Supporting Information

Hydrophobic Tagging–Induced Degradation of PDEδ in Colon Cancer Cells

Menglu Guo[a,†], Shipeng He[b,†], Junfei Cheng[a], Yu Li[a], Guoqiang Dong[a,*], Chunquan Sheng[a,*]

[a] School of Pharmacy, Second Military Medical University, 325 Guohe Road, Shanghai 200433, China

[b] Institute of Translational Medicine, Shanghai University, Shanghai 200444, China

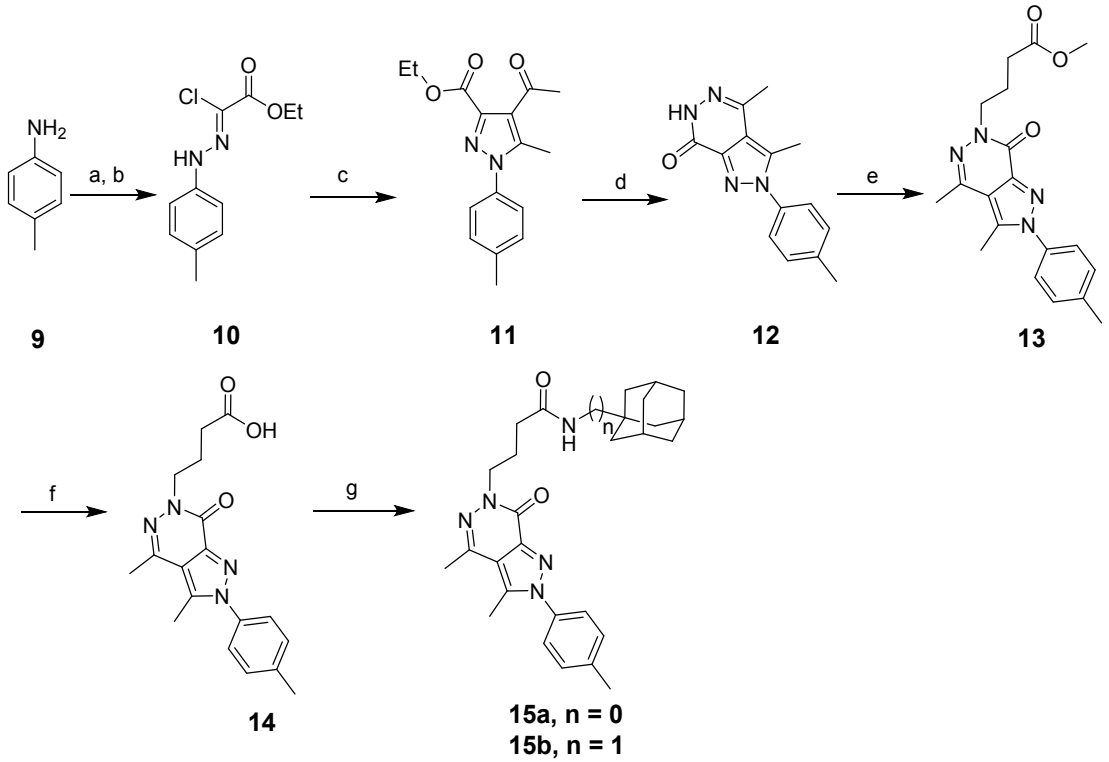
† These authors contributed equally to this work.

***Corresponding authors:** E-mail: gdong@smmu.edu.cn, shengcq@smmu.edu.cn

Table of Contents

Chemical Synthesis and Structural Characterization of Intermediates and Target Compounds.

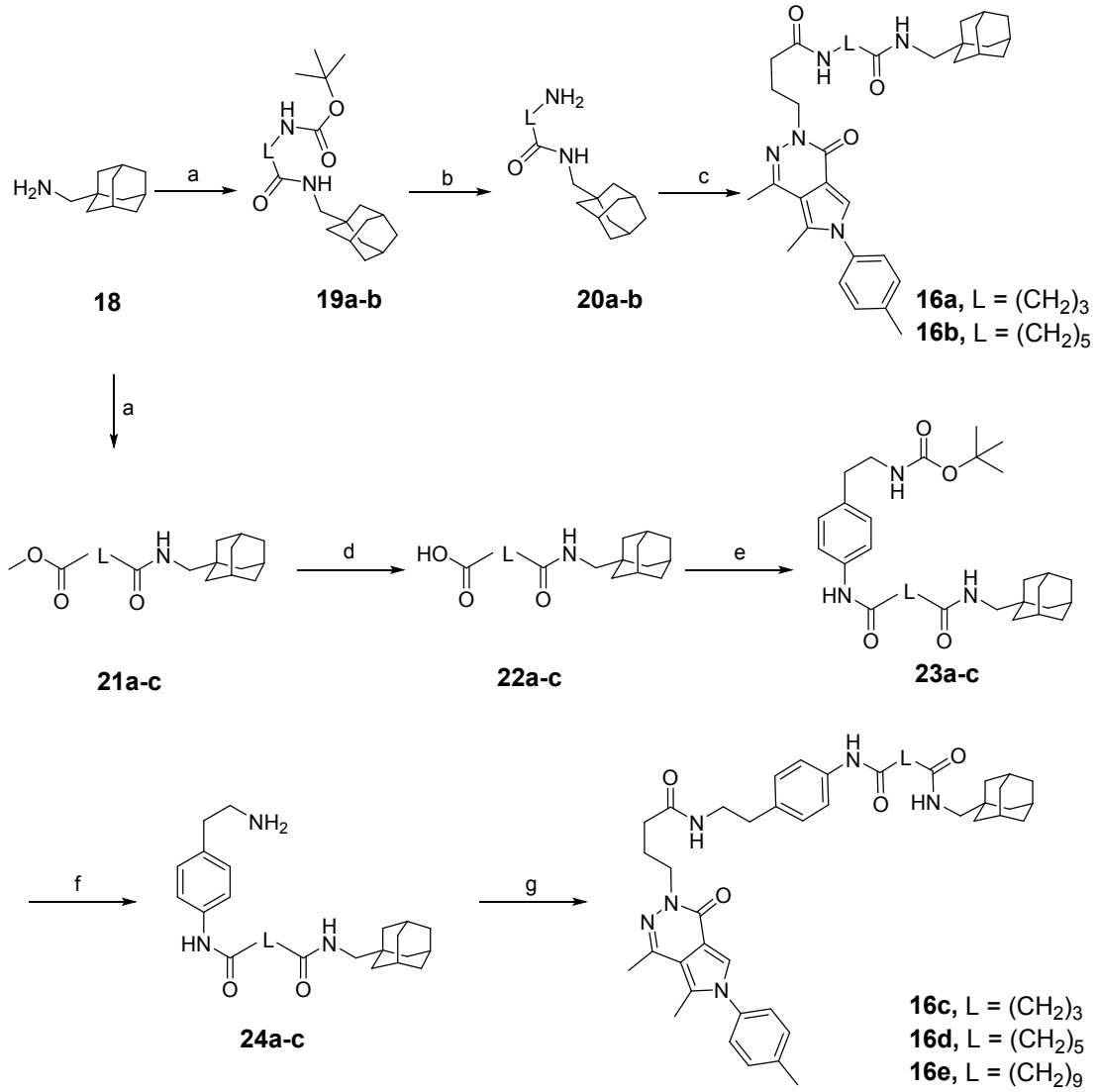
Scheme S1



9 **10** **11** **12** **13** **14**

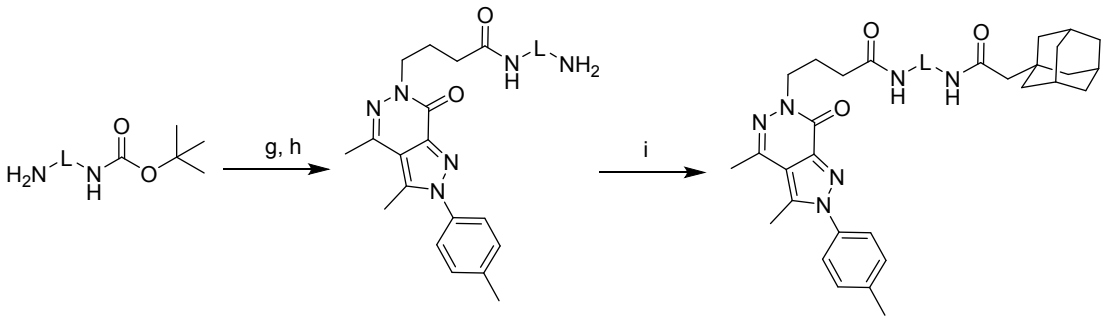
Reagents and conditions: (a) $NaNO_2$, 6 M HCl, 0 ^oC; (b) Ethyl 2-chloro-3-oxobutanoate, NaOAc, EtOH/H_2O = 7: 1, 0 ^oC, 4 h, 92%; (c) Pentane-2,4-dione, NaOEt, EtOH, rt, 16 h, 73%; (d) Hydrazine hydrate, EtOH, 110 ^oC, 6 h, 88%; (e) Methyl 4-bromobutanoate, NaH, DMF, 0 ^oC, 4 h, 76%; (f) LiOH, THF: MeOH: H_2O = 3: 2: 1, 1 h, 90%; (g) Amantadine/1-Adamantanemethylamine, HATU, DIPEA, DMF, rt, 4 h, 30-45%.

Scheme S2



Reagents and conditions: (a) HATU, DIPEA, DMF, rt, 10 h, 70-90%; (b) DCM, TFA, rt, 1 h, 80-95%; (c) **14**, HATU, DIPEA, DMF, rt, 12 h, 40-50%; (d) LiOH, THF: MeOH: H_2O =1: 1: 1, rt, 2 h, 75-95%; (e) *tert*-Butyl 4-aminophenethylcarbamate, HATU, DIPEA, DMF, rt, 6 h, 80-90%; (f) DCM, TFA, rt, 2 h, 90-95%; (g) **14**, HATU, DIPEA, DMF, rt, 12 h, 30-35%.

Scheme S3

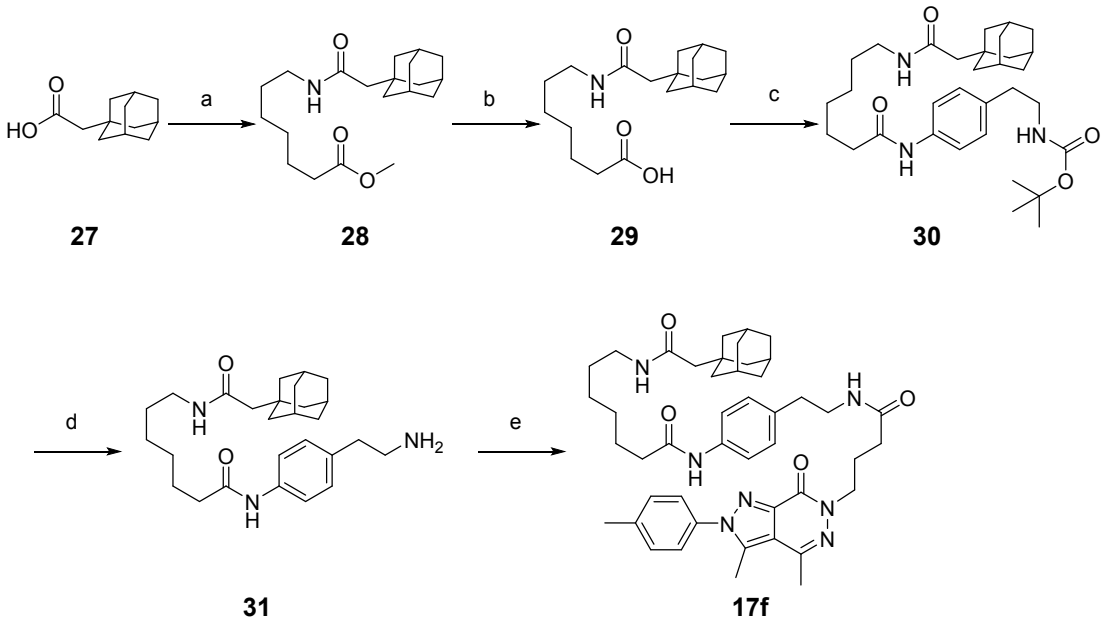


25a-e **26a-e**

17a, L = $(CH_2)_2$
17b, L = $(CH_2)_4$
17c, L = $(CH_2)_6$
17d, L = $(CH_2)_8$
17e, L = $CH_2(CH_2OCH_2)_2CH_2$

Reagents and conditions: (g) HBTU, DIPEA, DMF, rt, 4 h, 50-60% ; (h) DCM, TFA, rt, 1 h, 80-90%; (i) 1-Adamantaneacetic acid, HBTU, DIPEA, DMF, rt, 6 h, 10-80%.

Scheme S4



Reagents and conditions: (a) Methyl 7-aminoheptanoate, HATU, DIPEA, DMF, rt, 10 h， 90% (b) LiOH, THF: MeOH: H_2O = 1: 1: 1, rt, 2 h, 88%; (c) *tert*-Butyl 4-aminophenethylcarbamate, HATU, DIPEA, DMF, rt, 6 h, 90%; (d) DCM, TFA, rt, 2 h, 95%; (e) **10**, HATU, DIPEA, DMF, rt, 12 h, 27%

General. Unless otherwise noted, all reagents were obtained from commercial suppliers and used without further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AVANCE II 300 and AVANCE II 600 spectrometer (Bruker Company, Germany), using TMS as an internal standard and DMSO-d_6 as solvents. Chemical shifts were given in ppm (δ values) and coupling constants were given in Hz (*J* values). The mass spectra were recorded on an Esquire 3000 LC-MS mass spectrometer. TLC analysis was executed on silica gel thin-player plates GF254 (Qingdao Haiyang Chemical, China). Silica gel column chromatography was

performed with Silica gel 60 G (Qingdao Haiyang Chemical, China). The compounds were purified by HPLC (Agilent Eclipse Plus C18 5 μm, 4.6 mm × 250 mm).

4-(3,4-Dimethyl-7-oxo-2-(*p*-tolyl)-2,7-dihydro-6*H*-pyrazolo-[3,4-*d*]pyridazin-6-yl) butanoic Acid (14). Starting from commercially available 4-methylaniline (**9**), the key intermediate **14** was synthesized via five steps according to the reported protocols.[1] ^{1}H-NMR (DMSO-d_6, 600 MHz) δ: 12.03 (s, 1H), δ 7.49 (d, J = 8.3 Hz, 2H), 7.43 (d, J = 8.3 Hz, 2H), 4.08 (t, J = 6.9 Hz, 2H), 2.59 (s, 3H), 2.52 (s, 3H), 2.43 (s, 3H), 2.27 (t, J = 7.4 Hz, 2H), 1.91-1.96 (m, 2H).

***N*-((3*s*,5*s*,7*s*)-Adamantan-1-yl)-4-(3,4-dimethyl-7-oxo-2-(*p*-tolyl)-2,7-dihydro-6*H*-*p*yrazolo[3,4-*d*]pyridazin-6-yl)butanamidem (15a).** Compound **14** (72 mg, 0.21 mmol), HATU (95 mg, 0.25 mmol), DIPEA (54 mg, 0.42 mmol) and amantadine (35 mg, 0.23 mmol) were dissolved in DMF (6 mL). The reaction solution was stirred for 4 h at room temperature. Then, the mixture was poured into water (20 mL) and extracted with EtOAc (3 × 10 mL). The combined organic phase was washed with water (20 mL) and saturated NaCl solution (10 mL), dried over anhydrous Na_2SO_4 and concentrated under the reduced pressure to give crude product, which was further purified by silica gel column chromatography (DCM: MeOH = 100: 2) to give **15a** (34.8 mg, 35% yield) as a white solid. ^{1}H-NMR (DMSO-d_6, 600 MHz) δ: 7.50 (d, J = 8.3 Hz, 2H), 7.46 (d, J = 8.2 Hz, 2H), 7.28 (s, 1H), 4.05 (t, J = 7.2 Hz, 2H), 2.62 (s, 3H), 2.54 (s, 3H), 2.45 (s, 3H), 2.07 (t, J = 7.5 Hz, 2H), 2.00 (s, 3H), 1.94–1.85 (m,

8H), 1.66–1.58 (m, 6H). ^{13}C NMR (DMSO-d_6, 150 MHz) δ: 171.3, 155.6, 141.6, 141.4, 139.8, 137.9, 136.4, 130.4, 126.2, 117.6, 50.9, 49.1, 41.5, 36.5, 33.9, 29.3, 25.2, 21.2, 19.9, 12.3. HR-MS m/z Calcd. for $C_{28}H_{36}N_5O_2$ $[M+H]^+$ 474.2864, Found 474.2854.

Target compound **15b** was synthesized according to a similar procedure described for **15a**.

***N*-(((3*r*,5*r*,7*r*)-Adamantan-1-yl)methyl)-4-(3,4-dimethyl-7-oxo-2-(*p*-tolyl)-2,7-dihydro-6*H*-pyrazolo[3,4-*d*]pyridazin-6-yl)butanamide (15b).** White solid (61 mg, 45% yield). ^{1}H-NMR (DMSO-d_6, 600 MHz) δ: 7.68 (t, J = 6.1 Hz, 1H), 7.51 (d, J = 8.3 Hz, 2H), 7.46 (d, J = 8.1 Hz, 2H), 4.07 (t, J = 7.1 Hz, 2H), 2.77 (d, J = 6.2 Hz, 2H), 2.62 (s, 3H), 2.54 (s, 3H), 2.45 (s, 3H), 2.17 (t, J = 7.6 Hz, 2H), 1.96–1.90 (m, 5H), 1.66 (d, J = 12.0 Hz, 3H), 1.59 (d, J = 11.5 Hz, 3H), 1.43 (s, 6H). ^{13}C NMR (DMSO-d_6, 150 MHz) δ: 172.1, 155.6, 141.6, 141.5, 139.8, 137.9, 136.4, 130.4, 126.2, 117.6, 100.0, 50.5, 49.2, 37.0, 34.0, 33.2, 28.2, 25.4, 21.2, 19.9, 12.3. HR-MS m/z Calcd. for $C_{29}H_{37}N_5O_2Cl$ $[M+Cl]^-$ 522.2641, Found 522.2656

***tert*-Butyl (4-((((3*r*,5*r*,7*r*)-adamantan-1-yl)methyl)amino)-4-oxobutyl)carbamate (19a).** To a solution of 4-((*tert*-butoxycarbonyl)amino)butanoic acid (270 mg, 1.33 mmol), HATU (920 mg, 2.4 mmol) and DIPEA (429 mg, 3.63 mmol) in DMF (5 mL) was added 1-adamantanemethylamine (200 mg, 1.21 mmol). The reaction mixture was stirred for 8 h at room temperature. The reacted solution was poured into water

(30 mL), and extracted with EtOAc (3 × 10 mL). The combined organic phase was washed with saturated NaCl solution (30 mL), water (30 mL), dried over anhydrous Na_2SO_4. The organic layer was then concentrated under the reduced pressure to obtain crude product, which was purified by silica gel column chromatography (PE: EA = 1: 1) to give compound **19a** (400 mg, 90% yield) as a yellow oil. ^{1}H-NMR (DMSO-d_6, 600 MHz) δ: 7.62 (t, J = 6.2 Hz, 1H), 6.79 (t, J = 5.4 Hz, 1H), 2.91 (dd, J = 13.1, 6.7 Hz, 2H), 2.75 (d, J = 6.3 Hz, 2H), 2.70 (s, 1H), 2.09 (t, J = 7.5 Hz, 2H), 1.92 (s, 3H), 1.66 (d, J = 12.0 Hz, 3H), 1.58 (d, J = 8.2 Hz, 4H), 1.44–1.36 (m, 15H).

Compound **19b** was synthesized according to a similar procedure described for **19a.**

***tert*-Butyl (6-((((3*r*,5*r*,7*r*)-adamantan-1-yl)methyl)amino)-6-oxohexyl)carbamate (19b).** ^{1}H-NMR (DMSO-d_6, 600 MHz) δ: 7.59 (t, J = 6.1 Hz, 1H), 6.75 (t, J = 5.2 Hz, 1H), 2.90 (dd, J = 13.0, 6.9 Hz, 2H), 2.76 (d, J = 6.3 Hz, 2H), 2.71 (s, 1H), 2.10 (t, J = 7.4 Hz, 2H), 1.93 (s, 3H), 1.67 (d, J = 12.0 Hz, 3H), 1.59 (d, J = 11.4 Hz, 3H), 1.53–1.25 (m, 20H).

