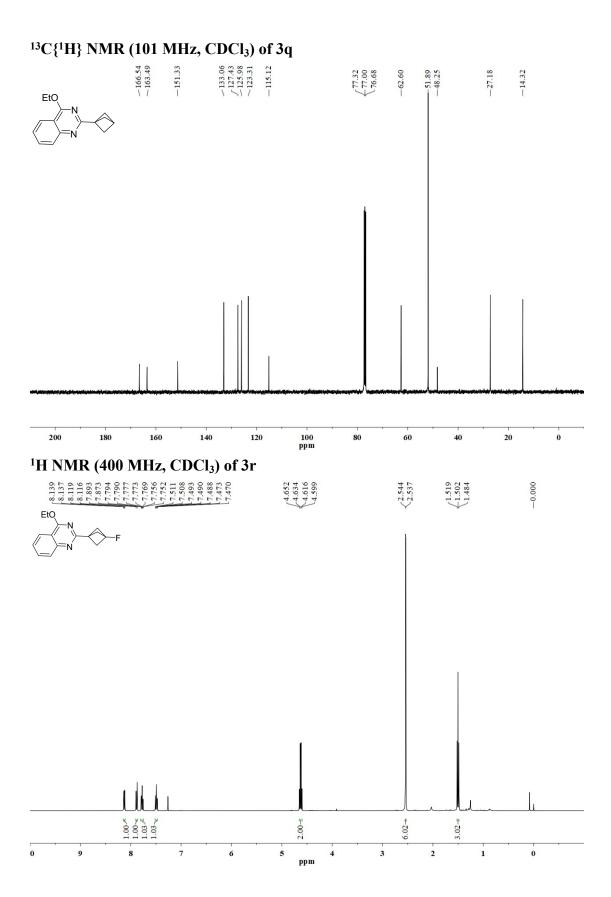




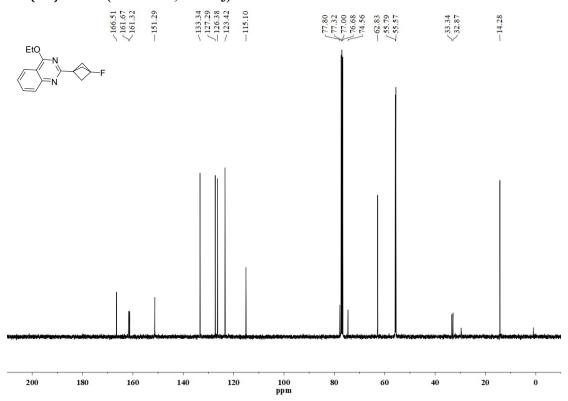
¹H NMR (400 MHz, CDCl₃) of 3p





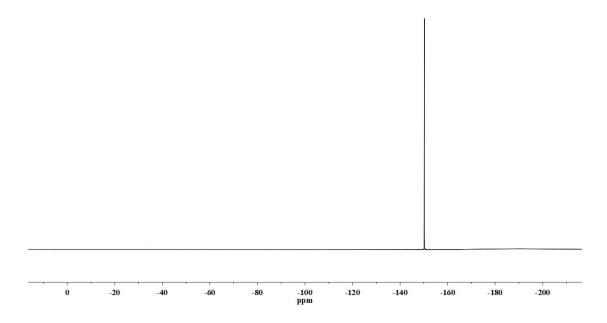




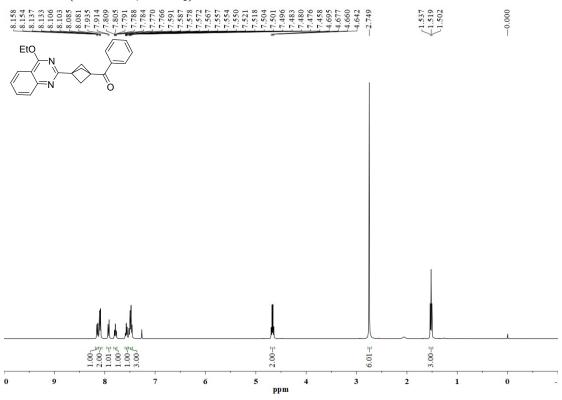


^{19}F NMR (565 MHz, CDCl₃) of 3r



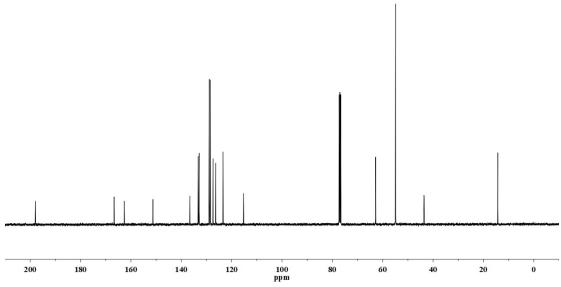


¹H NMR (400 MHz, CDCl₃) of 3s

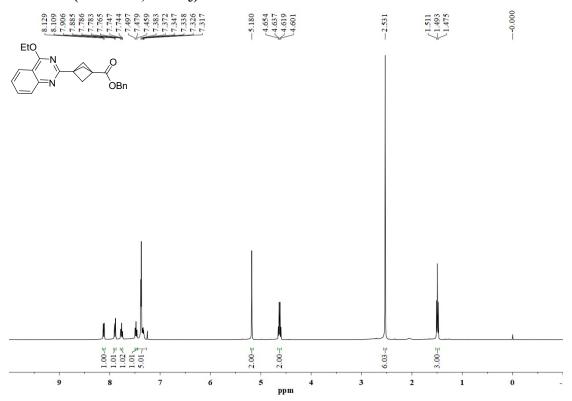


$^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl₃) of 3s



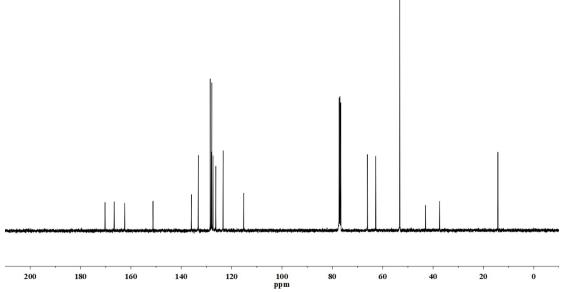


¹H NMR (400 MHz, CDCl₃) of 3t

