



SUPPLEMENTARY MATERIAL TO
**Design of novel quinazoline–chalcone hybrids as potent
epidermal growth factor receptor inhibitors**

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Table S-I The influence of the dropping time and temperature of POCl₃ on the yield of intermediate **2**.

No.	Temperature during POCl ₃ addition	Reaction Time (h)	Yield
1	60°C	3	71%
2	60°C	2	65%
3	60°C	1.5	60%
4	70°C	1.5	85%
5	70°C	2	95%
6	70°C	3	89%
7	80°C	2	71%
8	80°C	3	69%

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Table S-II The influence of different reaction time on the yield of intermediates **3a-3d**.

No.	Synthesized Intermediate	Reaction Time (h)	Yield
1	3a	4	68%
2		5	92%
3		6	75%
4	3b	4	63%
5		5	94%
6		6	72%
7	3c	4	68%
8		5	91%
9		6	75%
10	3d	4	65%
11		5	90%
12		6	71%

Table S-III The influence of different alkaline environment on the yield of intermediates **7a-7c**.

No.	Synthesized Intermediate	Basic Conditions	Yield
1	7a	Sodium carbonate	37%
2		Triethylamine	52%
3		Sodium hydroxide	93%
4	7b	Sodium carbonate	32%
5		Triethylamine	49%
6		Sodium hydroxide	92%
10	7c	Triethylamine	34%
11		Sodium carbonate	51%
12		Sodium hydroxide	91%

Table S-IV The influence of different molar ratio on the yield of intermediates **8a-8c**.

No.	Synthesized Intermediate	7a-7c: Chloroacetyl Chloride (molar ratio)	Yield
1	8a	1.0:2.0	41%
2		1.0:2.5	60%
3		1.0:3.0	54%
4	8b	1.0:2.0	40%
5		1.0:2.5	62%
6		1.0:3.0	52%
10	8c	1.0:2.0	35%
11		1.0:2.5	56%
12		1.0:3.0	49%

Table S-V The influence of different reaction time on the yield of intermediates **8a-8c**.

No.	Synthesized Intermediate	Addition Temperature (°C)	Yield
1	8a	10	45%
2		0	60%
3		-10	50%
4	8b	10	47%

5		0	62%
6		-10	50%
10		10	42%
11	8c	0	56%
12		-10	43%

Table S-VI The influence of different reaction temperature on the yield of target compounds **9a-9d**.

No.	Target Compound	Reaction Temperature (°C)	Yield
1		60	26%
2	9a	80	40%
3		100	27%
4		60	29%
5	9b	80	41%
6		100	29%
7		60	25%
8	9c	80	44%
9		100	27%
10		60	24%
11	9d	80	46%
12		100	25%

Table S-VII The influence of different alkaline environment on the yield of target compounds **9a-9d**.

No.	Target Compound	Basic Conditions	Yield
1		Sodium hydroxide	21%
2	9a	Potassium carbonate	40%
3		Sodium hydroxide	22%
4	9b	Potassium carbonate	41%
5		Sodium hydroxide	22%
6	9c	Potassium carbonate	44%
7		Sodium hydroxide	22%
8	9d	Potassium carbonate	46%

7-Methoxy-4-(phenylamino)quinazolin-6-yl acetate(3a).

Yield 92%, white solid, m. p. 103.4 - 105.6°C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.64 (s, 1H), 8.86 (d, *J* = 8.9 Hz, 2H), 7.74 (d, *J* = 7.8 Hz, 2H), 7.59 (s, 1H), 7.48 (t, *J* = 7.5 Hz, 2H), 7.34 (t, *J* = 7.3 Hz, 1H), 4.01 (s, 3H), 2.39 (s, 3H); IR (KBr), ν, cm⁻¹: 3256.35 (N-H), 2753.22 (CH₃), 1630.36 (C=O), 1563.35 (C=C_{Ar}), 1426.28 (C=N), 1218.82 (C-O-C).

7-Methoxy-4-[(4-methylphenyl)amino]quinazolin-6-yl acetate(3b).