***N*-(((3*r*,5*r*,7*r*)-Adamantan-1-yl)methyl)-4-(4-(3,4-dimethyl-7-oxo-2-(*p*-tolyl)-2,7-dihydro-6*H*-pyrazolo[3,4-*d*]pyridazin-6-yl)butanamido)butanamide (16a).** TFA (2 mL) was added to a stirred solution of compound **19a** (400 mg, 1.14 mmol) in dry DCM (3 mL) dropwise. The reaction mixture was stirred for 3 h at room temperature. The solvent was evaporated under reduced pressure to give crude product **20a**, which was then dissolved in DMF (3 mL). Subsequently, HATU (160 mg, 0.42 mmol),

DIPEA (80 mg, 0.63 mmol) and compound **14** (70 mg, 0.21 mmol) were added. The mixture solution was stirred for 2 h at room temperature. Then, the resulting solution was poured into water (20 mL) and extracted with EtOAc (3 × 10 mL). The combined organic phase was washed with saturated NaCl solution (10 mL), water (10 mL), dried over anhydrous Na_2SO_4. The organic layer was then concentrated under reduced pressure to obtain the crude product, which was purified by column chromatography (DCM: MeOH = 100: 10) to give compound **16a** as a white solid (57 mg, 47.5% yield). ^{1}H-NMR (DMSO-d_6, 600 MHz) δ: 7.82 (t, J = 5.4 Hz, 1H), 7.65 (t, J = 6.1 Hz, 1H), 7.50 (d, J = 8.3 Hz, 2H), 7.46 (d, J = 8.1 Hz, 2H), 4.06 (t, J = 7.0 Hz, 2H), 3.04 (dd, J = 12.9, 6.8 Hz, 2H), 2.76 (d, J = 6.2 Hz, 2H), 2.62 (s, 3H), 2.54 (s, 3H), 2.45 (s, 3H), 2.11 (dd, J = 10.6, 4.3 Hz, 4H), 1.99–1.87 (m, 5H), 1.65 (d, J = 11.5 Hz, 3H), 1.63–1.54 (m, 5H), 1.42–1.41 (m, 6H). ^{13}C NMR (DMSO-d_6, 150 MHz) δ: 172.3, 171.8, 155.6, 141.5, 139.8, 137.9, 136.4, 130.4, 126.2, 117.6, 50.5, 49.0, 38.67, 36.9, 34.0, 33.5, 33.1, 28.1, 26.2, 25.1, 21.2, 19.9, 12.3. HR-MS m/z Calcd. for $C_{33}H_{45}N_6O_3$ $[M+H]^+$ 573.3548, Found 573.3568

Compound **16b** was synthesized according to a similar procedure described for **16a.**

***N*-(((3*r*,5*r*,7*r*)-Adamantan-1-yl)methyl)-6-(4-(3,4-dimethyl-7-oxo-2-(*p*-tolyl)-2,7-dihydro-6*H*-pyrazolo[3,4-*d*]pyridazin-6-yl)butanamido)hexanamide (16b).** White solid (54 mg, 42.9% yield). ^{1}H-NMR (DMSO-d_6, 600 MHz) δ: 7.79 (t, J = 5.3 Hz, 1H), 7.60 (t, J = 6.0 Hz, 1H), 7.50 (d, J = 8.2 Hz, 2H), 7.45 (d, J = 8.2 Hz, 2H), 4.05 (t, J = 7.0 Hz, 2H), 3.02 (dd, J = 12.7, 6.5 Hz, 2H), 2.75 (d, J = 6.2 Hz, 2H), 2.61 (s,

3H), 2.54 (s, 3H), 2.45 (s, 3H), 2.10 (q, J = 7.5 Hz, 4H), 1.95-1.93 (m, 2H), 1.91 (s, 3H), 1.65 (d, J = 11.9 Hz, 3H), 1.57 (d, J = 11.7 Hz, 3H), 1.52-1.47 (m, 2H), 1.40 (s, 6H), 1.39-1.37 (m, 2H), 1.27-1.22 (m, 2H). ^{13}C NMR (DMSO-d_6, 150 MHz) δ: 172.7, 171.7, 155.6, 141.5, 139.8, 137.9, 136.3, 130.3, 126.2, 117.6, 50.5, 49.1, 38.8, 37.0, 35.8, 34.0, 33.1, 29.3, 28.1, 26.6, 25.7, 25.1, 21.2, 19.8, 12.3. HR-MS m/z Calcd. for $C_{35}H_{49}N_6O_3$ $[M+H]^+$ 601.3861, Found 601.3883

Methyl 5-((((3*r*,5*r*,7*r*)-adamantan-1-yl)methyl)amino)-5-oxopentanoate (21a). 5-Methoxy-5-oxopentanoic acid **14** (570 mg, 3.9 mmol), HATU (2660 mg, 7 mmol) and DIPEA (1241 mg, 10.5 mmol) were dissolved in anhydrous DMF (5 mL). After the addition of 1-adamantanemethylamine (579 mg, 3.5 mmol), the reaction mixture was stirred for 4 h at room temperature and then diluted with EtOAc (20 mL). The organic phase was washed with water (10 mL), saturated NaCl solution (10 mL) and dried over anhydrous Na_2SO_4. The resulting solution was concentrated under reduced pressure to give the crude product, which was purified by column chromatography (PE: EA = 1: 1) to give compound **21a** (835.1 mg, 81.3% yield) as a yellow oil. ^{1}H-NMR (DMSO-d_6, 600 MHz) δ: 7.62 (t, J = 5.9 Hz, 1H), 3.58 (s, 3H), 2.75 (d, J = 6.3 Hz, 2H), 2.29 (t, J = 7.4 Hz, 2H), 2.13 (t, J = 7.4 Hz, 2H), 1.91 (s, 3H), 1.77–1.70 (m, 2H), 1.66–1.64 (m, 3H), 1.58–1.56 (m, 3H), 1.42–1.41 (m, 6H).

Compounds **21b-c** were synthesized according to a similar procedure described for **21a.**

Methyl 7-((((3*r*,5*r*,7*r*)-adamantan-1-yl)methyl)amino)-7-oxoheptanoate (21b). ^{1}H-NMR (DMSO-d_6, 600 MHz) δ: 7.61 (t, J = 6.1 Hz, 1H), 3.58 (s, 3H), 2.75 (d, J = 6.3 Hz, 2H), 2.29 (t, J = 7.4 Hz, 2H), 2.09 (t, J = 7.4 Hz, 2H), 1.92 (s, 3H), 1.66 (d, J = 12.0 Hz, 3H), 1.60–1.55 (m, 3H), 1.55–1.46 (m, 4H), 1.41–1.40 (m, 6H), 1.28–1.22 (m, 2H).

Methyl 11-((((3*r*,5*r*,7*r*)-adamantan-1-yl)methyl)amino)-11-oxoundecanoate (21c). ^{1}H-NMR (DMSO-d_6, 600 MHz) δ: 7.56 (t, J = 6.2 Hz, 1H), 3.56 (s, 3H), 2.73 (d, J = 6.3 Hz, 2H), 2.26 (t, J = 7.4 Hz, 2H), 2.07 (t, J = 7.3 Hz, 2H), 1.90 (s, 3H), 1.65–1.63 (m, 3H), 1.56–1.54 (m, 3H), 1.50–1.45 (m, 4H), 1.40–1.39 (m, 6H), 1.23 (s, 10H).

5-((((3*r*,5*r*,7*r*)-Adamantan-1-yl)methyl)amino)-5-oxopentanoic acid (22a). To a solution of compound **21a** (350 mg, 1.2 mmol) in THF: MeOH: H_2O = 1: 1:1 (30 mL) was added 2 N LiOH (1.8 mL, 3.6 mmol). The reaction mixture was stirred for 2 h at room temperature. Then, the organic solvent was removed under the reduced pressure, and the pH of the residual aqueous solution was adjusted to 2 with 2 N aqueous HCl to afford precipitate. The precipitate was filtered and washed with water (3 × 5 mL) to give compound **22a** (280 mg, 84% yield) as white solid. ^{1}H-NMR (DMSO-d_6, 600 MHz) δ: 7.64 (t, J = 6.0 Hz, 1H), 2.76 (d, J = 6.3 Hz, 2H), 2.21 (t, J = 7.4 Hz, 2H), 2.13 (t, J = 7.4 Hz, 2H), 1.92 (s, 3H), 1.74–1.69 (m, 2H), 1.67–1.65 (m, 3H), 1.59–1.57 (m, 3H), 1.42–1.41 (m, 6H).

Compounds **22b-c** were synthesized according to a similar procedure described for **22a.**

7-((((3*r*,5*r*,7*r*)-Adamantan-1-yl)methyl)amino)-7-oxoheptanoic acid (22b). ^{1}H-NMR (DMSO-d_6, 600 MHz) δ: 11.95 (s, 1H), 7.57 (t, J = 6.1 Hz, 1H), 2.74 (d, J = 6.2 Hz, 2H), 2.18 (t, J = 7.4 Hz, 2H), 2.08 (t, J = 7.4 Hz, 2H), 1.91 (s, 3H), 1.65 (d, J = 12.0 Hz, 3H), 1.57 (d, J = 11.6 Hz, 3H), 1.53–1.45 (m, 4H), 1.41 (d, J = 2.0 Hz, 6H), 1.28–1.20 (m, 2H).

11-((((3*r*,5*r*,7*r*)-Adamantan-1-yl)methyl)amino)-11-oxoundecanoic acid (22c). ^{1}H-NMR (DMSO-d_6, 600 MHz) δ: 11.96 (s, 1H), 7.58 (t, J = 6.0 Hz, 1H), 2.76 (d, J = 6.3 Hz, 2H), 2.19 (t, J = 7.4 Hz, 2H), 2.09 (t, J = 7.3 Hz, 2H), 1.92 (s, 3H), 1.67–1.65 (m, 3H), 1.59–1.57 (m, 3H), 1.51–1.46 (m, 4H), 1.42–1.41 (m, 6H), 1.25 (s, 10H).

***tert*-Butyl (4-(5-((((3*r*,5*r*,7*r*)-adamantan-1-yl)methyl)amino)-5-oxopentanamido) phenethyl)carbamate (23a).** HATU (222 mg, 0.6 mmol), DIPEA (0.16 mL, 0.9 mmol) and 4-aminophenethylcarbamate (70 mg, 0.3 mmol) were added sequentially to a solution of **22a** (90 mg, 0.32 mmol) in DMF (5 mL). The solution was stirred for 6 h at room temperature. Then, the mixture was poured into water (20 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layer was washed with saturated NaCl solution (3 × 10 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure to get crude product, which was purified by

column chromatography (DCM : MeOH = 100 : 9) to give intermediate **23a** as a yellow oil (135 mg, 85% yield). ^{1}H-NMR (DMSO-d_6, 600 MHz) δ: 9.82 (s, 1H), 7.66 (t, J = 6.2 Hz, 1H), 7.51 (d, J = 8.4 Hz, 2H), 7.25 (d, J = 8.3 Hz, 1H), 7.11 (d, J = 8.4 Hz, 2H), 6.96 (d, J = 8.3 Hz, 1H), 3.11 (dd, J = 14.3, 6.7 Hz, 2H), 2.78 (d, J = 6.2 Hz, 2H), 2.71 (s, 2H), 2.64 (t, J = 7.6 Hz, 2H), 2.31 (t, J = 7.4 Hz, 2H), 2.17 (t, J = 7.5 Hz, 2H), 1.93 (s, 3H), 1.84–1.79 (m, 2H), 1.68–1.66 (m 3H), 1.60–1.58 (m, 3H), 1.38–1.37 (m, 12H).

Compounds **23b-c** were synthesized according to a similar procedure described for **23a.**

***tert*-Butyl (4-(7-((((3*r*,5*r*,7*r*)-adamantan-1-yl)methyl)amino)-7-oxoheptanamido) phenethyl)carbamate (23b).** ^{1}H-NMR (DMSO-d_6, 600 MHz) δ: 9.78 (s, 1H), 7.59 (t, J = 6.1 Hz, 1H), 7.49 (d, J = 8.4 Hz, 2H), 7.09 (d, J = 8.4 Hz, 2H), 6.85 (t, J = 5.5 Hz, 1H), 3.10 (dd, J = 14.1, 6.5 Hz, 2H), 2.76–2.73 (m, 2H), 2.67–2.59 (m, 2H), 2.27 (t, J = 7.4 Hz, 2H), 2.11 (t, J = 7.4 Hz, 2H), 1.91 (s, 3H), 1.66–1.64 (m, 3H), 1.60–1.56 (m, 5H), 1.54–1.50 (m, 3H), 1.37–1.36 (m, 10H), 1.28–1.24 (m, 6H).

***tert*-Butyl (4-(11-((((3*r*,5*r*,7*r*)-adamantan-1-yl)methyl)amino)-11-oxoundecan amido)phenethyl)carbamate (23c)** ^{1}H-NMR (DMSO-d_6, 600 MHz) δ: 9.77 (s, 1H), 7.59 (t, J = 6.1 Hz, 1H), 7.49 (d, J = 8.4 Hz, 2H), 7.09 (d, J = 8.3 Hz, 2H), 6.84 (t, J = 5.3 Hz, 1H), 3.10 (dd, J = 13.9, 6.6 Hz, 2H), 2.75 (t, J = 4.8 Hz, 2H), 2.63 (t, J = 7.5

Hz, 2H), 2.27 (t, *J* = 7.4 Hz, 2H), 2.09 (t, *J* = 7.3 Hz, 2H), 1.91 (s, 3H), 1.66–1.64 (m, 3H), 1.58–1.56 (m, 5H), 1.53–1.44 (m, 3H), 1.37–1.36 (m, 10H), 1.28–1.24 (m, 14H).

***N*^{1}-(((3*r*,5*r*,7*r*)-Adamantan-1-yl)methyl)-*N*^{5}-(4-(2-(4-(3,4-dimethyl-7-oxo-2-(*p*-tolyl)-2,7-dihydro-6*H*-pyrazolo[3,4-*d*]pyridazin-6-yl)butanamido)ethyl)phenyl)glutaramide (16c).** HATU (160 mg, 0.25 mmol) and DIPEA (0.12 mL, 0.63 mmol) were added to a solution of compound 6 (70 mg, 0.21 mmol) in DMF (5 mL), followed by the addition of compound **24a** (98 mg, 0.25 mmol). The solution was stirred for 6 h at room temperature. The reaction mixture was poured into water (20 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layer was washed with saturated NaCl solution (3 × 20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give the impure product. The crude product was purified by column chromatography (DCM: MeOH = 100: 9) to give target compound **16c** as a white solid (44.6 mg, 30% yield). ^{1}H-NMR (DMSO-d_6, 600 MHz) δ: 9.80 (s, 1H), 7.87 (t, *J* = 5.8 Hz, 1H), 7.64 (t, *J* = 6.8 Hz, 1H), 7.49 (dd, *J* = 8.0, 5.9 Hz, 4H), 7.44 (d, *J* = 8.3 Hz, 2H), 7.11 (d, *J* = 8.3 Hz, 2H), 4.03 (t, *J* = 7.1 Hz, 2H), 3.22 (dd, *J* = 13.7, 7.2 Hz, 2H), 2.76 (d, *J* = 6.2 Hz, 2H), 2.63 (t, *J* = 7.4 Hz, 2H), 2.60 (s, 3H), 2.53 (s, 3H), 2.44 (s, 3H), 2.29 (t, *J* = 7.5 Hz, 2H), 2.16 (t, *J* = 7.5 Hz, 2H), 2.10 (t, *J* = 7.6 Hz, 2H), 1.94–1.89(m, 5H), 1.83–1.77 (m, 2H), 1.66–1.64 (m, 3H), 1.58–1.56 (m, 3H), 1.41 (s, 6H). ^{13}C NMR (DMSO-d_6, 150 MHz) δ: 172.3, 171.8, 171.1, 155.1, 141.5, 139.8, 137.9, 136.3, 134.5, 130.3, 129.1, 126.2, 119.5, 117.6, 50.5, 49.0, 36.9,

36.3, 35.1, 34.0, 33.1, 28.2, 25.1, 21.9, 21.2, 19.9. HR-MS m/z Calcd. for $C_{42}H_{54}N_7O_4$ $[M+H]^+$ 720.4232, Found 720.4250

Compounds **16d-e** were synthesized according to a similar procedure described for **16c.**

***N*^{1}-(((3*r*,5*r*,7*r*)-Adamantan-1-yl)methyl)-*N*^{7}-(4-(2-(4-(3,4-dimethyl-7-oxo-2-(*p*-tolyl)-2,7-dihydro-6*H*-pyrazolo[3,4-*d*]pyridazin-6-yl)butanamido)ethyl)phenyl) heptanediamide (16d).** White solid (58.7 mg, 35.7% yield). ^{1}H-NMR (DMSO-d_6, 600 MHz) δ: 9.77 (s, 1H), 7.87 (t, J = 5.4 Hz, 1H), 7.58 (t, J = 6.0 Hz, 1H), 7.48 (d, J = 8.3 Hz, 4H), 7.43 (d, J = 8.1 Hz, 2H), 7.09 (d, J = 8.3 Hz, 2H), 4.02 (t, J = 7.0 Hz, 2H), 3.21 (dd, J = 13.3, 6.8 Hz, 2H), 2.73 (d, J = 6.2 Hz, 2H), 2.65–2.55 (m, 5H), 2.52 (s, 3H), 2.42 (s, 3H), 2.25 (t, J = 7.4 Hz, 2H), 2.09 (t, J = 6.1 Hz, 4H), 1.93–1.85 (m, 5H), 1.64–1.62(m, 3H), 1.58–1.49 (m, 7H), 1.39 (s, 6H), 1.31–1.21 (m, 2H). ^{13}C NMR (DMSO-d_6, 150 MHz) δ: 172.7, 171.8, 171.4, 155.6, 141.6, 141.4, 139.8, 137.9, 136.3, 134.5, 130.3, 129.1, 126.1, 119.5, 117.6, 50.5, 49.0, 40.7, 37.0, 36.7, 35.8, 35.1, 34.0, 33.1, 28.8, 28.2, 25.8, 25.4, 25.1, 21.2, 19.9, 12.3. HR-MS m/z Calcd. for $C_{44}H_{58}N_7O_4$ $[M+H]^+$ 748.4545, Found 748.4558

***N1*-(((3*r*,5*r*,7*r*)-Adamantan-1-yl)methyl)-*N11*-(4-(2-(4-(3,4-dimethyl-7-oxo-2-(*p*-tolyl)-2,7-dihydro-6*H*-pyrazolo[3,4-*d*]pyridazin-6-yl)butanamido)ethyl)phenyl) undecanediamide (16e).** White solid (47 mg, 34.4% yield). ^{1}H-NMR (DMSO-d_6, 600 MHz) δ: 9.77 (s, 1H), 7.88 (s, 1H), 7.60 (s, 1H), 7.48 (d, J = 8.3 Hz, 4H), 7.44 (d, J =

8.1 Hz, 2H), 7.10 (d, *J* = 8.2 Hz, 2H), 4.03 (t, *J* = 6.9 Hz, 2H), 3.22 (dd, *J* = 13.1, 6.8 Hz, 2H), 2.74 (d, *J* = 6.1 Hz, 2H), 2.65–2.57 (m, 5H), 2.53 (s, 3H), 2.43 (s, 3H), 2.25 (t, *J* = 7.4 Hz, 2H), 2.11–2.07 (m, 4H), 1.92–1.90 (m, 5H), 1.65–1.63 (m, 3H), 1.56–1.55 (m, 5H), 1.48 (s, 3H), 1.41–1.40 (m, 7H), 1.27–1.25 (m, 8H). ^{13}C NMR (DMSO-d_6, 150 MHz) δ: 172.8, 171.9, 171.5, 155.7, 141.6, 139.8, 137.9, 136.5, 134.5, 130.4, 129.2, 126.2, 119.6, 117.6, 50.5, 49.0, 40.7, 37.0, 36.8, 35.9, 35.1, 34.1, 33.1, 29.3, 29.1, 28.2, 25.9, 25.6, 25.1, 21.2, 19.8, 12.3. HR-MS m/z Calcd. for $C_{48}H_{66}N_7O_4$ $[M+H]^+$ 804.5171, Found 804.5198

***tert*-Butyl (2-(4-(3,4-dimethyl-7-oxo-2-(*p*-tolyl)-2,7-dihydro-6*H*-pyrazolo[3,4-*d*] pyridazin-6-yl)butanamido)ethyl)carbamate (26a).** HBTU (67 mg, 0.18 mmol), DIPEA (0.07 mL, 0.36 mmol) and compound **14** (40 mg, 0.12 mmol) were added to a solution of *tert*-butyl (2-aminoethyl)carbamate **25a** (29 mg, 0.18 mmol) in anhydrous DMF (2 mL). The solution was stirred for 4 h at room temperature. Then the reaction mixture was poured into water (20 mL) and extracted with EtOAc (3 × 5 mL). The combined organic phase was washed with saturated NaCl solution (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford the crude product. The crude product was purified by column chromatography (DCM: MeOH = 100: 7) to give compound **26a** (50.3 mg, 88.4% yield) as a yellow oil. ^{1}H-NMR (DMSO-d_6, 600 MHz) δ: 7.82 (t, *J* = 5.5 Hz, 1H), 7.49 (d, *J* = 8.3 Hz, 2H), 7.44 (d, *J* = 8.3 Hz, 2H), 6.78 (t, *J* = 5.6 Hz, 1H), 4.05 (t, *J* = 7.0 Hz, 2H), 3.05 (dd, *J*

= 12.3, 6.2 Hz, 2H), 2.96 (dd, *J* = 12.4, 6.2 Hz, 2H), 2.60 (s, 3H), 2.53 (s, 3H), 2.44 (s, 3H), 2.11 (t, *J* = 7.6 Hz, 2H), 1.97–1.89 (m, 2H), 1.36 (s, 9H).