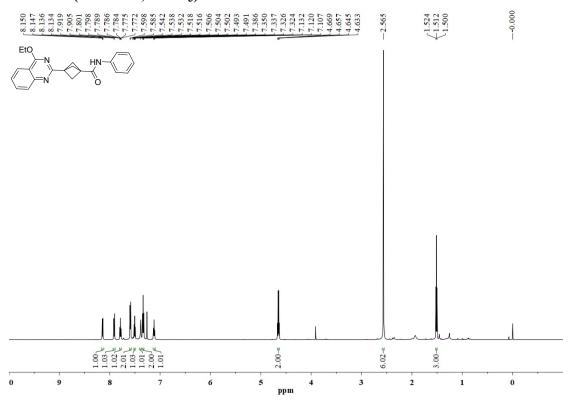


$^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl₃) of 3t

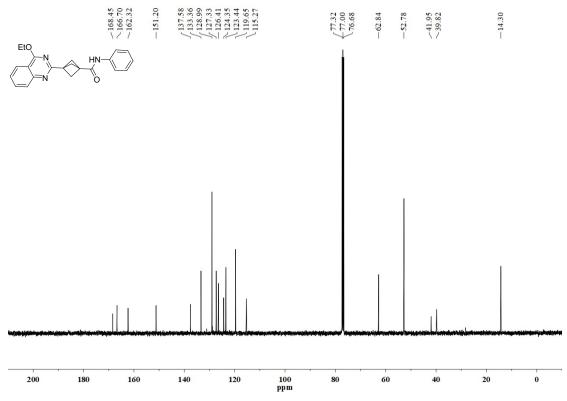




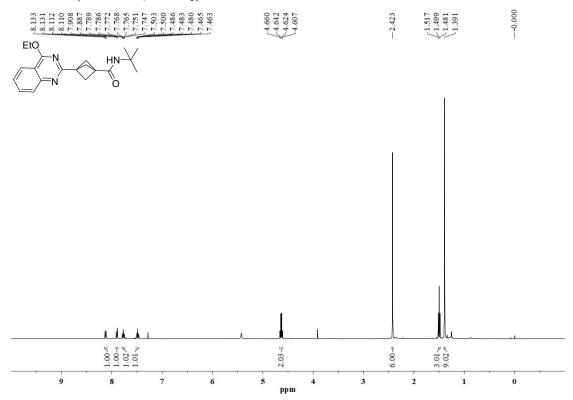
¹H NMR (600 MHz, CDCl₃) of 3u



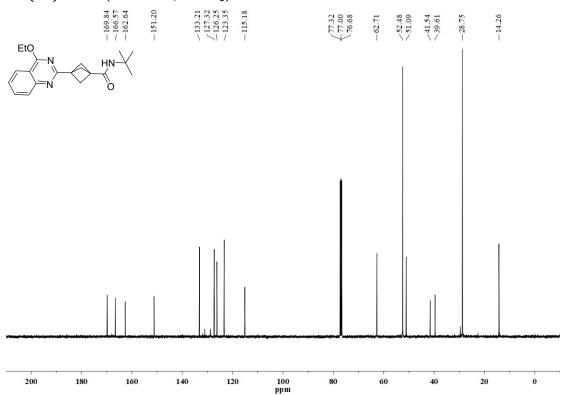
$^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl₃) of 3u



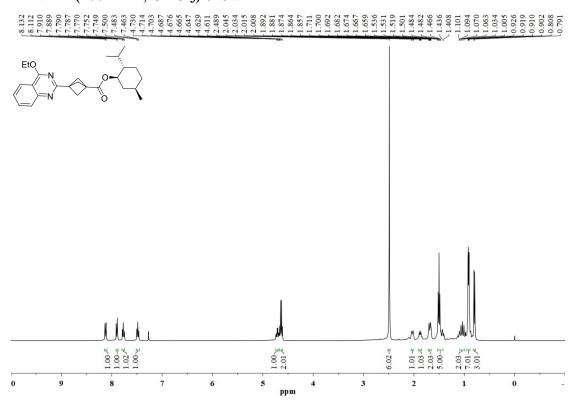
¹H NMR (400 MHz, CDCl₃) of 3v



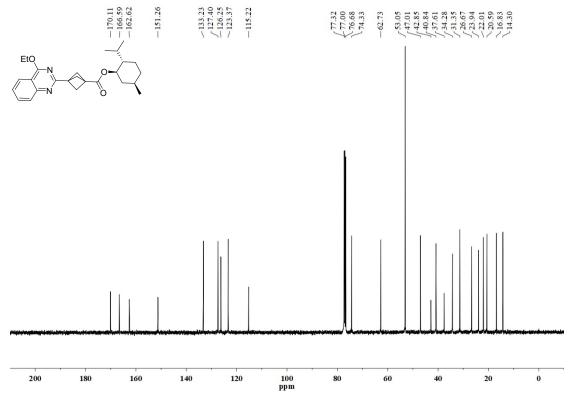
$^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl₃) of 3v