Yield 94%, light-yellow solid, m. p. 112.1 - 114.5°C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.62 (s, 1H), 8.87 (d, *J* = 3.8 Hz, 2H), 7.58 (d, *J* = 1.5 Hz, 2H), 7.58 (s, 1H), 7.29 (d, *J* = 7.8 Hz, 2H), 4.00 (s, 3H), 2.38 (s, 3H), 2.35 (s, 3H); IR (KBr), ν, cm⁻¹: 3255.32 (N-H), 2753.03 (CH₃), 1642 (C=O), 1509 (C=C_{Ar}), 1397 (C-N), 1247 (C-O-C).

7-Methoxy-4-[(4-methoxyphenyl)amino]quinazolin-6-yl acetate(3c).

Yield 91%, white solid, m. p. 101.2 - 105.4°C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.66 (s, 1H), 8.90 (s, 1H), 8.86 (s, 1H), 7.60 (dd, *J* = 6.6, 2.3 Hz, 3H), 7.06-7.01 (m, 2H), 3.99 (s, 3H), 3.80 (s, 3H), 2.38 (s, 3H); IR (KBr), ν, cm⁻¹: 3223.05(N-H), 2838.37(CH₃), 1670.79 (C=O), 1625.71 (C=C_{Ar}), 1465.55 (C=N), 1327.88 (C-N), 1252.17 (C-O-C).

4-[(4-Chloro-2-methylphenyl)amino]-7-methoxyquinazolin-6-yl acetate(3d).

Yield 90%, white solid, m. p. 113.3 - 115.7°C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.20 (s, 1H), 8.83 (s, 1H), 8.56 (s, 1H), 7.63 (d, *J* = 6.0, 2H), 7.12-7.01 (m, 2H), 3.82 (s, 3H), 2.35 (s, 3H); IR (KBr), ν, cm⁻¹: 3266.25 (N-H), 2865.31 (CH₃), 1625.38 (C=O), 1568.51 (C=C_{Ar}), 1488.51 (C-C), 1331.57 (C-N), 1272.81 (C-O-C), 775.62 (C-Cl).

4-[(2-Fluorophenyl)amino]-7-methoxyquinazolin-6-yl acetate(3e).

Yield 89%, light-yellow solid, m. p. 109.1 - 111.3°C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.31 (s, 1H), 8.90 (s, 1H), 8.74 (d, *J* = 5.2 Hz, 1H), 7.58 (s, 1H), 7.56-7.51 (m, 1H), 7.52-7.43 (m, 1H), 7.48-7.40 (m, 1H), 7.39-7.30 (m, 1H), 4.02 (s, 3H), 2.40 (s, 3H); IR (KBr), ν, cm⁻¹: 3245.21 (N-H), 2945.98 (CH₃), 1627.89 (C=O), 1532.22 (C=N), 1458.88 (C=C_{Ar}), 1371.45 (C-N), 1203.77 (C-O-C), 993.71 (C-F).

4-[(3-Chloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl acetate(3f).

Yield 89%, white solid, m. p. 112.1 - 114.9°C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.71 (s, 1H), 8.85 (s, 1H), 8.58 (s, 1H), 7.57 (s, 1H), 7.48 (s, 1H), 7.39 (s, 1H), 7.28-7.06 (m, 1H), 3.83 (s, 3H), 2.27 (s, 3H); IR (KBr), ν, cm⁻¹: 3261.76 (N-H), 2821.38 (CH₃), 1661.80 (C=O), 1458.28 (C=C_{Ar}), 1318.90 (C-N), 1291.04 (C-O-C), 1148.39 (C-F), 728.29 (C-Cl).

4-[(2,4-Dimethylphenyl)amino]-7-methoxyquinazolin-6-yl acetate(3g).

Yield 83%, light-yellow solid, m. p. 105.2-108.7°C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.73 (s, 1H), 8.90 (s, 1H), 8.77 (s, 1H), 7.64 (s, 1H), 7.22-7.15 (m, 2H), 7.08 (d, *J* = 7.2 Hz, 1H), 4.00 (s, 3H), 2.38 (s, 3H), 2.33 (s, 3H), 2.17 (s, 3H); IR (KBr), ν, cm⁻¹: 3015.64 (N-H), 2837.02 (CH₃), 1637.46 (C=O), 1435.26 (C=C_{Ar}), 1376.00 (C-N), 1182.06 (C-O-C).

7-Methoxy-4-[(3-methoxyphenyl)amino]quinazolin-6-yl acetate(3h).