Compounds **26b-e** were synthesized according to a similar procedure described for **26a**.

***tert*-Butyl (4-(4-(3,4-dimethyl-7-oxo-2-(*p*-tolyl)-2,7-dihydro-6*H*-pyrazolo[3,4-*d*] pyridazin-6-yl)butanamido)butyl)carbamate (26b).** ^{1}H-NMR (DMSO-d_6, 600 MHz) δ: 7.77 (t, *J* = 5.4 Hz, 1H), 7.48 (d, *J* = 8.3 Hz, 2H), 7.43 (d, *J* = 8.1 Hz, 2H), 6.76 (t, *J* = 5.3 Hz, 1H), 4.03 (t, *J* = 7.0 Hz, 2H), 3.00 (d, *J* = 5.3 Hz, 2H), 2.88 (d, *J* = 5.5 Hz, 2H), 2.59 (s, 3H), 2.52 (s, 3H), 2.43 (s, 3H), 2.09 (t, *J* = 7.6 Hz, 2H), 1.94–1.87 (m, 2H), 1.37–1.34 (m, 13H).

***tert*-Butyl (6-(4-(3,4-dimethyl-7-oxo-2-(*p*-tolyl)-2,7-dihydro-6*H*-pyrazolo[3,4-*d*] pyridazin-6-yl)butanamido)hexyl)carbamate (26c).** ^{1}H-NMR (DMSO-d_6, 600 MHz) δ: 7.75 (d, *J* = 5.3 Hz, 1H), 7.49 (d, *J* = 8.3 Hz, 2H), 7.45 (d, *J* = 8.3 Hz, 2H), 6.75 (s, 1H), 4.05 (t, *J* = 7.1 Hz, 2H), 3.10 (t, *J* = 7.2 Hz, 1H), 3.01 (dd, *J* = 12.9, 6.7 Hz, 2H), 2.61 (s, 3H), 2.53 (s, 3H), 2.44 (s, 3H), 2.10 (t, *J* = 7.7 Hz, 2H), 1.93 (dd, *J* = 14.6, 7.3 Hz, 2H), 1.52 (s, 1H), 1.37 (s, 9H), 1.26–1.23 (m, 8H).

***tert*-Butyl (8-(4-(3,4-dimethyl-7-oxo-2-(*p*-tolyl)-2,7-dihydro-6*H*-pyrazolo[3,4-*d*] pyridazin-6-yl)butanamido)octyl)carbamate (26d).** ^{1}H-NMR (DMSO-d_6, 600 MHz) δ: 7.76 (s, 1H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.45 (d, *J* = 8.2 Hz, 2H), 6.75 (s, 1H),

5.77 (s, 5H), 4.04 (t, J = 7.1 Hz, 2H), 3.10 (dd, J = 13.3, 3.8 Hz, 1H), 3.01 (dd, J = 12.5, 6.7 Hz, 2H), 2.61 (s, 3H), 2.53 (s, 3H), 2.44 (s, 3H), 2.13–2.07 (m, 2H), 1.92 (t, J = 7.4 Hz, 2H), 1.37 (s, 9H), 1.27–1.24 (m, 8H).

***tert*-Butyl (2-(2-(2-(4-(3,4-dimethyl-7-oxo-2-(*p*-tolyl)-2,7-dihydro-6*H*-pyrazolo [3,4-*d*]pyridazin-6-yl)butanamido)ethoxy)ethoxy)ethyl)carbamate (26e).** ^{1}H-NMR (DMSO-d_6, 600 MHz) δ: 7.90 (t, J = 5.5 Hz, 1H), 7.50 (d, J = 8.3 Hz, 2H), 7.45 (d, J = 8.2 Hz, 2H), 6.78 (t, J = 5.4 Hz, 1H), 4.06 (t, J = 7.1 Hz, 2H), 3.50 (s, 4H), 3.43–3.37 (m, 4H), 3.20 (q, J = 5.8 Hz, 2H), 3.06 (q, J = 6.0 Hz, 2H), 2.61 (s, 3H), 2.54 (s, 3H), 2.45 (s, 3H), 2.14 (t, J = 7.6 Hz, 2H), 1.97–1.89 (m, 2H), 1.38 (s, 9H).

Compounds **17a-e** were synthesized according to a similar procedure described for **16a-b.**

***N*-(2-(2-((3*r*,5*r*,7*r*)-Adamantan-1-yl)acetamido)ethyl)-4-(3,4-dimethyl-7-oxo-2-(*p*-tolyl)-2,7-dihydro-6*H*-pyrazolo[3,4-*d*]pyridazin-6-yl)butanamide (17a).** White solid (45.5 mg, 84.9% yield). ^{1}H-NMR (DMSO-d_6, 600 MHz) δ: 7.80 (s, 1H), 7.70 (s, 1H), 7.49 (d, J = 6.3 Hz, 2H), 7.44 (d, J = 6.8 Hz, 2H), 4.05 (t, J = 6.7 Hz, 2H), 3.07 (s, 4H), 2.60 (s, 3H), 2.53 (s, 3H), 2.43 (s, 3H), 2.10 (t, J = 7.3 Hz, 2H), 1.96-1.91 (m, 2H), 1.86 (s, 3H), 1.80 (s, 2H), 1.61–1.59 (m, 3H), 1.54–1.52 (m, 9H). ^{13}C NMR (DMSO-d_6, 150 MHz) δ: 172.1, 170.5, 155.7, 141.5, 139.8, 137.9, 136.3, 130.4, 126.2, 117.6, 50.6, 48.9, 42.5, 38.9, 38.6, 36.9, 33.0, 32.5, 28.5, 24.9, 21.2, 19.9, 12.3. HR-MS m/z Calcd. for $C_{32}H_{43}N_6O_3$ $[M+H]^+$ 559.3392, Found 559.3423.

***N*-(4-(2-((3*r*,5*r*,7*r*)-Adamantan-1-yl)acetamido)butyl)-4-(3,4-dimethyl-7-oxo-2-(*p*-tolyl)-2,7-dihydro-6*H*-pyrazolo[3,4-*d*]pyridazin-6-yl)butanamide (17b).** White solid (18 mg, 11.8% yield). ^{1}H-NMR (DMSO-d_6, 600 MHz) δ: 7.78 (t, J = 5.4 Hz, 1H), 7.62 (t, J = 5.5 Hz, 1H), 7.48 (d, J = 8.4 Hz, 2H), 7.44 (d, J = 8.2 Hz, 2H), 4.04 (t, J = 7.0 Hz, 2H), 3.01 (dd, J = 11.2, 5.5 Hz, 4H), 2.60 (s, 3H), 2.52 (s, 3H), 2.43 (s, 3H), 2.10 (t, J = 7.6 Hz, 2H), 1.92 (dd, J = 14.7, 7.8 Hz, 2H), 1.88 (s, 3H), 1.79 (s, 2H), 1.62–1.61 (m, 3H), 1.55–1.53 (m, 9H), 1.37–1.36 (m, 4H) ^{13}C NMR (DMSO-d_6, 150 MHz) δ: 171.7, 170.2, 155.6, 141.6, 141.4, 139.8, 137.9, 136.3, 130.4, 126.15, 117.6, 50.5, 49.1, 42.6, 38.6, 36.9, 33.1, 32.6, 28.5, 27.2, 25.2, 21.2, 19.9, 12.3. HR-MS m/z Calcd. for $C_{34}H_{47}N_6O_3$ $[M+H]^+$ 587.3705, Found 587.3721.

***N*-(6-(2-((3*r*,5*r*,7*r*)-Adamantan-1-yl)acetamido)hexyl)-4-(3,4-dimethyl-7-oxo-2-(*p*-tolyl)-2,7-dihydro-6*H*-pyrazolo[3,4-*d*]pyridazin-6-yl)butanamide (17c).** Light yellow oil (36 mg, 29% yield). ^{1}H-NMR (DMSO-d_6, 600 MHz) δ: 7.77 (t, J = 5.5 Hz, 1H), 7.62 (t, J = 5.4 Hz, 1H), 7.49 (d, J = 8.3 Hz, 2H), 7.44 (d, J = 8.2 Hz, 2H), 4.04 (t, J = 7.1 Hz, 2H), 3.01 (dt, J = 13.8, 6.8 Hz, 4H), 2.60 (s, 3H), 2.53 (s, 3H), 2.44 (s, 3H), 2.10 (t, J = 7.6 Hz, 2H), 1.93 (dd, J = 14.8, 7.5 Hz, 2H), 1.89 (s, 3H), 1.79 (s, 2H), 1.64–1.62 (m, 3H), 1.56–1.54 (m, 9H), 1.38–1.35 (m, 4H), 1.25–1.24 (m, 4H). ^{13}C NMR (DMSO-d_6, 150 MHz) δ: 171.7 , 170.1, 155.6, 141.6, 141.4, 139.8, 137.8, 136.3, 130.3, 126.2, 117.6, 50.5, 49.1, 42.6, 38.8, 38.6, 36.9, 33.1, 32.6, 29.6, 28.5,

26.6, 25.15, 21.18, 19.86, 12.30. HR-MS m/z Calcd. for $C_{36}H_{51}N_6O_3$ $[M+H]^+$ 615.4018, Found 615.4023.

***N*-(8-(2-((3*r*,5*r*,7*r*)-Adamantan-1-yl)acetamido)octyl)-4-(3,4-dimethyl-7-oxo-2-(*p*-tolyl)-2,7-dihydro-6*H*-pyrazolo[3,4-*d*]pyridazin-6-yl)butanamide (17d).** Light yellow oil (42 mg, 40.6% yield).^{1}H-NMR (DMSO-d_6, 600 MHz) δ: 7.75 (t, J = 5.4 Hz, 1H), 7.60 (d, J = 5.5 Hz, 1H), 7.49 (d, J = 8.4 Hz, 2H), 7.45 (d, J = 8.2 Hz, 2H), 4.05 (t, J = 7.0 Hz, 2H), 3.00 (dq, J = 9.6, 6.8 Hz, 4H), 2.61 (s, 3H), 2.53 (s, 3H), 2.44 (s, 3H), 2.10 (t, J = 7.7 Hz, 2H), 1.95–1.92 (m, 2H), 1.90 (s, 3H), 1.80 (s, 2H), 1.66–1.64 (m, 3H), 1.57–1.55 (m, 9H), 1.35–1.38 (m, 4H), 1.24 (s, 8H). ^{13}C NMR (DMSO-d_6, 150 MHz) δ: 171.6, 170.1, 155.6, 141.6, 141.4, 139.8, 137.9, 136.3, 130.4, 126.2, 117.6, 50.6, 49.1, 42.6, 38.9, 38.6, 36.9, 33.1, 32.6, 29.6, 29.2, 28.5, 26.8, 25.2, 21.2, 19.8, 12.3. HR-MS m/z Calcd. for $C_{38}H_{55}N_6O_3$ $[M+H]^+$ 643.4331, Found 643.4354.

***N*-(2-(2-(2-(2-((3*r*,5*r*,7*r*)-Adamantan-1-yl)acetamido)ethoxy)ethoxy)ethyl)-4-(3,4-dimethyl-7-oxo-2-(*p*-tolyl)-2,7-dihydro-6*H*-pyrazolo[3,4-*d*]pyridazin-6-yl)butanamide (17e).** Yellow oil (49.2 mg, 64.7% yield). ^{1}H-NMR (DMSO-d_6, 600 MHz) δ: 7.86 (t, J = 5.6 Hz, 1H), 7.68 (t, J = 5.6 Hz, 1H), 7.48 (d, J = 8.3 Hz, 2H), 7.43 (d, J = 8.2 Hz, 2H), 4.05-4.02 (m, 2H), 3.49 (s, 4H), 3.38 (dd, J = 13.3, 6.0 Hz, 4H), 3.17 (dq, J = 15.2, 5.8 Hz, 4H), 2.59 (s, 3H), 2.52 (s, 3H), 2.43 (s, 3H), 2.12 (t, J = 7.6 Hz, 2H), 1.90-1.94 (m, 7.6 Hz, 2H), 1.88 (s, 3H), 1.80 (s, 2H), 1.63–1.61 (m, 3H), 1.55–

1.53 (m, 9H) ^{13}C NMR (DMSO-d_6, 150 MHz) δ: 172.0, 170.4, 155.6, 141.6, 141.4, 139.8, 137.9, 136.4, 130.4, 126.2, 117.6, 69.9, 69.6, 60.2, 50.4, 49.0, 42.5, 38.9, 38.8, 36.9, 33.0, 32.6, 28.5, 25.1, 21.2, 19.9, 14.55, 12.3. HR-MS m/z Calcd. for $C_{36}H_{51}N_6O_5$ $[M+H]^+$ 647.3916, Found 647.3909.

Methyl 7-(2-((3*r*,5*r*,7*r*)-adamantan-1-yl)acetamido)heptanoate (28) This compound was synthesized according to a similar procedure described for **22a**. ^{1}H-NMR (DMSO-d_6, 600 MHz) δ: 7.62 (t, J = 5.4 Hz, 1H), 3.59 (s, 3H), 3.00 (dd, J = 12.7, 6.8 Hz, 2H), 2.29 (t, J = 7.4 Hz, 2H), 1.91 (s, 3H), 1.81 (s, 2H), 1.67–1.65 (m, 3H), 1.58–1.55 (m, 9H), 1.53–1.50 (m, 2H), 1.38–1.36 (m, 2H), 1.27–1.25 (m, 4H).

7-(2-((3*r*,5*r*,7*r*)-Adamantan-1-yl)acetamido)heptanoic acid (29). This compound was synthesized according to a similar procedure described for **22a**. ^{1}H-NMR (DMSO-d_6, 600 MHz) δ: 7.60 (s, 1H), 2.98 (dd, J = 12.8, 6.8 Hz, 2H), 2.17 (t, J = 7.4 Hz, 2H), 1.89 (s, 3H), 1.79 (s, 2H), 1.65–1.63 (m, 3H), 1.56–1.53 (m, 9H), 1.49–1.43 (m, 2H), 1.39–1.31 (m, 2H), 1.25–1.23 (m, 4H).

***tert*-Butyl**

(4-(7-(2-((3*r*,5*r*,7*r*)-adamantan-1-yl)acetamido)heptanamido)phenethyl)

carbamate (30). This compound was synthesized according to a similar procedure described for **23a**. ^{1}H-NMR (DMSO-d_6, 600 MHz) δ: 9.77 (s, 1H), 7.62 (t, J = 5.4 Hz, 1H), 7.49 (d, J = 8.4 Hz, 2H), 7.09 (d, J = 8.4 Hz, 2H), 6.83 (t, J = 5.4 Hz, 1H), 3.10

(dd, *J* = 14.0, 6.5 Hz, 2H), 3.01 (dd, *J* = 12.7, 6.7 Hz, 2H), 2.63 (t, *J* = 7.5 Hz, 2H), 2.27 (t, *J* = 7.4 Hz, 2H), 1.91 (s, 3H), 1.81 (s, 2H), 1.66–1.64 (m, 3H), 1.58–1.56 (m, 12H), 1.37 (s, 9H), 1.30–1.27 (m, 5H).

7-(2-((3*r*,5*r*,7*r*)-Adamantan-1-yl)acetamido)-*N*-(4-(2-(4-(3,4-dimethyl-7-oxo-2-(*p*-tolyl)-2,7-dihydro-6*H*-pyrazolo[3,4-*d*]pyridazin-6-yl)butanamido)ethyl)phenyl)heptanamide (17f). White solid (45.3 mg, 27% yield).This compound was synthesized according to a similar procedure described for **16c**. ^{1}H-NMR (DMSO-d_6, 600 MHz) δ: 9.78 (s, 1H), 7.88 (t, *J* = 5.2 Hz, 1H), 7.64 (t, *J* = 5.2 Hz, 1H), 7.48 (d, *J* = 8.1 Hz, 4H), 7.44 (d, *J* = 7.7 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 4.03 (t, *J* = 6.6 Hz, 2H), 3.22 (dd, *J* = 12.9, 6.7 Hz, 2H), 3.00 (dd, *J* = 11.9, 5.9 Hz, 2H), 2.63 (t, *J* = 7.0 Hz, 2H), 2.59 (s, 3H), 2.53 (s, 3H), 2.43 (s, 3H), 2.26 (t, *J* = 7.3 Hz, 2H), 2.10 (t, *J* = 7.3 Hz, 2H), 1.94-1.91 (m, 2H), 1.90 (s, 3H), 1.80 (s, 2H), 1.65–1.63 (m, 3H), 1.56–1.54 (m, 11H), 1.38–1.37 (m, 2H), 1.28 (s, 4H). ^{13}C NMR (DMSO-d_6, 150 MHz) δ: 171.8, 171.5, 170.1, 155.6, 141.6, 141.4, 139.8, 137.9, 136.4, 134.4, 130.4, 129.2, 126.2, 119.5, 117.6, 50.6, 49.0, 42.6, 40.7, 38.7, 36.9, 35.1, 33.1, 32.6, 29.5, 28.8, 28.5, 26.7, 25.6, 25.1, 21.2, 19.9, 12.3. HR-MS m/z Calcd. for $C_{45}H_{60}N_7O_4$. $[M+H]^+$ 762.4702, Found 762.4726.

Fluorescence Polarization Assay

Determination of equilibrium dissociation constants K_i for each compound was performed using the fluorescence polarization assay with Atrovastatin-PEG3-FITC as ligand in black flat–bottom 96–well plates (Corning # 3993). A 2–fold serial dilution

of each compound (40 μL) containing 0.2% DMSO was added to 40 μL of a solution of fluorescent probe (50 nM final concentration) and 80 nM PDEδ protein in PBS-buffer (containing 0.05% Chaps, 0.4% DMSO). The fluorescence polarization value was measured on Biotek Synergy H2 with the 485 nm excitation and 535 nm emission filters after 2 h incubation at room temperature. The K_i of each compound tested was determined by fitting the displacement curves (AOBS, the experimentally measured anisotropy vs LT, the test compound concentration) to following equation using Origin (OriginPro 7, function codec from origin)

$$\mathrm{d} = K_D + K_i + L_{ST} + L_T - R_T \quad (1)$$

$$e = (L_T - R_T) \times K_D + (L_{ST} - R_T) \times K_i + K_D \times K_i \quad (2)$$

$$f = -K_D \times K_i \times R_T \quad (3)$$

$$\theta = cos^{-1}\left[\frac{-2 \times d^3 + 9 \times d \times e - 27f}{2 \times \pm \sqrt{(d^2 - 3 \times e)^3}}\right] \quad (4)$$

$$F = \frac{2 \times \sqrt{d^2 - 3 \times e} \times cos\left(\frac{\theta}{3}\right) - d}{3 \times K_{D1} + 2 \times \sqrt{d^2 - 3 \times e} \times cos\left(\frac{\theta}{3}\right) - d} \quad (5)$$

$$A = \frac{Q \times F \times A_B + (1 - F) \times A_F}{1 - (1 - Q) \times F} \quad (6)$$

In these equations, Q is the ratio of the fluorescence intensity of the probe in the bound and free status, FSB is the fraction of bound probe, AB and AF represent the anisotropies of bound and free probe, K_D is the equilibrium dissociation constant of the fluorescent probe, LST is the concentration of probe, RT is the receptor S35 protein concentration, LT is total concentration of unlabeled small molecule competitor and K_i is the test compound's equilibrium dissociation constant.