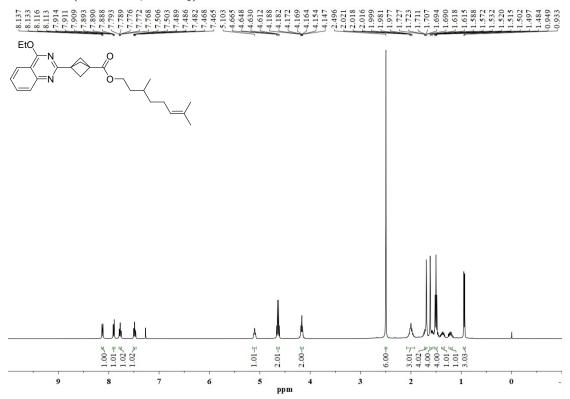
¹H NMR (400 MHz, CDCl₃) of 3w



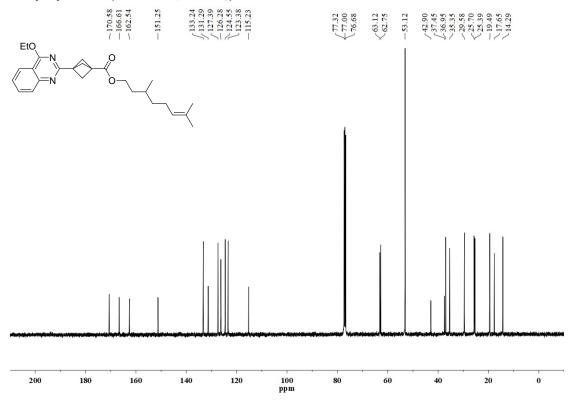
$^{13}C\{^1H\}$ NMR (101 MHz, CDCl3) of 3w