Yield 85%, white solid, m. p. 106.1 - 109.9°C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.56 (s, 1H), 8.93 (s, 1H), 8.89 (s, 1H), 7.61 (s, 1H), 7.44 - 7.32 (m, 3H), 6.94-6.87 (m, 1H), 4.01 (s, 3H), 3.79 (s, 3H), 2.39 (s, 3H); IR (KBr), ν, cm⁻¹: 3274.08 (N-H), 2927.72 (CH₃), 1639.12 (C=O), 1494.16 (C=C_{Ar}), 1267.58 (C-N), 1159.34 (C-O-C).

7-Methoxy-4-(phenylamino)quinazolin-6-ol(4a).

Yield 90%, white solid, m. p. 123.7 - 125.2°C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.36 (s, 1H), 8.43(s, 1H), 7.90-7.69 (m, 3H), 7.35 (t, *J* = 7.7 Hz, 2H), 7.20 (s, 1H), 7.06 (t, *J* = 7.3 Hz, 1H), 3.98 (s, 3H); IR (KBr), ν, cm⁻¹: 3621.25 (-OH), 3390.22 (N-H), 1605.58 (C=N), 1579.22 (C=C_{Ar}), 1243.16 (C-O-C).

7-Methoxy-4-[(4-methylphenyl)amino]quinazolin-6-ol(4b).

Yield 88%, white solid, m. p. 125.1 - 128.7°C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.61 (s, 1H), 9.29 (s, 1H), 8.40 (s, 1H), 7.80 (s, 1H), 7.73 (s, 1H), 7.71 (s, 1H), 7.18 (d, *J* = 5.6 Hz, 2H), 7.15 (s, 1H), 3.97 (s, 3H), 2.30 (s, 3H); IR (KBr), ν, cm⁻¹: 3625.24 (-OH), 3304.96 (N-H), 2795.30 (CH₃), 1569.36 (C=C_{Ar}), 1531.07 (C=N), 1287.67 (C-O-C).

7-Methoxy-4-[(4-methoxyphenyl)amino]quinazolin-6-ol(4c).

Yield 85%, white solid, m. p. 121.7 - 124.2°C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.29 (s, 1H), 8.36 (s, 1H), 7.80(s, 1H), 7.74-7.66 (m, 2H), 7.17 (s, 1H), 6.97-6.91 (m, 2H), 3.97 (s, 3H), 3.76 (s, 3H), 2.53-2.49 (m, 1H); IR (KBr), ν, cm⁻¹: 3625.20 (-OH), 3338.02 (N-H), 2836.80 (CH₃), 1560.35 (C=C_{Ar}), 1513.42 (C=N), 1225.60 (C-O-C).

4-[(4-Chloro-2-methylphenyl)amino]-7-methoxyquinazolin-6-ol(4d).

Yield 88%, white solid, m. p. 123.5 - 124.3°C. ¹H-NMR(400 MHz, DMSO-*d*₆) δ 9.82 (s, 1H), 8.48 (s, 1H), 8.23 (s, 1H), 7.55-7.46 (m, 2H), 7.37(s, 1H), 7.29 (t, *J* = 7.8 Hz, 1H), 3.96 (s, 3H), 2.37 (s, 3H); IR (KBr), ν, cm⁻¹: 3622.50 (-OH), 3337.01 (N-H), 2837.69 (CH₃), 1560.36 (C=C_{Ar}), 1501.42 (C=N), 1241.26 (C-O-C), 731.57 (C-Cl).

4-[(2-Fluorophenyl)amino]-7-methoxyquinazolin-6-ol(4e).

Yield 90%, white solid, m. p. 121.2 - 124.2°C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.70 (s, 1H), 9.34 (s, 1H), 8.31 (s, 1H), 7.61 (d, *J* = 6.0 Hz, 2H), 7.24 (d, *J* = 9.6 Hz, 4H), 3.97 (s, 3H); IR (KBr), ν, cm⁻¹: 3634.86 (-OH), 3313.96 (N-H), 2843.21 (CH₃), 1552.69 (C=C_{Ar}), 1523.78 (C=N), 1256.97 (C-O-C), 927.20 (C-F).

4-[(3-Chloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-ol(4f).