Western Blot.

The SW480 cells were cultivated (5.0×10^5 cells/well) on 6-well transparent plates. The test compounds were added following seeding after 24 h. The cells were incubated for another 24 h, and washed with cold PBS for 2 times. Then, 80 μL of cold lysis buffer containing 1% protease and phosphatase inhibitors was added to the plates for 30 min on ice. The cell lysates were centrifuged for 12000 rpm for 15 min at 4 °C. The protein extract was denatured at 100 °C bath and protein concentration was measured by BCA protein assay. Equal amounts of protein (20 μg) were separated and analyzed on 10−15% SDS-PAGE gels. The gels were transferred to PVDF membrane and blocked with 5% bovine serum albumin buffer for 2 h. The membranes were incubated with primary antibody overnight at 4 °C and washed with TBST three times. Then, the membranes were incubated with infrared secondary antibodies for 1 h. The immunoblots were scanned by LI-COR Odyssey infrared imaging system. The primary antibodies were: PDEδ (GeneTex, CTX109240, 1:1000), p-Ert (CST # 4370, 1:1000), p-Akt (CST # 4060, 1:1000), t-Akt (Epitomics # 2118, 1:10000), t-Erk (CST # 9107, 1:1000) and GAPDH (Abcam, ab8245).

The Molecular Docking Study.

The crystal structure of PDEδ was obtained from protein database bank (PDB ID: 5E80) and prepared for docking using the protein preparation tool in Discovery Studio 3.0.2. During this process, the ligands and waters were removed and hydrogens were added to the structure. Staged minimization was performed with default setting. The docking studies were carried out using GOLD 5.0. Binding site was defined as whole

residues within a 10 Å radius subset encompassing the ligand. Conformations were generated by genetic algorithm and scored using GoldScore as fitness function. The best pose was chosen to explore the ligand–protein interaction. The image representing the best structure docking was prepared using PyMol 2.0.

In Vitro Antitumor Assay.

The test cancer cells (SW480, HCT116 and MIAPACA-2), which were in the logarithmic stage, were seeded in 96-well transparent plates at a density of 6.5×10^3 cells per well and incubated in a cell incubator for 24 h. Test compounds were added onto 96-well plates with gradient concentrations and complete medium containing 0.1% DMSO for control. After incubated for 72 h, CCK8 (10 μL) was added to each well and the 96-well plate was incubated for 0.5−2 h. Finally, the absorbance (OD) was read on a Biotek Synergy H2 (Lab systems) at 450 nm and IC_{50} was calculated by Logit method. All experiments were performed at least three independent assays.

Apoptosis Analysis by Flow Cytometry.

SW480 cells (4.0×10^5 cells/well) were cultivated on six-well plates, and following treated with vehicle, compound **17c** (at 40 μM) and deltazinone (at 50 μM) for 24 h, respectively. Then, the cells were trypsinized and washed with cold PBS. After centrifugation and removal of the supernatants, the cells were resuspended in 1× binding buffer (300 μL). Treated with annexin V-FITC (5 μL) and PI (10 μL) in turn,

the stained cells were incubated at room temperature for 15 min in dark and measured by flow cytometer (BD Accuri C6).

The three independent assays for inhibiting the growth of MIAPACA-2

	1	17c	17d
$IC_{50}(\mu M)$	45.36	21.5	73.37
	37.13	13.46	67.83
	127.6	52.66	15.2

The mean values of IC_{50}

1 (IC_{50}=41.2 ± 4.1 μM)

17c (IC_{50}=17.5 ± 4.0 μM)

17d (IC_{50}=70.6 ± 2.8 μM)

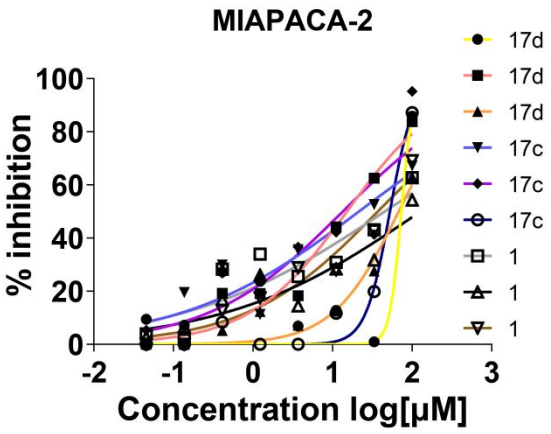
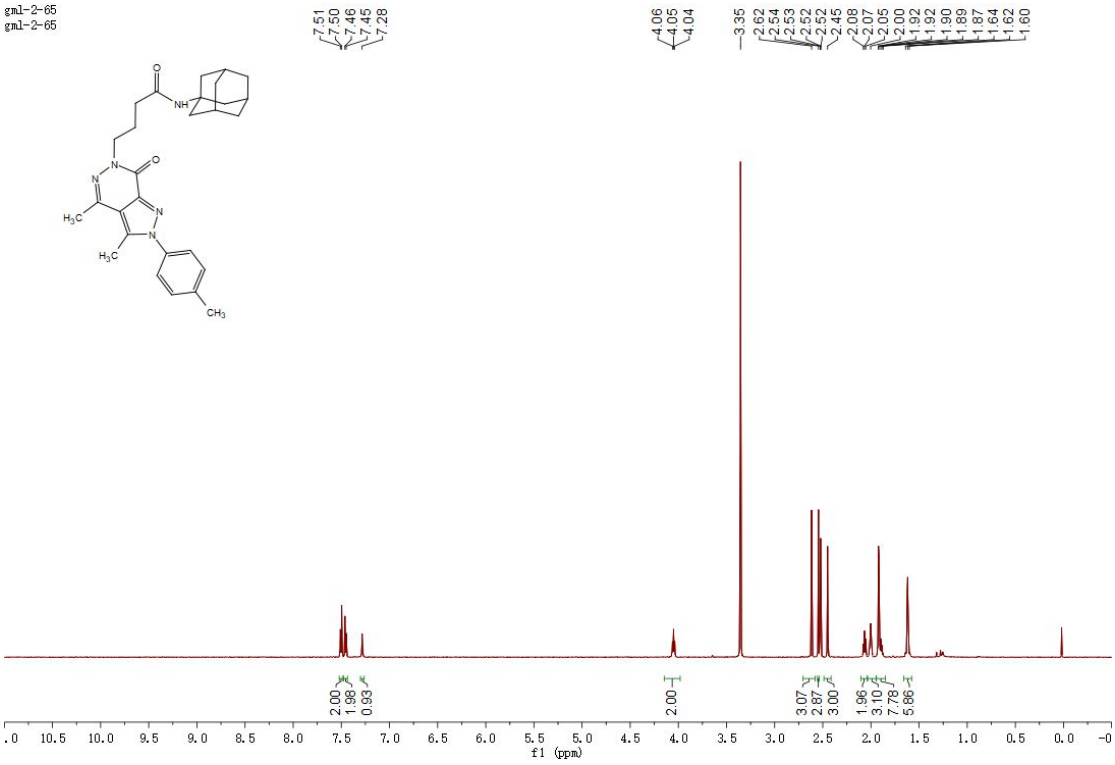


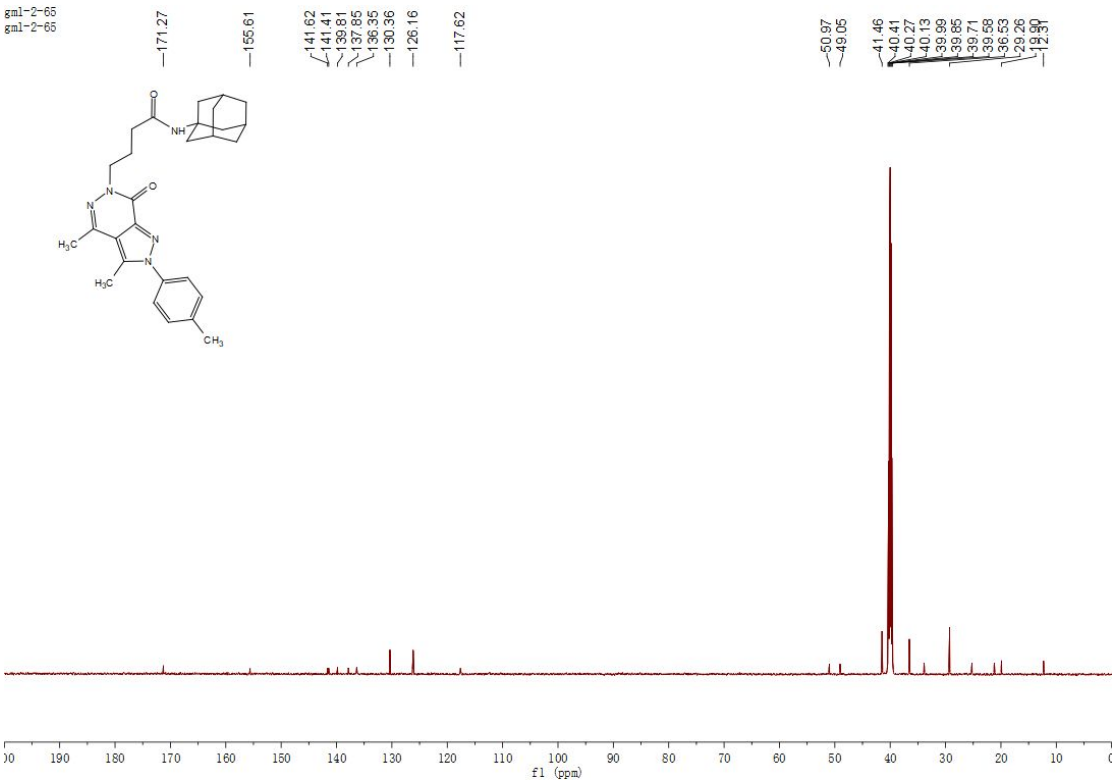
Figure S1. The anti-proliferative activities of test compounds against MIAPACA-2

Spectral data

Copies of the NMR and HRMS for representative compounds

Compound 15a





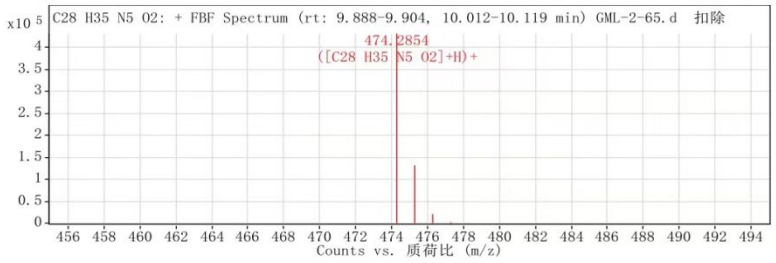
定性分析报告

数据文件名称	GML-2-65.d	**样品名称**	
样品类型	Sample	**位置**	P1-C1
仪器名称	Instrument 1	**用户名**	
采集方法	SERUM-POS-15MIN.m	**采集时间**	2021/12/14 11:33:43
IRM 校正状态	成功	**DA 方法**	123.m
注释			

设备类型	QuadrupoleTimeOfFlight	**Sample Group**	
Info.		**Stream Name**	LC 1
Acquisition SW Version	6200 series TOF/6500 series Q-TOF 10.1 (48.0)		

用户质谱图

裂解电压	碰撞能量	电离模式
0	0	未指定



峰列表

m/z	z	丰度	分子式	离子
474.2854	1	431936.75	C28 H35 N5 O2	(M+H)+
475.2886	1	131883.23	C28 H35 N5 O2	(M+H)+
476.2902	1	20734.84	C28 H35 N5 O2	(M+H)+
477.2922	1	2532.22	C28H36N5O2	
478.2934	1	323.09	C28H36N5O2	
497.2677	1	927.54	C28H36N5O2	
498.2692	1	136.51	C28H36N5O2	
513.2435	1	78.34	C28H36N5O2	

分子式计算器元素限制

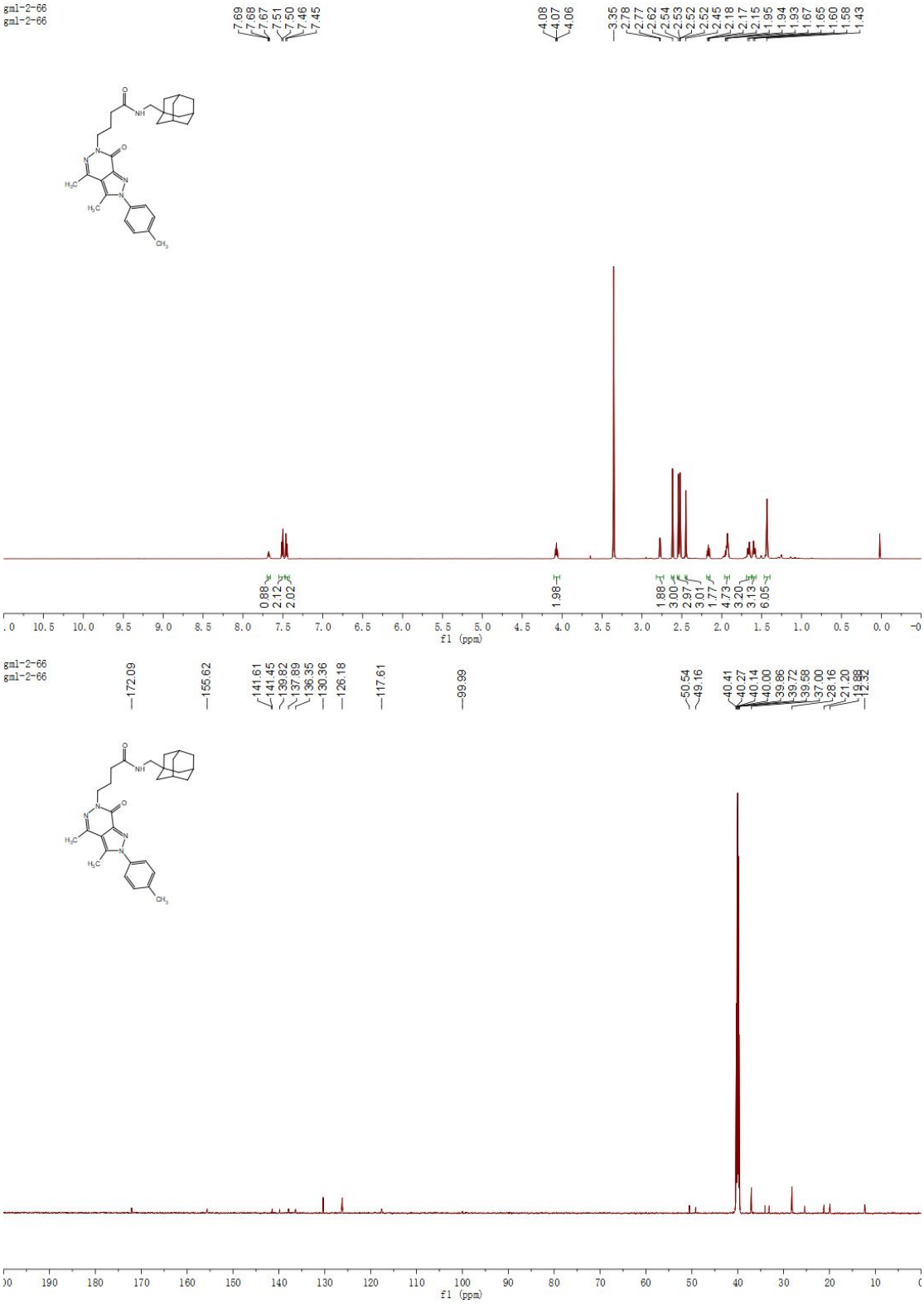
元素	最小	最大
C	3	28
H	0	36
O	0	2
N	0	5

分子式计算器结果

分子式	最佳	质量	目标质量	差 (ppm)	离子种类	分数
C28 H35 N5 O2	TRUE	473.2781	473.2791	2.12	C28 H36 N5 O2	97.06

--- 报告结束 ---

Compound 15b



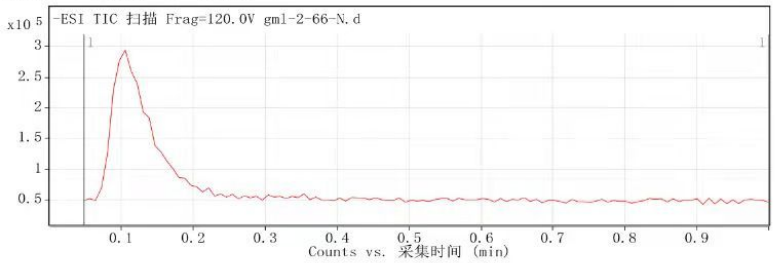
定性分析报告

数据文件名称	gml-2-66-N.d	**样品名称**	
样品类型	Sample	**位置**	P1-B4
仪器名称	Instrument 1	**用户名**	
采集方法	MS-NEG.m	**采集时间**	2021/9/10 17:29:00
IRM 校正状态	成功	**DA 方法**	Default.m
注释			

设备类型	QuadrupoleTimeOfFlight	**Sample Group**	
Info.		**Stream Name**	LC 1
Acquisition SW Version	6200 series TOF/6500 series Q-TOF 10.1 (48.0)		