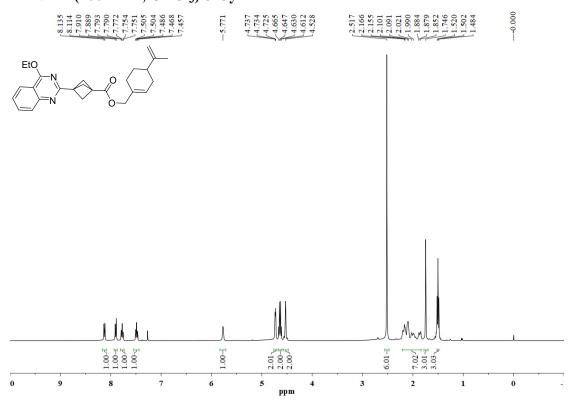
¹H NMR (400 MHz, CDCl₃) of 3x



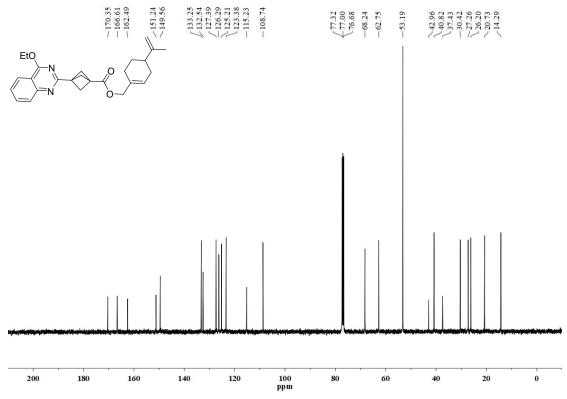
¹³C{¹H} NMR (101 MHz, CDCl₃) of 3x



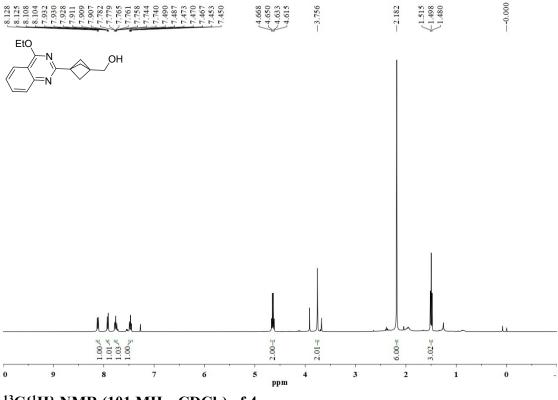
¹H NMR (400 MHz, CDCl₃) of 3y



$^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl₃) of 3y

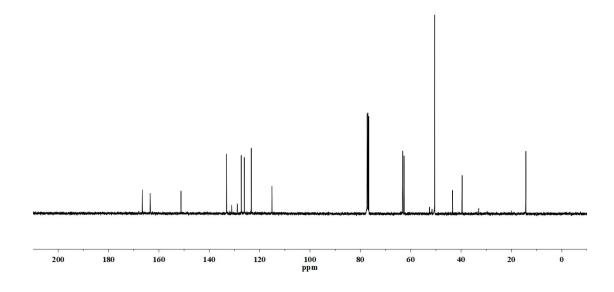


¹H NMR (400 MHz, CDCl₃) of 4

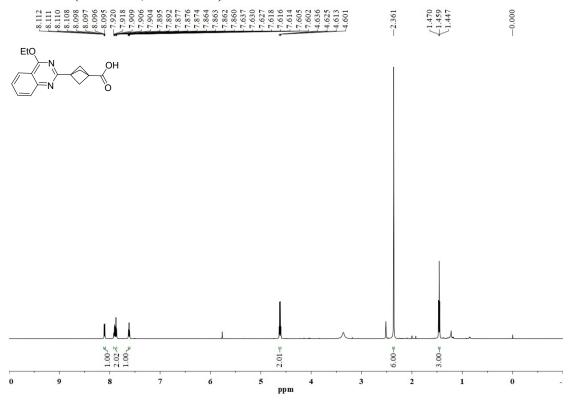