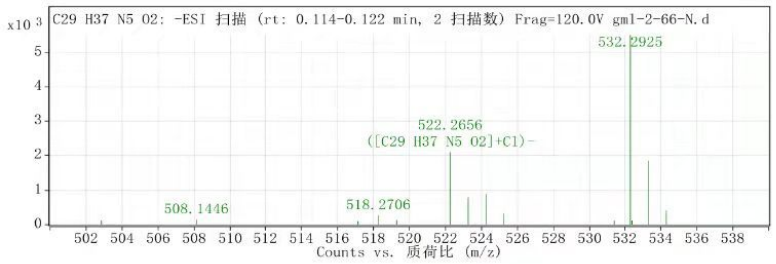
用户色谱图

裂解电压 120 **碰撞能量** 0 **电离模式** ESI



用户质谱图

裂解电压 120 **碰撞能量** 0 **电离模式** ESI



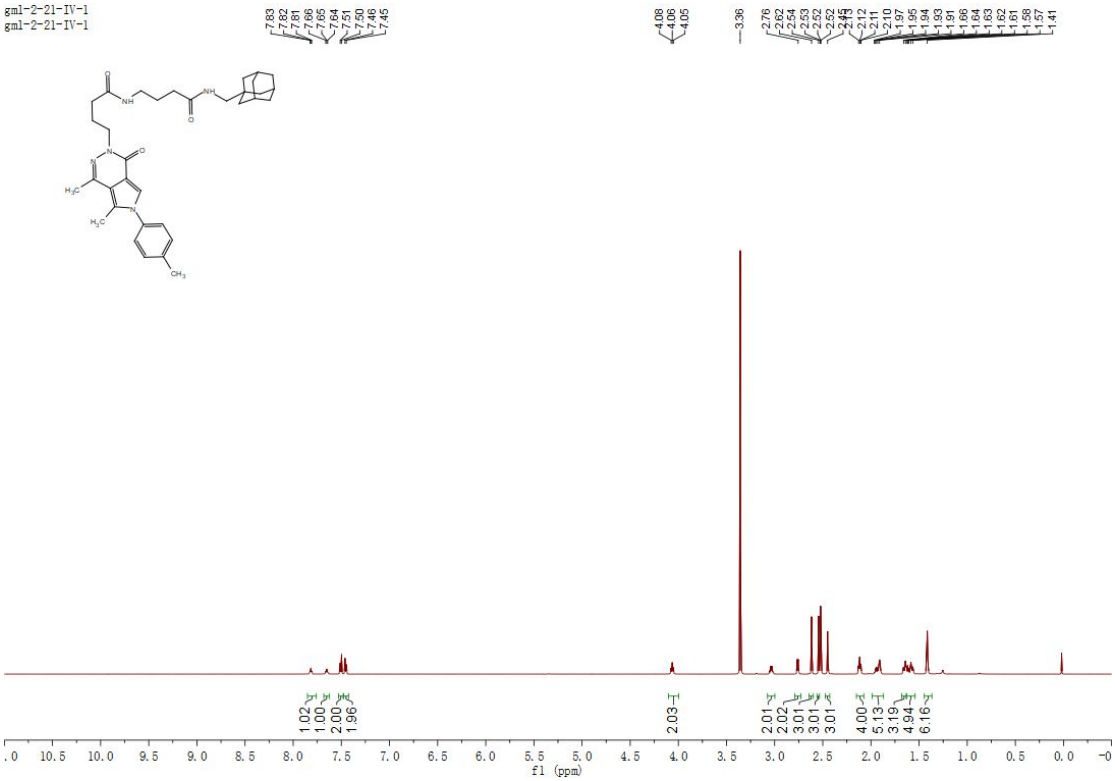
峰列表

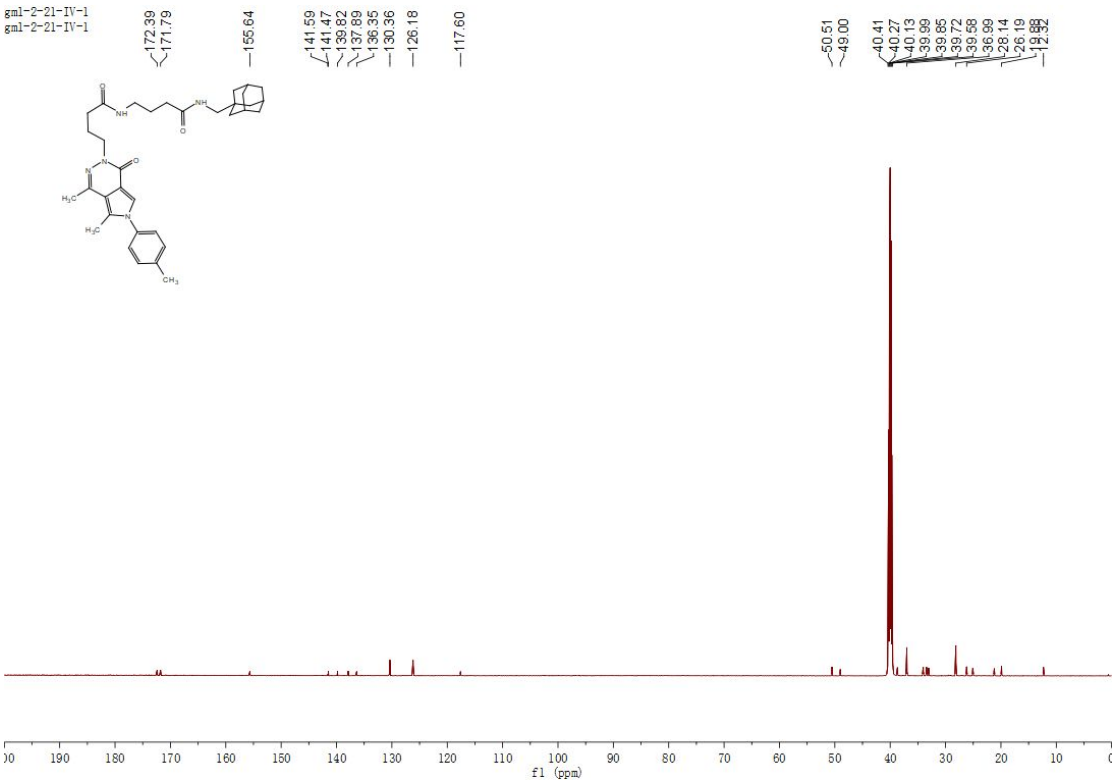
m/z	z	丰度
112.9862		4860.19
144.9657		149466.89
242.1776	1	3822.93
255.2324	1	2611.69
283.2641	1	4115.61
312.9195		7444.28
375.2759	1	2431.58
403.305	1	3396.3
532.2925	1	5502.57
966.0007	1	8693.76

分子式计算器元素限制

元素	最小	最大
C	3	60

Compound 16a





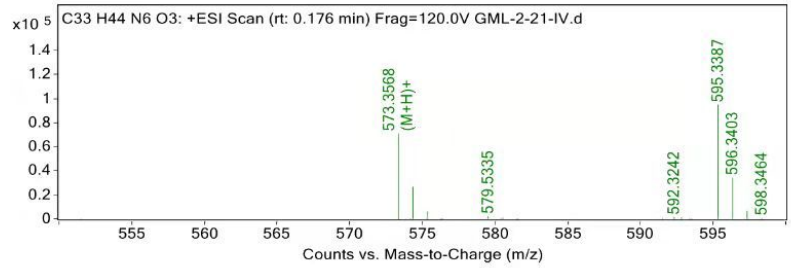
Qualitative Analysis Report

Data Filename	GML-2-21-IV.d	**Sample Name**	
Sample Type	Sample	**Position**	P1-B4
Instrument Name	Instrument 1	**User Name**	
Acq Method	MS-POS.m	**Acquired Time**	12/17/2020 9:51:56 AM (UTC+08:00)
IRM Calibration Status	Success	**DA Method**	mz-300.m
Comment			

Sample Group		**Info.**	
Stream Name	LC 1	**Acquisition Time (Local)**	12/17/2020 9:51:56 AM (UTC+08:00)
Acquisition SW Version	6200 series TOF/6500 series Q-TOF 10.1 (48.0)	**QTOF Driver Version**	10.01.00
QTOF Firmware Version	9.808	**Tune Mass Range Max.**	3200

Spectra

Fragmentor Voltage	Collision Energy	Ionization Mode
120	0	ESI



Peak List

m/z	z	Abund	Formula	Ion
338.341		3004.55		
573.3568	1	71008.09	C33 H44 N6 O3	(M+H)+
574.3583	1	26773.11	C33 H44 N6 O3	(M+H)+
575.3592	1	6295.09	C33 H44 N6 O3	(M+H)+
595.3387	1	94957.54		
596.3403	1	34375.99		
597.3414	1	6775.13		
611.3156	1	2640.21		
922.0098		2543.94		
1167.6796	1	2321.51		

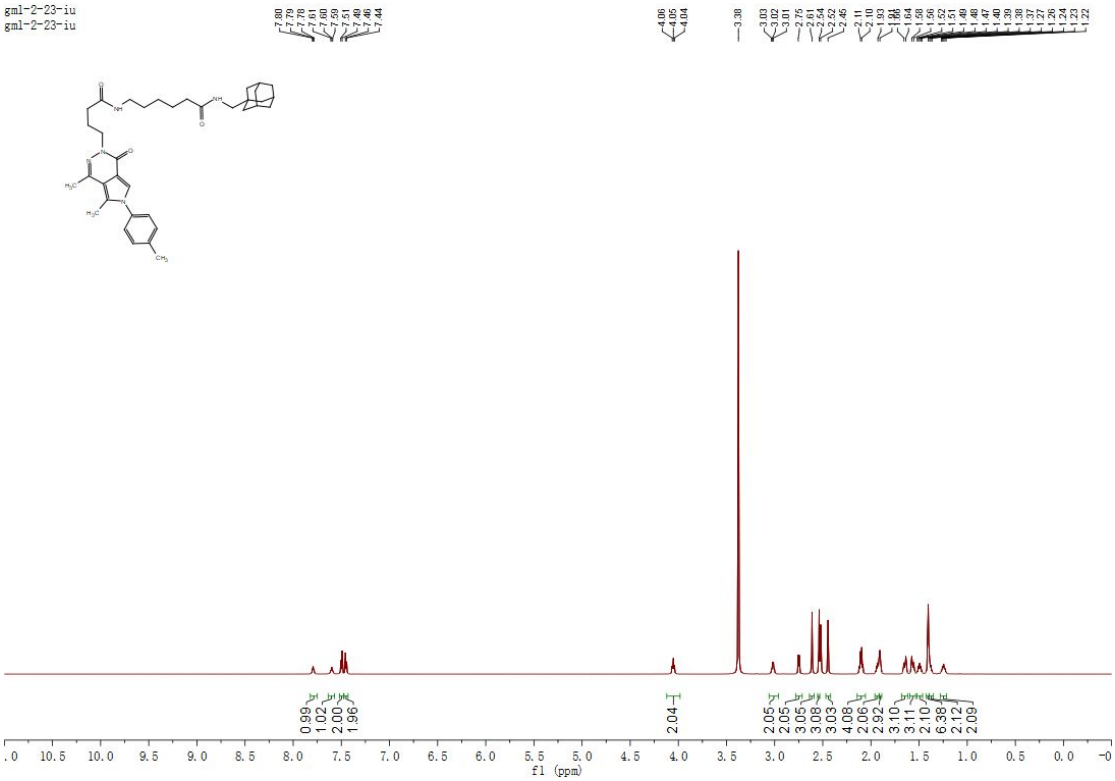
Formula Calculator Element Limits

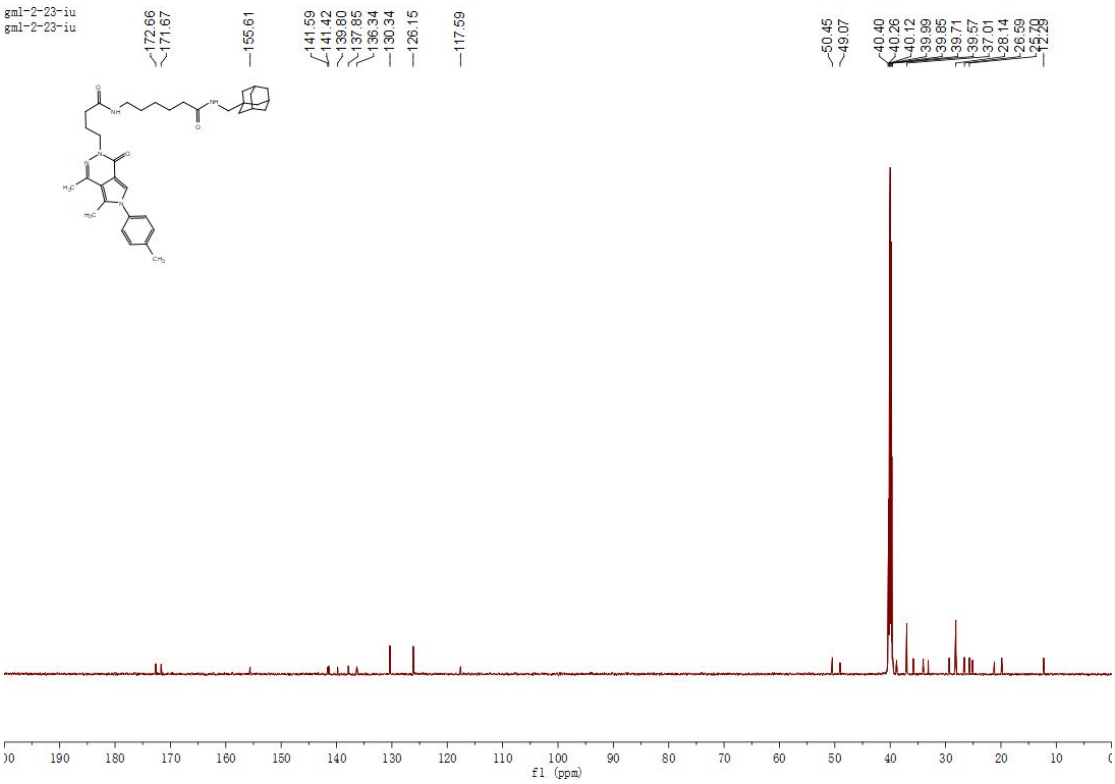
Element	Min	Max
C	3	60
H	0	120
O	0	5
N	0	6
S	0	0
Cl	0	0

Formula Calculator Results

Formula	Best	Mass	Tgt Mass	Diff (ppm)	Ion Species	Score

Compound 16b





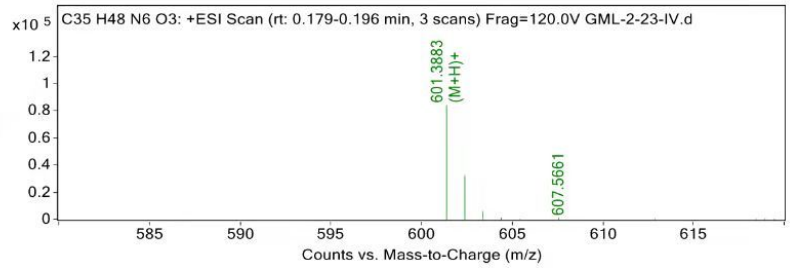
Qualitative Analysis Report

Data Filename	GML-2-23-IV.d	**Sample Name**	
Sample Type	Sample	**Position**	P1-B5
Instrument Name	Instrument 1	**User Name**	
Acq Method	MS-POS.m	**Acquired Time**	12/17/2020 9:53:36 AM (UTC+08:00)
IRM Calibration Status	Success	**DA Method**	mz-300.m
Comment			

Sample Group Info.			
Stream Name	LC 1	**Acquisition Time (Local)**	12/17/2020 9:53:36 AM (UTC+08:00)
Acquisition SW Version	6200 series TOF/6500 series Q-TOF 10.1 (48.0)	**QTOF Driver Version**	10.01.00
QTOF Firmware Version	9.808	**Tune Mass Range Max.**	3200

Spectra

Fragmentor Voltage	Collision Energy	Ionization Mode
120	0	ESI



Peak List

m/z	z	Abund	Formula	Ion
320.1718	2	8814.32		
338.3408	1	6700.1		
601.3883	1	84069.01	C35 H48 N6 O3	(M+H)+
602.3902	1	32515.74	C35 H48 N6 O3	(M+H)+
603.3918	1	6145.97	C35 H48 N6 O3	(M+H)+
620.3584	2	6496.31		
620.8624	2	4566.75		
623.3698	1	97130.84		
624.3716	1	36905.13		
625.3729	1	6794.59		

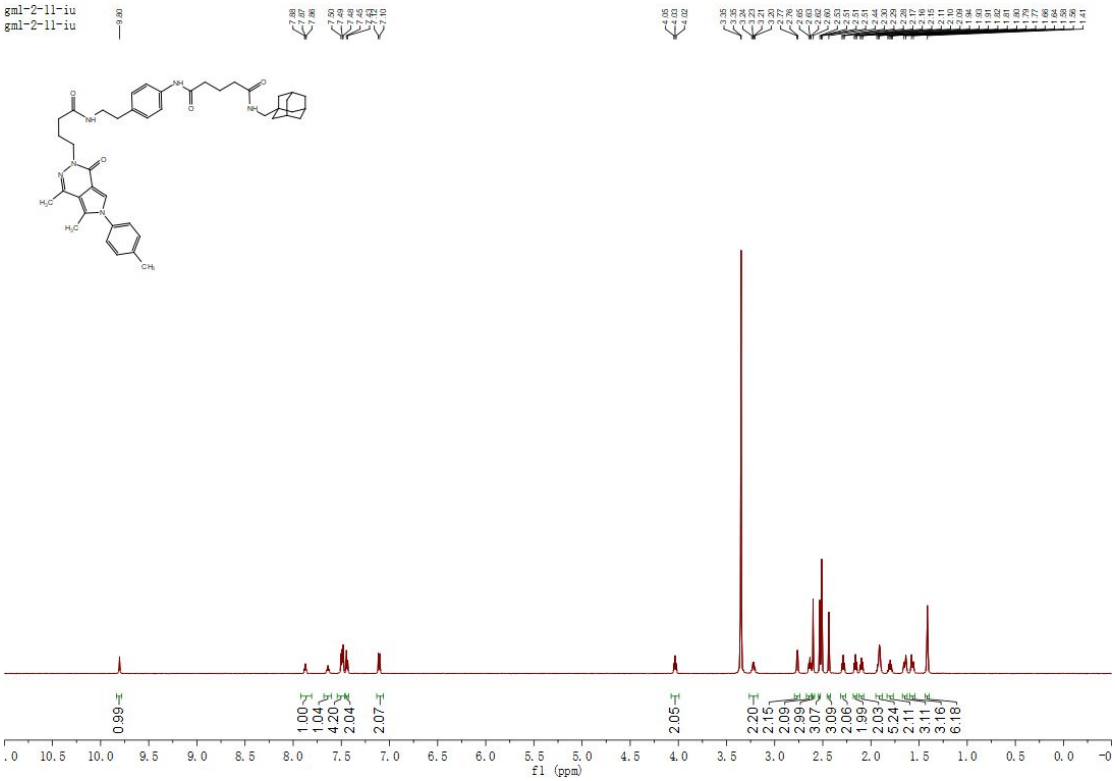
Formula Calculator Element Limits

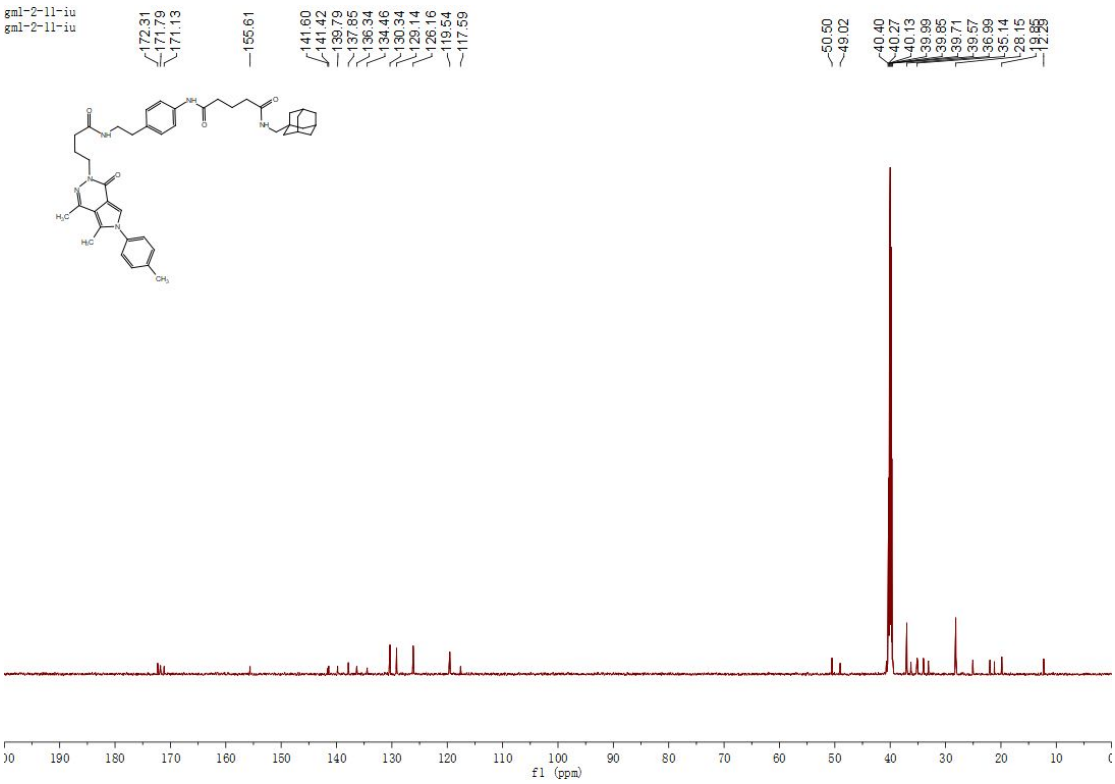
Element	Min	Max
C	3	60
H	0	120
O	0	5
N	0	6
S	0	0
Cl	0	0

Formula Calculator Results

Formula	Best	Mass	Tgt Mass	Diff (ppm)	Ion Species	Score

Compound 16c





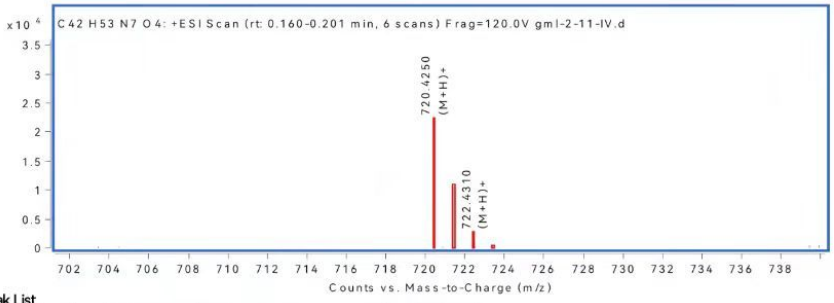
Qualitative Analysis Report

Data Filename	gml-2-11-IV.d	Sample Name	
Sample Type	Sample	Position	P1-B2
Instrument Name	Instrument 1	User Name	
Acq Method	MS-POS.m	Acquired Time	12/3/2020 11:00:41 AM (UTC+08:00)
IRM Calibration Status	Success	DA Method	mz-300.m
Comment			

Sample Group		Info.	
Stream Name	LC 1	Acquisition Time (Local)	12/3/2020 11:00:41 AM (UTC+08:00)
Acquisition SW Version	6200 series TOF/6500 series Q-TOF 10.1 (48.0)	QTOF Driver Version	10.01.00
QTOF Firmware Version	9.808	Tune Mass Range Max.	3200

Spectra

Fragmentor Voltage	Collision Energy	Ionization Mode
120	0	ESI



Peak List

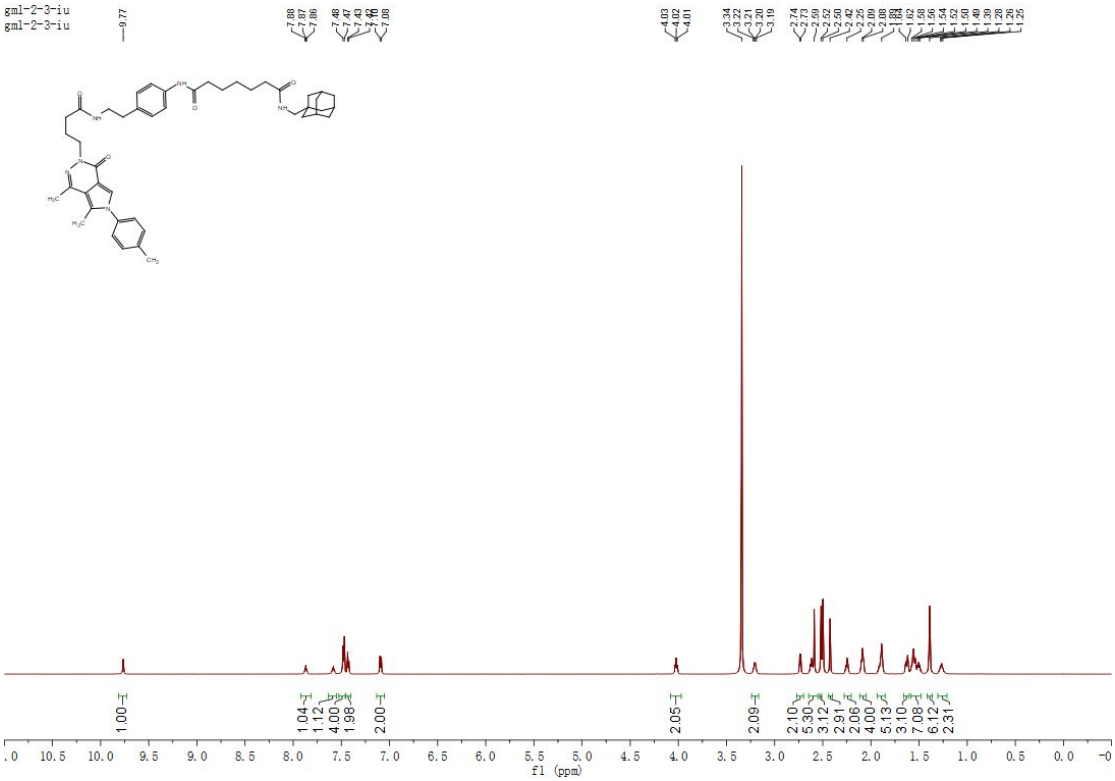
m/z	z	Abund	Formula	Ion
141.1135	1	16949.14		
338.3433	1	31014.87		
339.3463	1	7977.55		
360.7186	2	9310.55		
408.3096	1	7963.56		
437.1942	1	9573.3		
720.425	1	22425.79	C42 H53 N7 O4	(M+H)+
721.4273	1	10755.41	C42 H53 N7 O4	(M+H)+
742.4074	1	54214.5		
743.4104	1	25058.61		

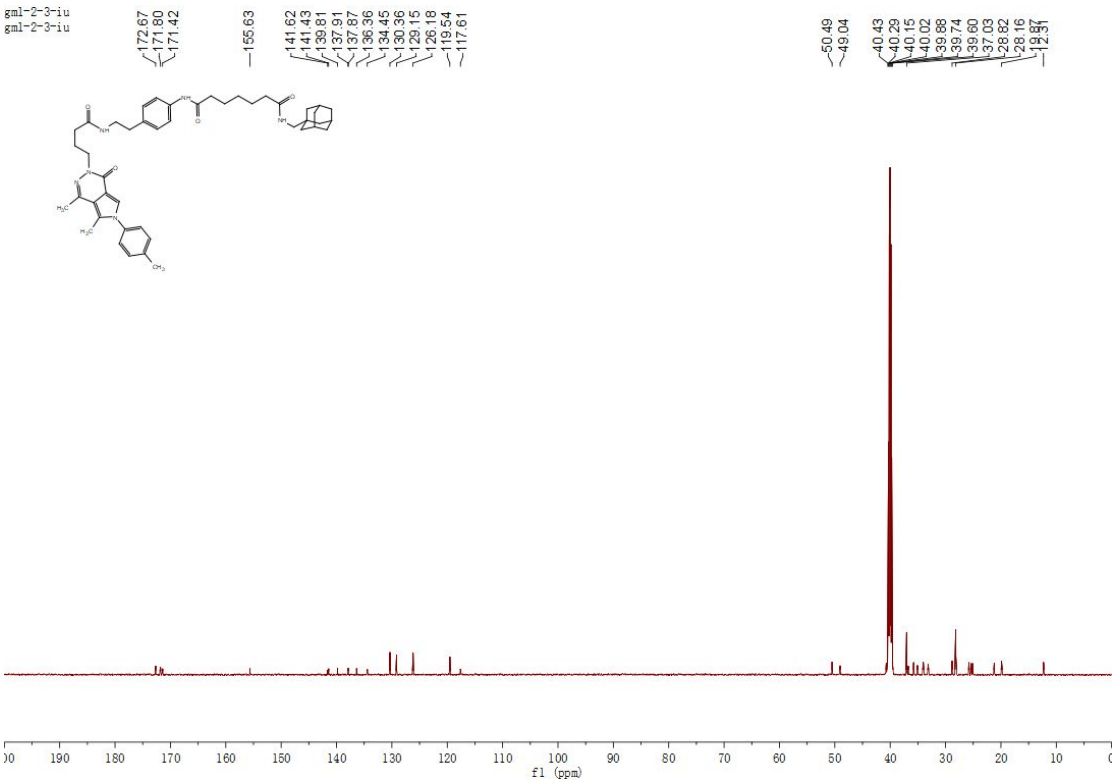
Formula Calculator Element Limits

Element	Min	Max
C	3	60
H	0	120
O	4	4
N	7	7
S	0	0
Cl	0	0

Printed at: 4:26:34 on: 2021/9/10

Compound 16d





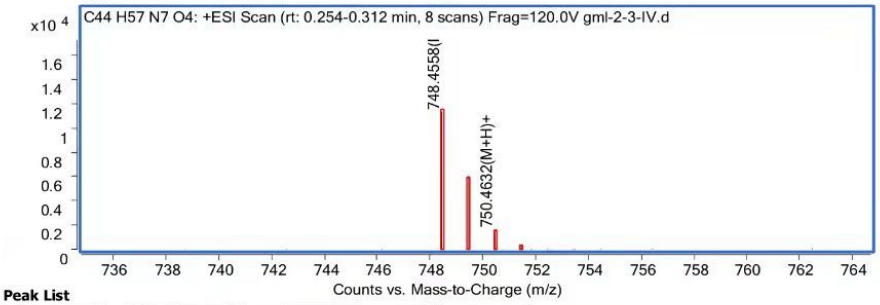
Qualitative Analysis Report

Data Filename	gml-2-3-IV.d	**Sample Name**	
Sample Type	Sample	**Position**	P1-A9
Instrument Name	Instrument 1	**User Name**	
Acq Method	MS-POS.m	**Acquired Time**	12/3/2020 10:57:18 AM (UTC+08:00)
IRM Calibration Status	Success	**DA Method**	mz-300.m
Comment			

Sample Group		**Info.**	
Stream Name	LC 1	**Acquisition Time (Local)**	12/3/2020 10:57:18 AM (UTC+08:00)
Acquisition SW Version	6200 series TOF/6500 series Q-TOF 10.1 (48.0)	**QTOF Driver Version**	10.01.00
QTOF Firmware Version	9.808	**Tune Mass Range Max.**	3200

Spectra

Fragmentor Voltage	Collision Energy	Ionization Mode
120	0	ESI



Peak List

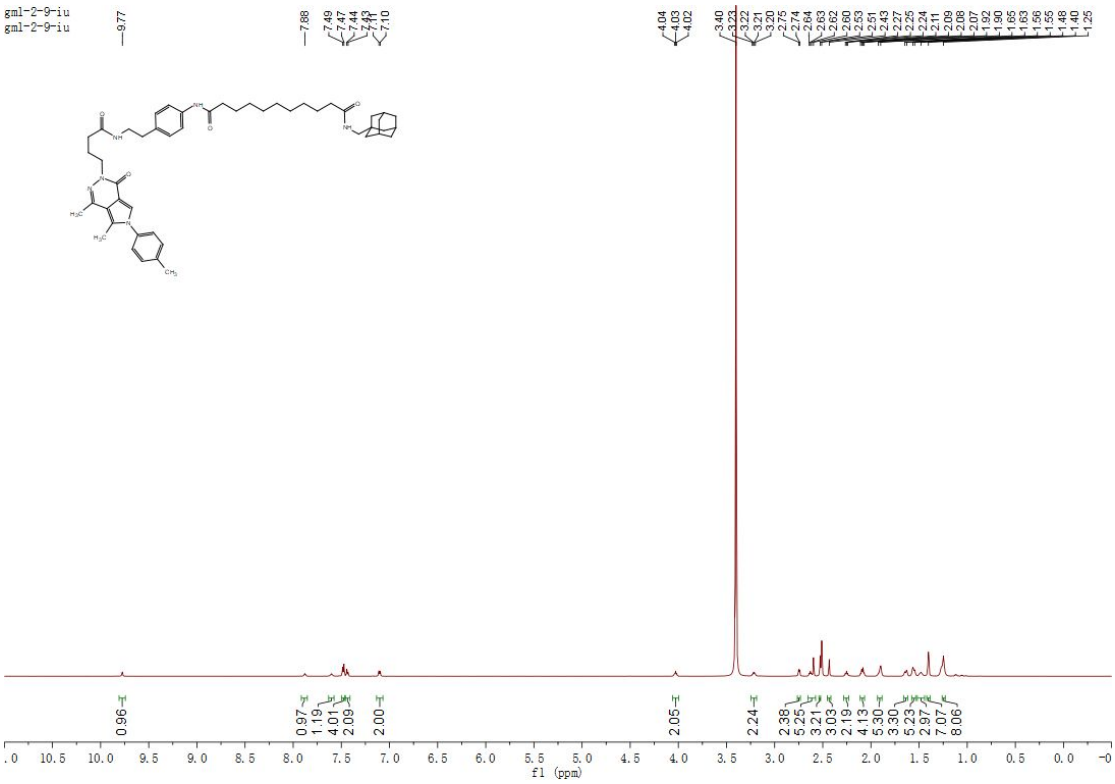
m/z	z	Abund	Formula	Ion
121.0509		5265.37		
130.1589		3874.49		
141.1136	1	23441.35		
374.7345	2	6719.99		
748.4558	1	11309.09	C44 H57 N7 O4	(M+H)+
749.46	1	6078.86	C44 H57 N7 O4	(M+H)+
770.4377	1	29860.83		
771.4408	1	14892.37		
772.443	1	3855.94		
922.0098	1	5247.64		

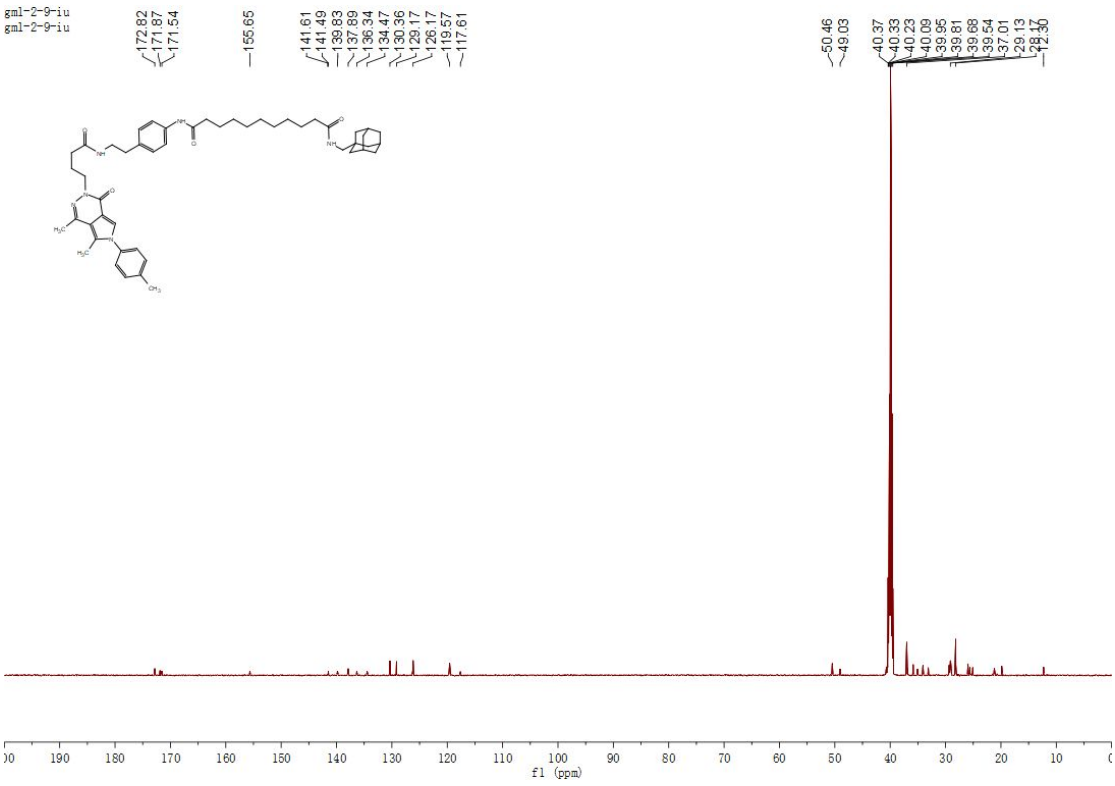
Formula Calculator Element Limits

Element	Min	Max
C	3	60
H	0	120
O	4	4
N	7	7
S	0	0

Printed at: 16:55:15 on: 2020/12/05

Compound 16e





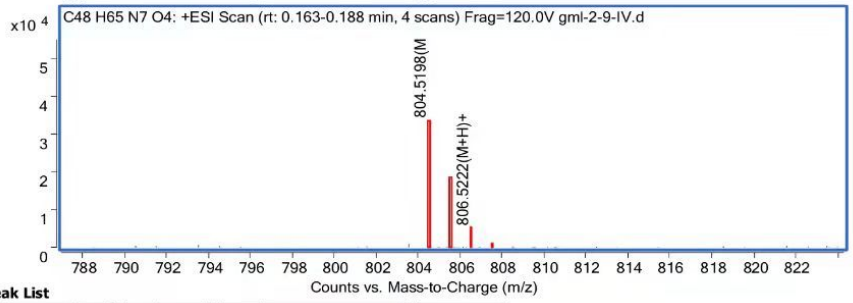
Qualitative Analysis Report

Data Filename	gml-2-9-IV.d	**Sample Name**	
Sample Type	Sample	**Position**	P1-B1
Instrument Name	Instrument 1	**User Name**	
Acq Method	MS-POS.m	**Acquired Time**	12/3/2020 10:58:59 AM (UTC+08:00)
IRM Calibration Status	Success	**DA Method**	mz-300.m
Comment			

Sample Group		**Info.**	
Stream Name	LC 1	**Acquisition Time (Local)**	12/3/2020 10:58:59 AM (UTC+08:00)
Acquisition SW Version	6200 series TOF/6500 series Q-TOF 10.1 (48.0)	**QTOF Driver Version**	10.01.00
QTOF Firmware Version	9.808	**Tune Mass Range Max.**	3200

Spectra

Fragmentor Voltage	Collision Energy	Ionization Mode
120	0	ESI



Peak List

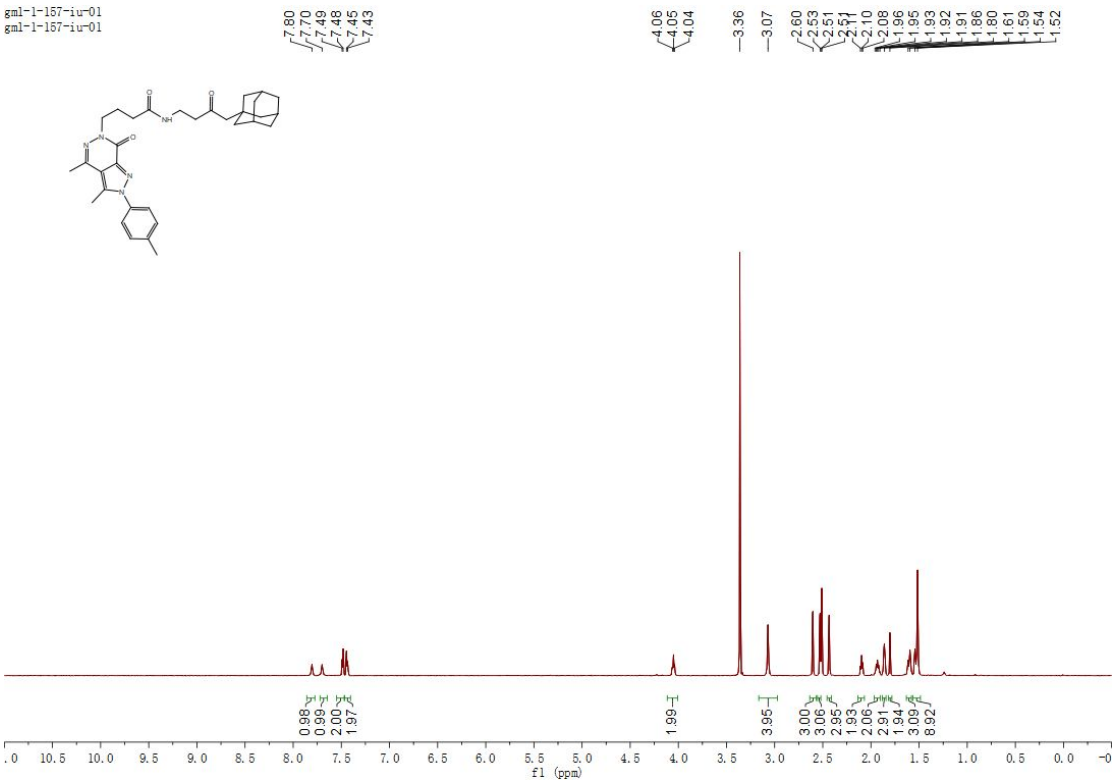
m/z	z	Abund	Formula	Ion
141.114	1	16748.61		
402.7649	2	15467.37		
433.3804	1	18285.81		
447.396	1	17517.19		
580.4607	1	17402.95		
804.5198	1	33636.29	C48 H65 N7 O4	(M+H)+
805.5205	1	18349.43	C48 H65 N7 O4	(M+H)+
826.5008	1	84612.23		
827.5037	1	44429.85		
828.5035	1	12282.5		