$^{13}C\{^1H\}$ NMR (101 MHz, CDCl₃) of 4

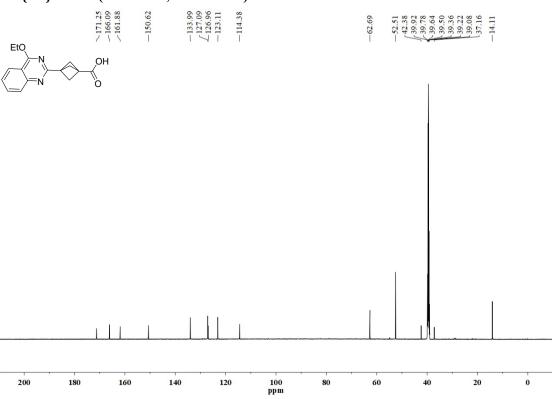




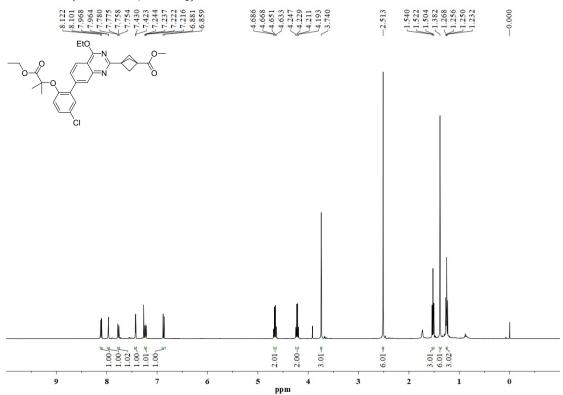




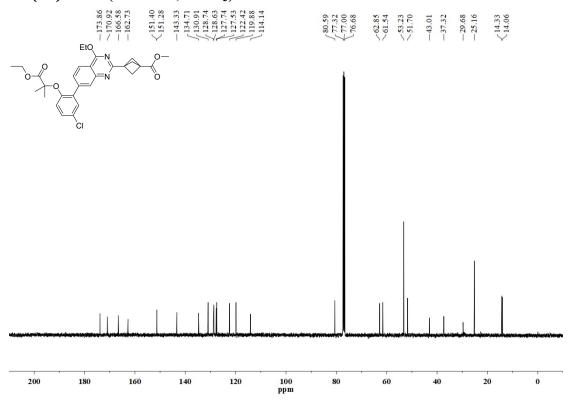
$^{13}\mathrm{C}\{^{1}\mathrm{H}\}$ NMR (151 MHz, DMSO-d6) of 5



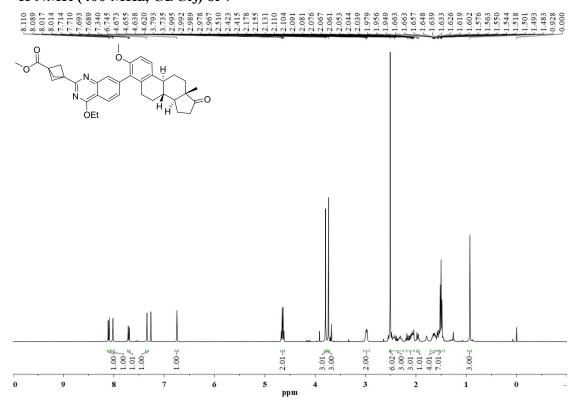




$^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl₃) of 6



¹H NMR (400 MHz, CDCl₃) of 7



$^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl₃) of 7