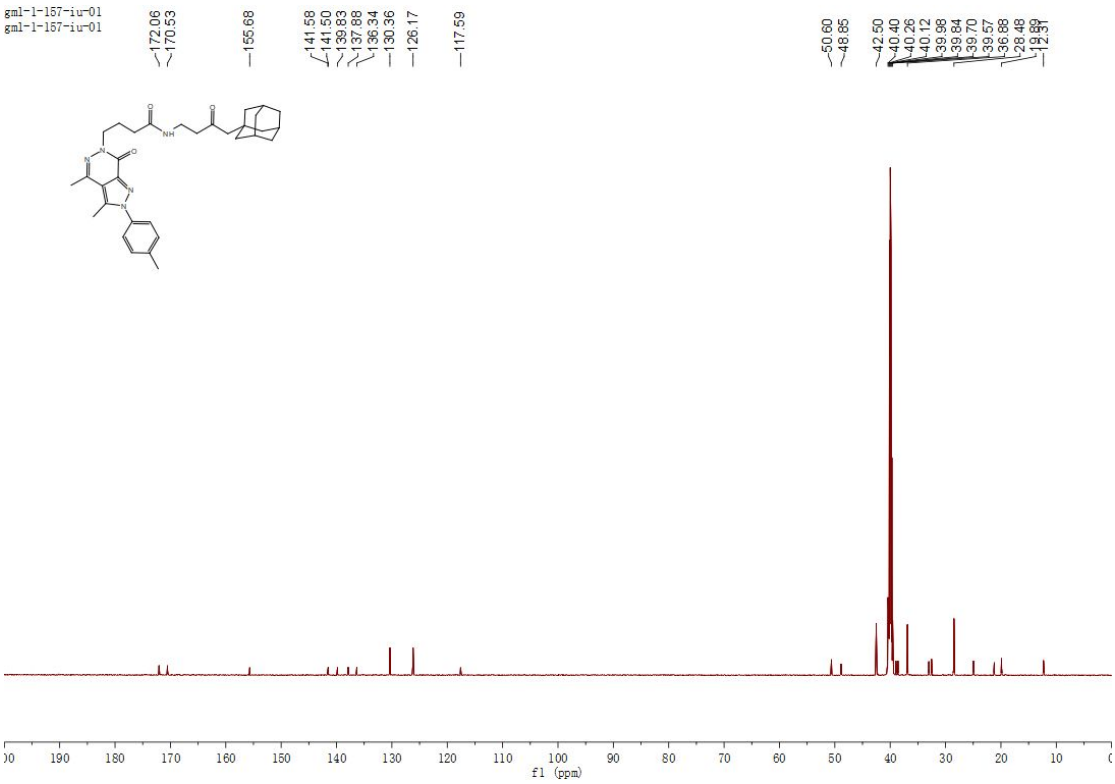
Formula Calculator Element Limits

Element	Min	Max
C	3	60
H	0	120
O	4	4
N	7	7
S	0	0

Printed at: 16:55:32 on: 2020/12/05

Compound 17a





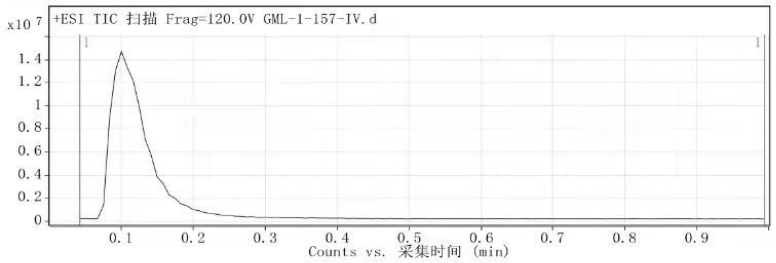
定性分析报告

数据文件名称	GML-1-157-IV.d	**样品名称**	
样品类型	Sample	**位置**	P1-A9
仪器名称	Instrument 1	**用户名**	
采集方法	MS-POS.m	**采集时间**	2020/9/21 10:00:17
IRM 校正状态	成功	**DA 方法**	Default.m
注释			

设备类型	QuadrupoleTimeOfFlight	**Sample Group**	
Info.		**Stream Name**	LC 1
Acquisition SW Version	6200 series TOF/6500 series Q-TOF 10.1 (48.0)		

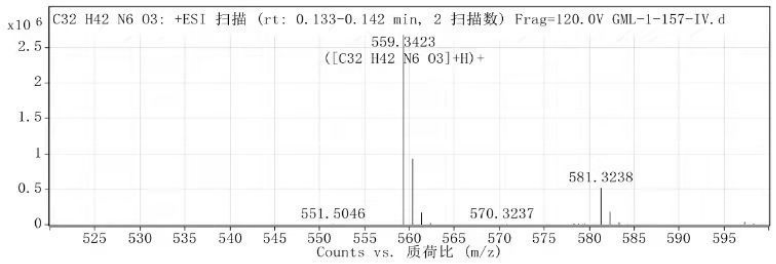
用户色谱图

裂解电压 120 **碰撞能量** 0 **电离模式** ESI



用户质谱图

裂解电压 120 **碰撞能量** 0 **电离模式** ESI



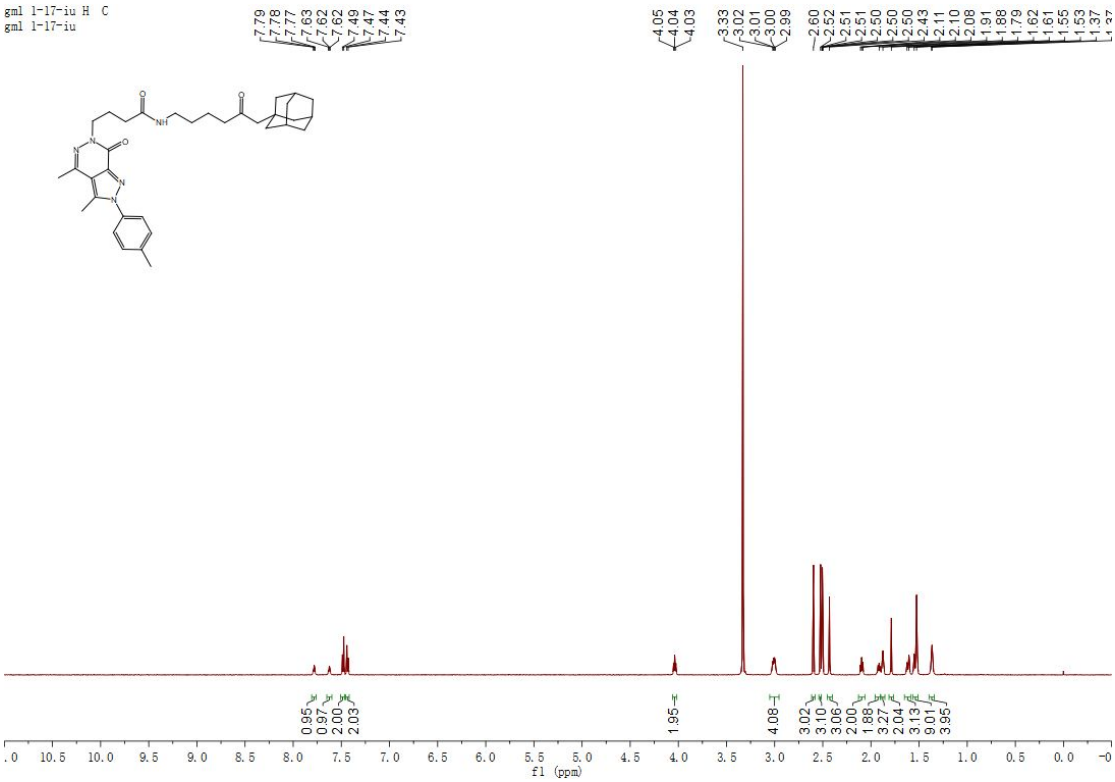
峰列表

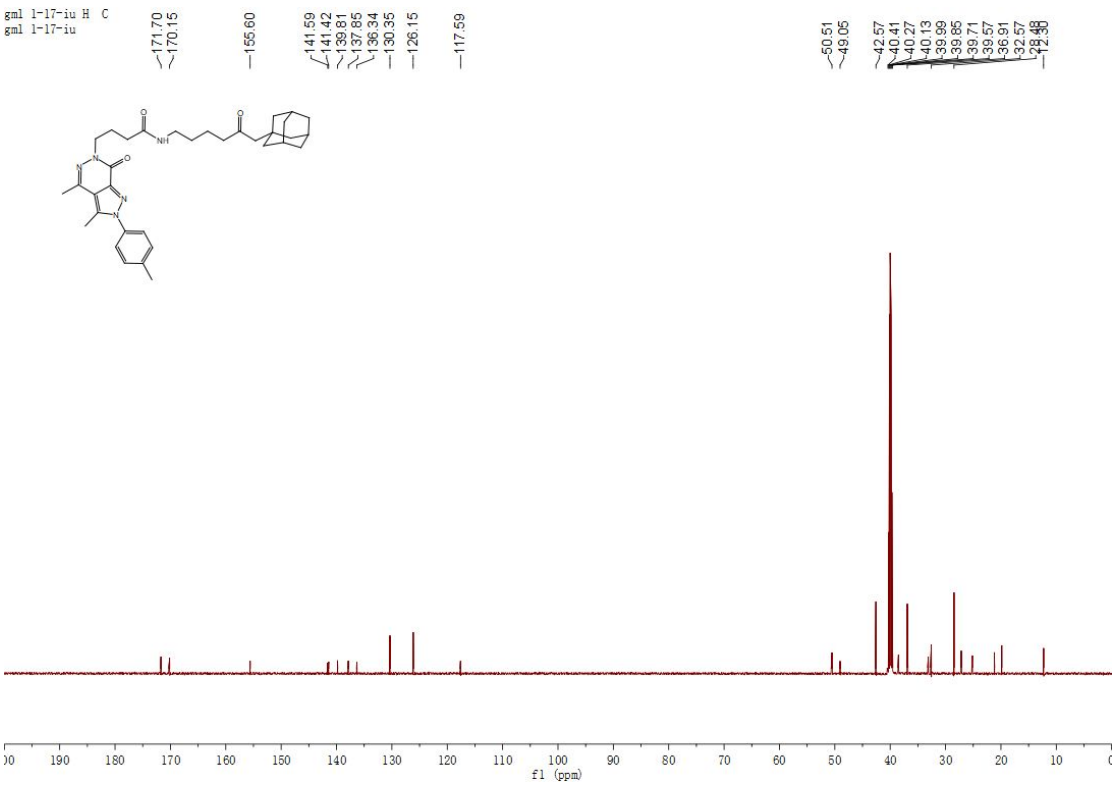
m/z	z	丰度	分子式	离子
338.3426	1	100284.5		
559.3423	1	2678648	C32 H42 N6 O3	(M+H)+
560.3451	1	931370.63	C32 H42 N6 O3	(M+H)+
561.3481	1	172290.69	C32 H42 N6 O3	(M+H)+
581.3238	1	518739.31		
582.3276	1	182687.94		
597.2967	1	41374.18		
1139.6584	1	304473.22		
1140.6612	1	226944.97		
1141.6626	1	82426.88		

分子式计算器元素限制

元素	最小	最大
C	3	60

Compound 17b





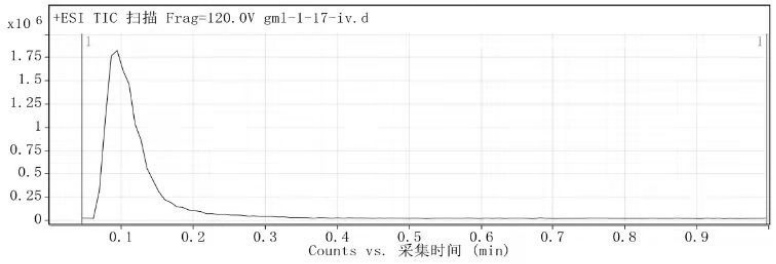
定性分析报告

数据文件名称	gml-1-17-iv.d	**样品名称**	
样品类型	Sample	**位置**	P1-B5
仪器名称	Instrument 1	**用户名**	
采集方法	MS-POS.m	**采集时间**	2021/9/16 11:14:24
IRM 校正状态	成功	**DA 方法**	Default.m
注释			

设备类型	QuadrupoleTimeOfFlight	**Sample Group**	
Info.		**Stream Name**	LC 1
Acquisition SW Version	6200 series TOF/6500 series Q-TOF 10.1 (48.0)		

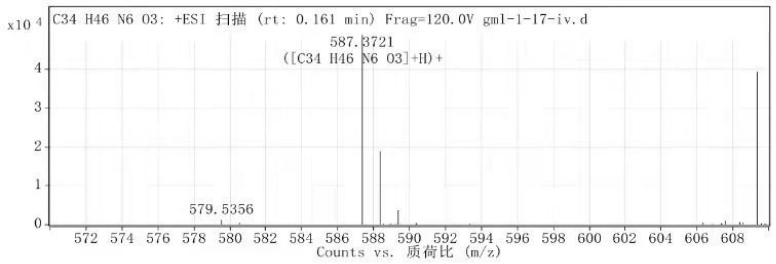
用户色谱图

裂解电压 120 **碰撞能量** 0 **电离模式** ESI



用户质谱图

裂解电压 120 **碰撞能量** 0 **电离模式** ESI



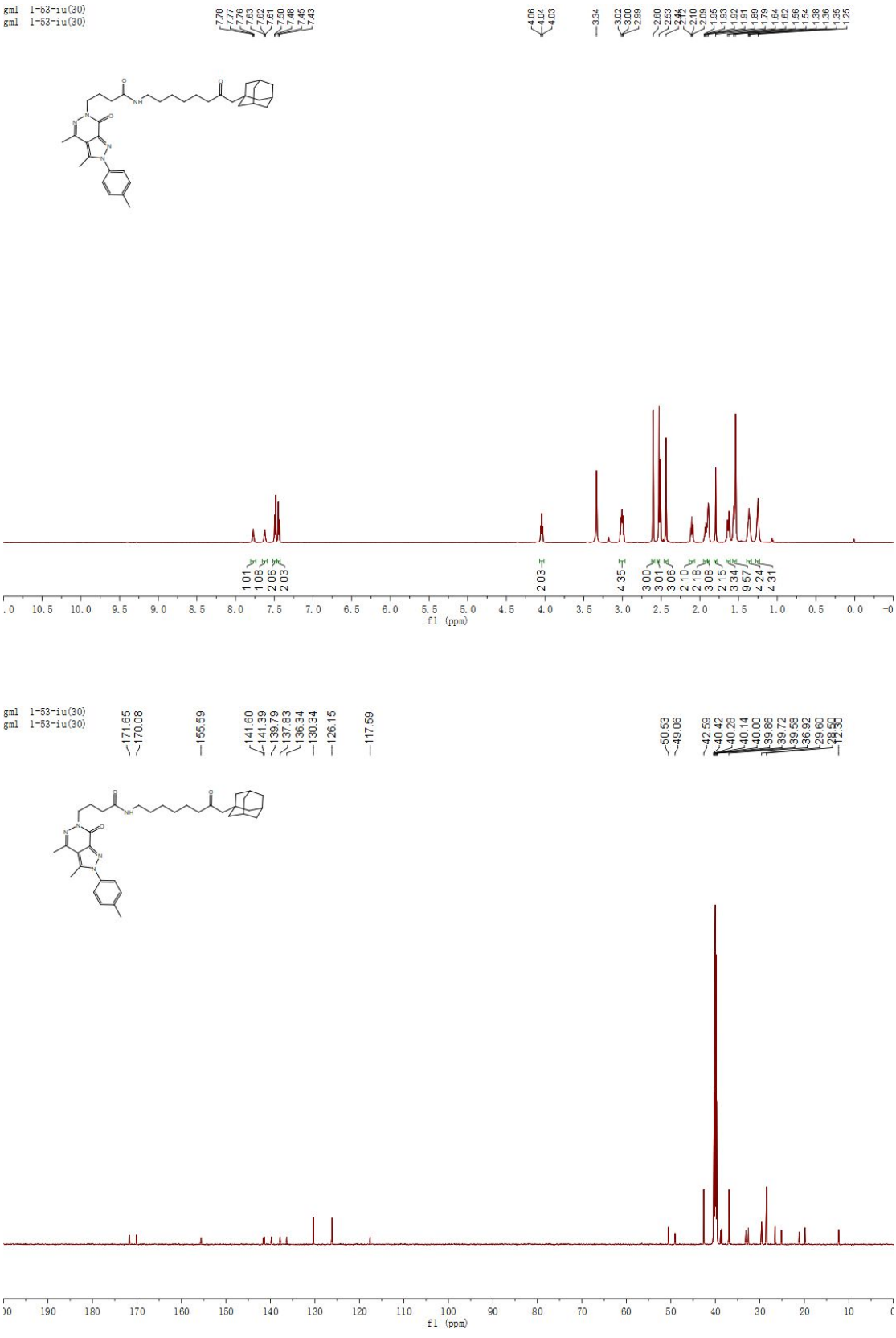
峰列表

m/z	z	丰度	分子式	离子
274.276		1793.96		
294.1954	2	1893.47		
338.3439	1	5006.17		
587.3721	1	48861.73	C34 H46 N6 O3	(M+H)+
588.3748	1	18955.71	C34 H46 N6 O3	(M+H)+
589.3764	1	3779.68	C34 H46 N6 O3	(M+H)+
609.3533	1	39430.03		
610.3542	1	14201.76		
611.3582	1	3183.04		
922.0098	1	3276.77		

分子式计算器元素限制

元素	最小	最大
C	3	34

Compound 17c



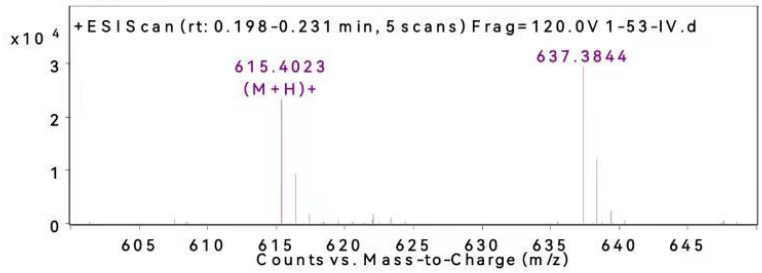
Qualitative Analysis Report

Data Filename	1-53-IV.d	Sample Name	
Sample Type	Sample	Position	P1-A3
Instrument Name	Instrument 1	User Name	
Acq Method	MS-POS.m	Acquired Time	7/28/2020 1:09:30 PM
IRM Calibration Status	Success	DA Method	MZ-500.m
Comment			
Sample Group		Info.	
Stream Name	LC 1	Acquisition SW Version	6200 series TOF/6500 series Q-TOF B.06.01 (B6157)

Data Filename	1-53-IV-N.d	Sample Name	
Sample Type	Sample	Position	P1-A3
Instrument Name	Instrument 1	User Name	
Acq Method	MS-NEG.m	Acquired Time	7/28/2020 1:38:42 PM
IRM Calibration Status	Success	DA Method	MZ-500.m
Comment			
Sample Group		Info.	
Stream Name	LC 1	Acquisition SW Version	6200 series TOF/6500 series Q-TOF B.06.01 (B6157)

User Spectra

Fragmentor Voltage	Collision Energy	Ionization Mode
120	0	ESI



Peak List

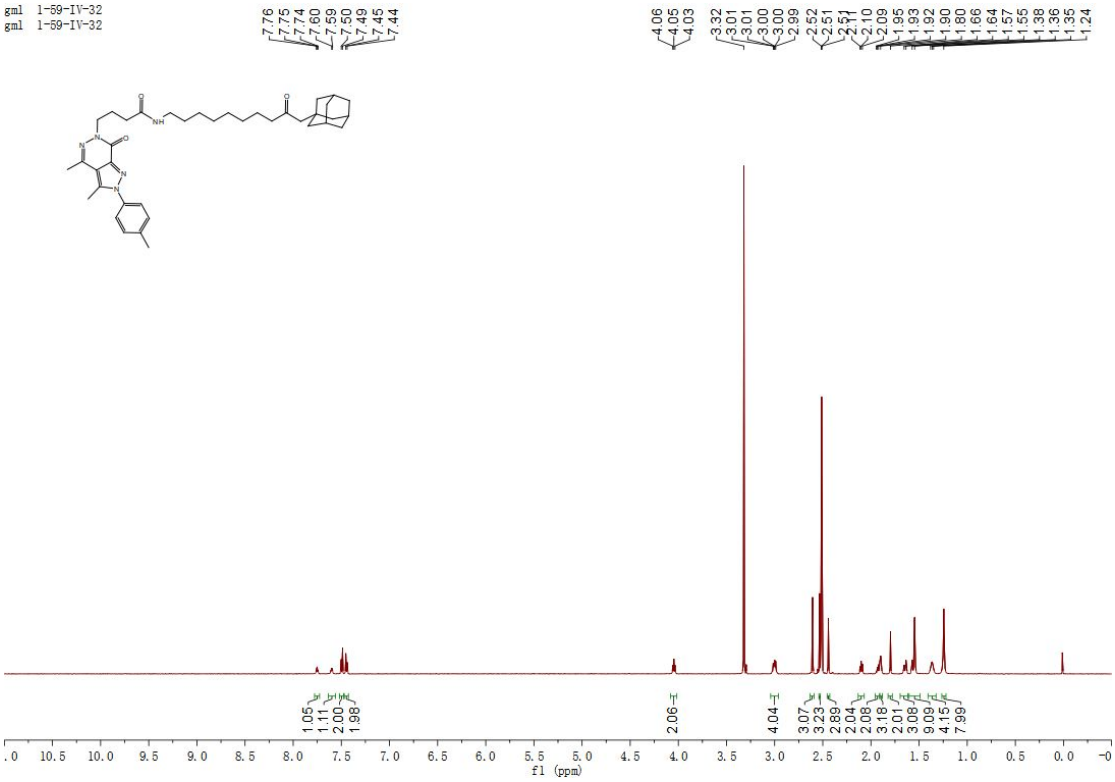
m/z	z	Abund	Formula	Ion
121.052		10522.01		
130.1606		16921.51		
141.1031		16574.65		
141.1163		31637.17		
410.111	1	37221.41		
412.1082	1	25790.39		
615.4023	1	23249.92	C36 H50 N6 O3	(M+H)+
637.3844	1	29390.03		
638.3866	1	12126.36		
922.0097		16723.47		

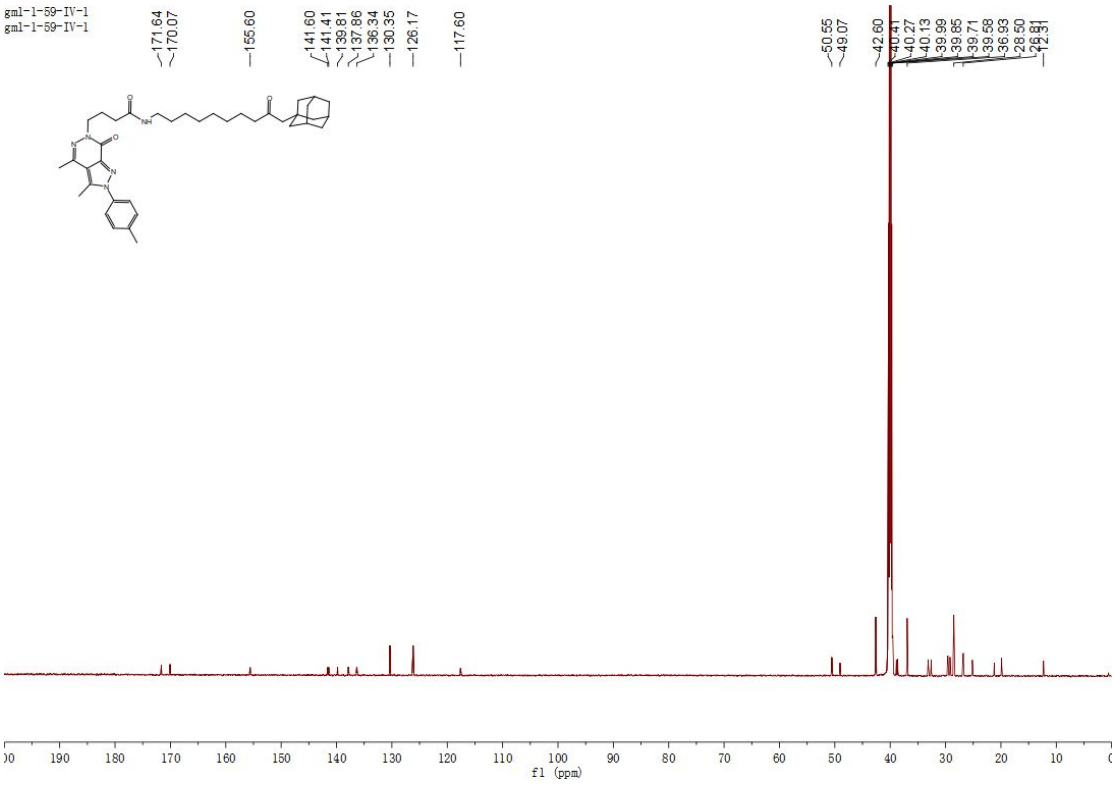
Formula Calculator Element Limits

Element	Min	Max

Printed at: 10:49:38 on: 2021/9/11

Compound 17d





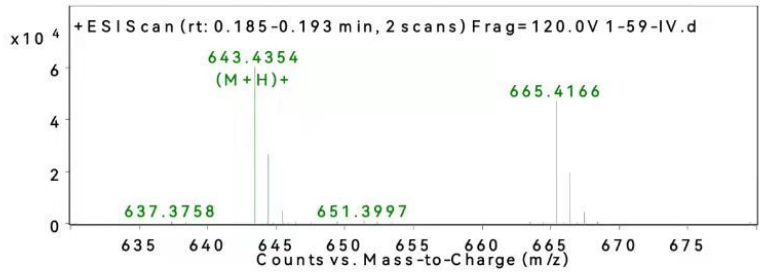
Qualitative Analysis Report

Data Filename	1-59-IV.d	Sample Name	
Sample Type	Sample	Position	P1-A4
Instrument Name	Instrument 1	User Name	
Acq Method	MS-POS.m	Acquired Time	7/28/2020 1:11:11 PM
IRM Calibration Status	Success	DA Method	MZ-500.m
Comment			
Sample Group		Info.	
Stream Name	LC 1	Acquisition SW Version	6200 series TOF/6500 series Q-TOF B.06.01 (B6157)

Data Filename	1-59-IV-N.d	Sample Name	
Sample Type	Sample	Position	P1-A4
Instrument Name	Instrument 1	User Name	
Acq Method	MS-NEG.m	Acquired Time	7/28/2020 1:40:23 PM
IRM Calibration Status	Success	DA Method	MZ-500.m
Comment			
Sample Group		Info.	
Stream Name	LC 1	Acquisition SW Version	6200 series TOF/6500 series Q-TOF B.06.01 (B6157)

User Spectra

Fragmentor Voltage	Collision Energy	Ionization Mode
120	0	ESI



Peak List

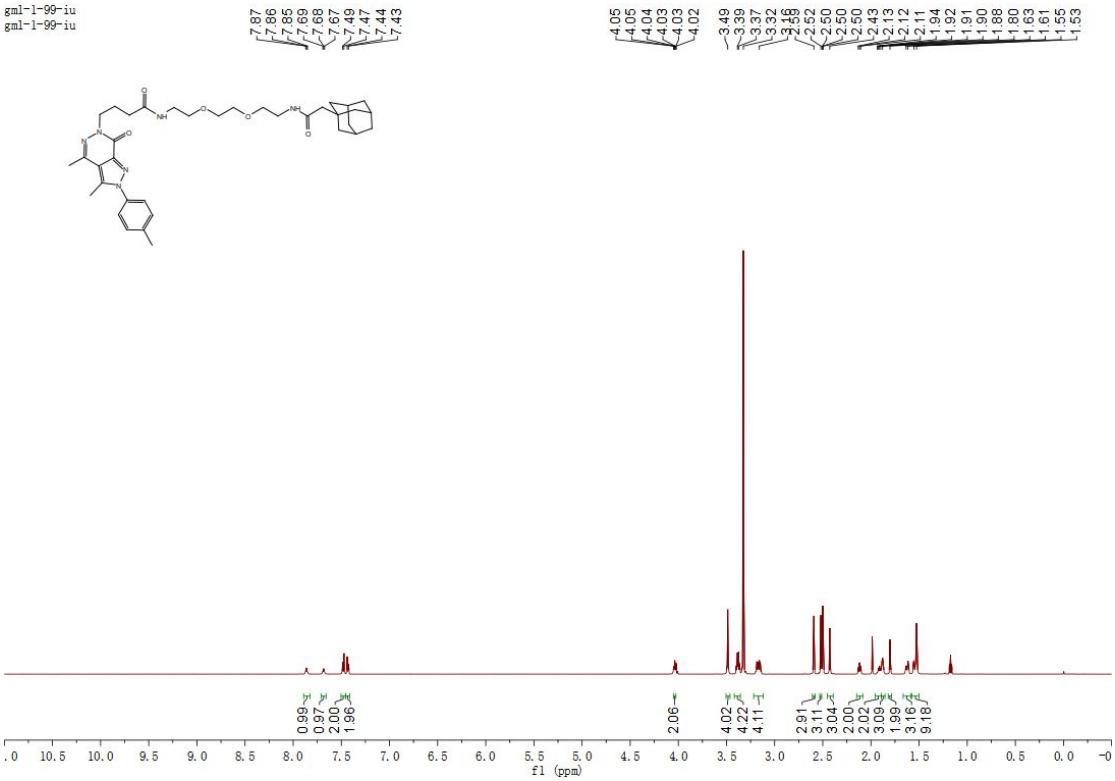
m/z	z	Abund	Formula	Ion
121.0551		9229.91		
130.1591	1	13458.72		
141.1137	1	31990.68		
410.1114	1	22654.98		
412.1085	1	16046.29		
643.4354	1	60309.74	C38 H54 N6 O3	(M+H)+
644.4365	1	26819.41	C38 H54 N6 O3	(M+H)+
665.4166	1	47190.78		
666.419	1	19572.62		
922.0098	1	12972.92		

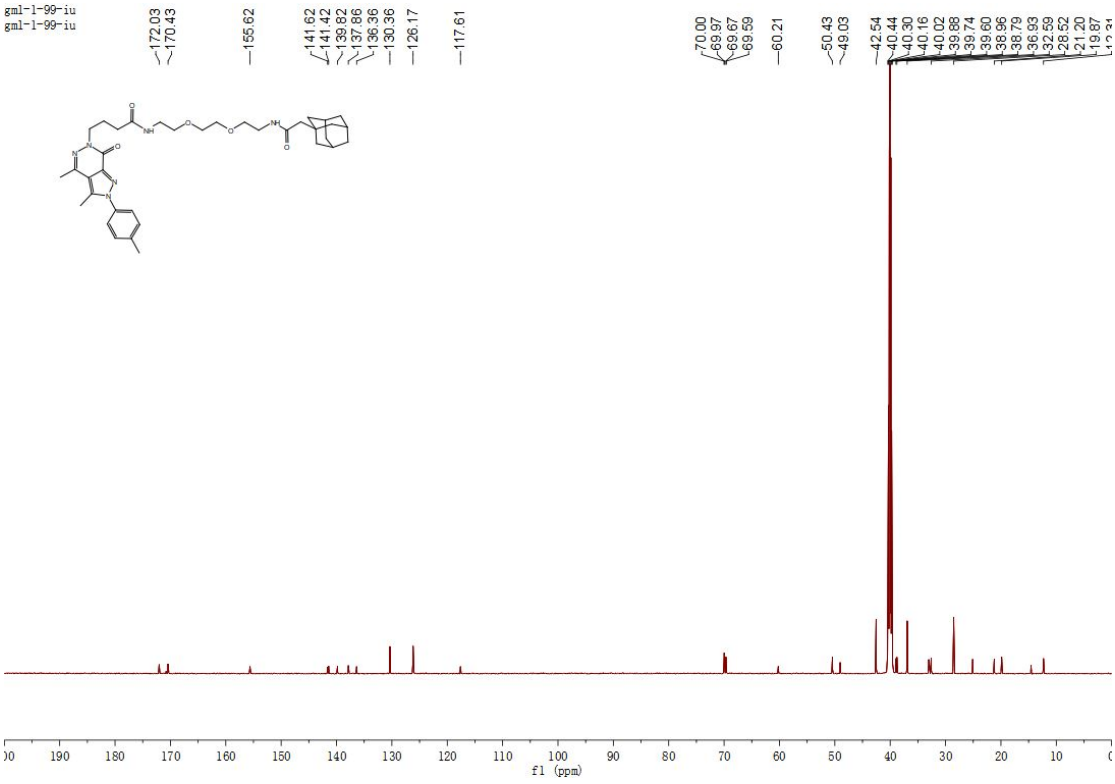
Formula Calculator Element Limits

Element	Min	Max

Printed at: 10:51:39 on: 2021/9/11

Compound 17e





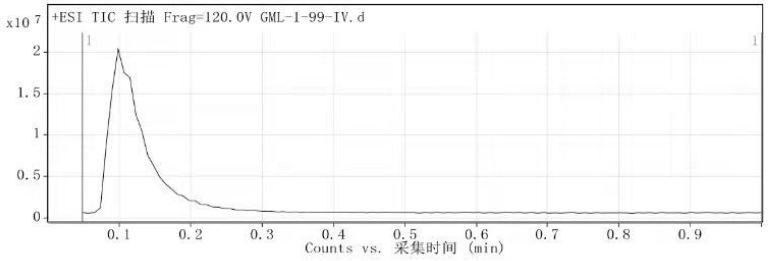
定性分析报告

数据文件名称	GML-1-99-IV.d	**样品名称**	
样品类型	Sample	**位置**	P1-B3
仪器名称	Instrument 1	**用户名**	
采集方法	MS-POS.m	**采集时间**	2020/9/2 10:10:36
IRM 校正状态	成功	**DA 方法**	Default.m
注释			

设备类型	QuadrupoleTimeOfFlight	**Sample Group Info.**	
		Stream Name	LC 1
Acquisition SW Version	6200 series TOF/6500 series Q-TOF 10.1 (48.0)		

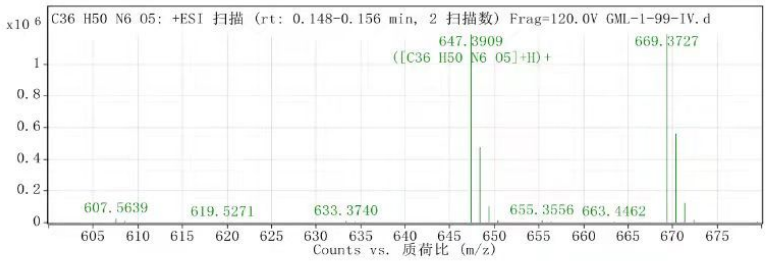
用户色谱图

裂解电压 120 **碰撞能量** 0 **电离模式** ESI



用户质谱图

裂解电压	碰撞能量	电离模式
120	0	ESI



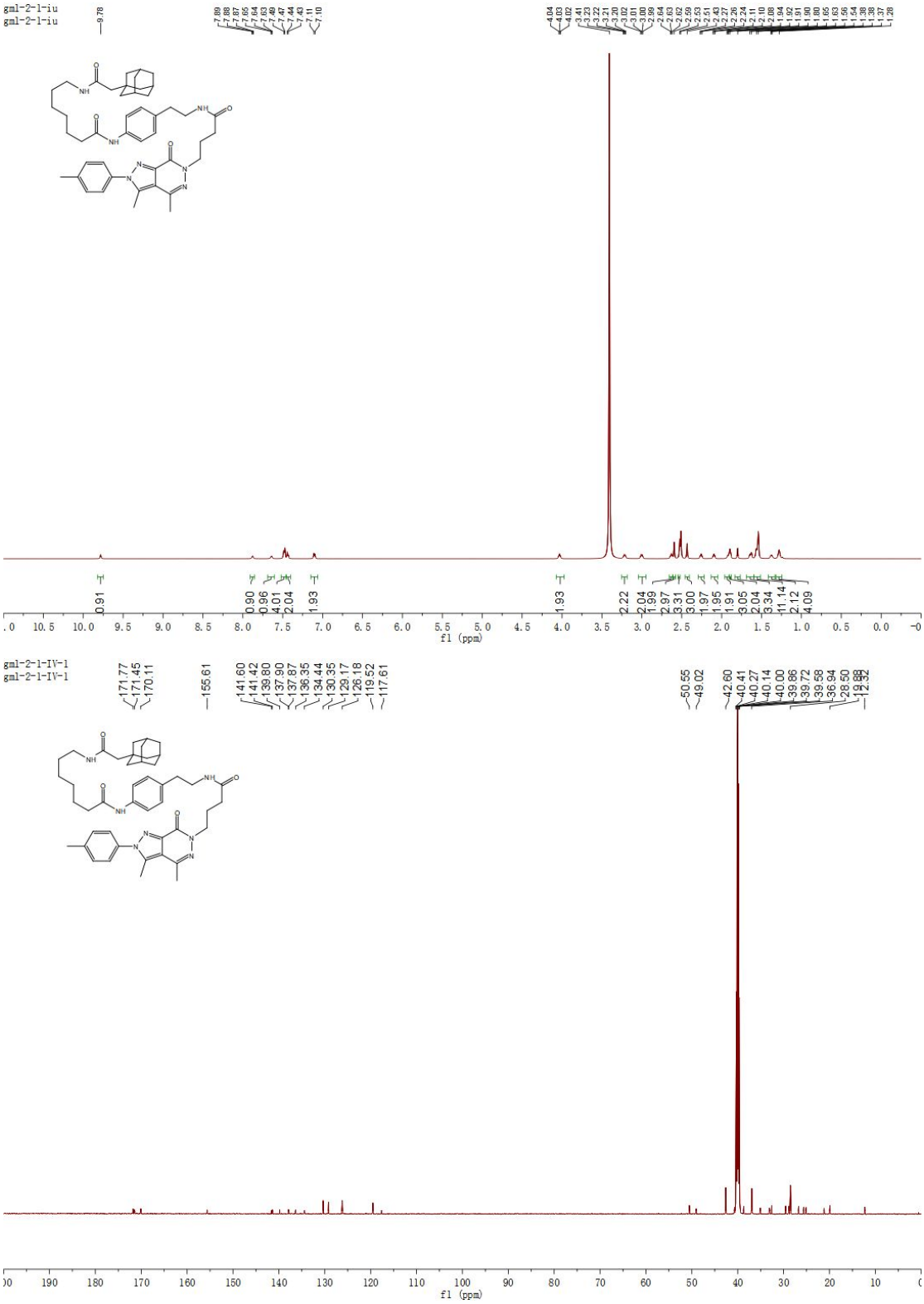
峰列表

m/z	z	丰度	分子式	离子
130.1581	1	105812.92		
324.1991	2	33817.92		
579.5335	1	34547.67		
607.5639	1	26849.52		
647.3909	1	1186818.63	C36 H50 N6 O5	(M+H)+
648.3936	1	476818.38	C36 H50 N6 O5	(M+H)+
649.3968	1	104044.53	C36 H50 N6 O5	(M+H)+
669.3727	1	1443115		
670.376	1	561308.5		
671.379	1	126028.61		

分子式计算器元素限制

元素	最小	最大
C	3	60

Compound 17f



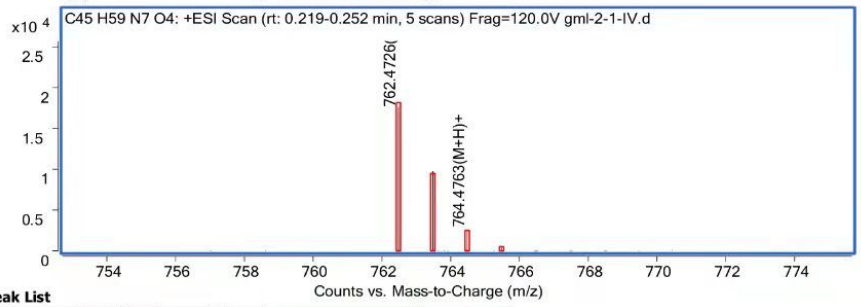
Qualitative Analysis Report

Data Filename	gml-2-1-IV.d	**Sample Name**	
Sample Type	Sample	**Position**	P1-A8
Instrument Name	Instrument 1	**User Name**	
Acq Method	MS-POS.m	**Acquired Time**	12/3/2020 10:55:37 AM (UTC+08:00)
IRM Calibration Status	Success	**DA Method**	mz-300.m
Comment			

Sample Group		**Info.**	
Stream Name	LC 1	**Acquisition Time (Local)**	12/3/2020 10:55:37 AM (UTC+08:00)
Acquisition SW Version	6200 series TOF/6500 series Q-TOF 10.1 (48.0)	**QTOF Driver Version**	10.01.00
QTOF Firmware Version	9.808	**Tune Mass Range Max.**	3200

Spectra

Fragmentor Voltage	Collision Energy	Ionization Mode
120	0	ESI



Peak List

m/z	z	Abund	Formula	Ion
121.0509		5222.86		
141.1133	1	23221.11		
381.7412	2	8335.76		
382.2434	2	4409.66		
762.4726	1	17656.51	C45 H59 N7 O4	(M+H)+
763.476	1	9824.15	C45 H59 N7 O4	(M+H)+
784.4556	1	50156.51		
785.458	1	25850.09		
786.4593	1	6388.18		
922.0098	1	6228.22		

Formula Calculator Element Limits

Element	Min	Max
C	3	60
H	0	120
O	4	4
N	7	7
S	0	0

Printed at: 16:49:47 on: 2020/12/05

Reference:

1. Cheng, J.; Li, Y.; Wang, X.; Dong, G.; Sheng, C. Discovery of novel pded degraders for the treatment of kras mutant colorectal cancer. *J. Med. Chem.* **2020**, 63, 7892-7905.