Yield 88%, white solid, m. p. 123.2 - 125.9°C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.48 (s, 1H), 8.49 (s, 1H), 8.28(s, 1H), 7.91-7.72 (m, 2H), 7.31 (s, 1H), 7.02 (s, 1H), 6.93 (s, 1H), 3.83 (s, 3H); IR (KBr), ν, cm⁻¹: 3658.18 (-OH), 3345.18 (N-H), 2859.71 (CH₃), 1568.29 (C=C_{Ar}), 1528.39 (C=N), 1279.39 (C-O-C), 929.37 (C-F), 720.18 (C-Cl).

4-[(2,4-Dimethylphenyl)amino]-7-methoxyquinazolin-6-ol(4g).

Yield 86%, white solid, m. p. 125.3 - 128.6°C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.57 (s, 1H), 9.10 (s, 1H), 8.21 (s, 1H), 7.70 (s, 1H), 7.17 (d, *J* = 7.6 Hz, 2H), 7.10 (s, 1H), 7.03 (d, *J* = 7.6 Hz, 1H), 3.96 (s, 3H), 2.31 (s, 3H), 2.12 (s, 3H); IR (KBr), ν, cm⁻¹: 3648.79 (-OH), 3324.36 (N-H), 2814.29 (CH₃), 1569.39 (C=C_{Ar}), 1523.11 (C=N), 1249.11 (C-O-C).

7-Methoxy-4-[(3-methoxyphenyl)amino]quinazolin-6-ol(4h).

Yield 84%, white solid, m. p. 128.1 - 130.4°C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.35 (s, 1H), 8.47 (s, 1H), 7.86 (s, 1H), 7.58 (t, *J* = 1.9 Hz, 1H), 7.53 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.26 (t, *J* = 8.3 Hz, 1H), 7.20 (s, 1H), 6.66 (dd, *J* = 7.9, 1.9 Hz, 1H), 3.98 (s, 3H), 3.78 (s, 3H); IR (KBr), ν, cm⁻¹: 3653.90 (-OH), 3358.63 (N-H), 2819.13 (CH₃), 1602.18 (C=C_{Ar}), 1527.12 (C=N), 1273.73 (C-O-C).

N-{4-[(2E)-3-(3-Methylphenyl)-1-oxoprop-2-en-1-yl]phenyl}-2-chloroacetamide(8a).

Yield 60%, white solid, m. p. 126.8 - 129.1°C. ¹H NMR (400 MHz, CDCl₃) δ 8.44 (s, 1H), 8.07 (d, *J* = 8.4 Hz, 2H), 7.85-7.69 (m, 3H), 7.55 (s, 1H), 7.47 (s, 2H), 7.31 (d, *J* = 7.9 Hz, 1H), 4.24 (s, 2H), 2.41 (s, 3H); IR (KBr), ν, cm⁻¹: 3335.22 (N-H), 2872.03 (CH₃), 1671.20 (C=O), 1597.10 (C=C), 1335.25 (C-N), 786.33 (C-Cl).

N-{4-[(2E)-3-(3-Methoxyphenyl)-1-oxoprop-2-en-1-yl]phenyl}-2-chloroacetamide(8b).

Yield 62%, white solid, m. p. 125.7 - 128.5°C. ¹H NMR (400 MHz, CDCl₃) δ 8.45 (s, 1H), 8.07 (s, 1H), 8.05 (s, 1H), 7.84-7.68 (m, 3H), 7.51 (d, *J* = 8.7 Hz, 1H), 7.35 (t, *J* = 7.9 Hz, 1H), 7.16 (s, 1H), 6.98 (d, *J* = 8.2 Hz, 1H), 4.23 (s, 2H), 3.86 (s, 3H); IR (KBr), ν, cm⁻¹: 3354.21 (N-H), 2834.25 (CH₃), 1645.33 (C=O), 1580.72 (C=C), 1339.81 (C-N), 1259.90 (C-O-C), 779.21 (C-Cl).

N-{4-[(2*E*)-3-(4-methoxyphenyl)-1-oxoprop-2-en-1-yl]phenyl}-2-chloroacetamide(**8c**).

Yield 56%, white solid, m. p. 151.9 - 154.6°C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.14 (d, *J* = 8.6 Hz, 2H), 7.99 - 7.90 (m, 1H), 7.85 (d, *J* = 8.5 Hz, 2H), 7.76 (d, *J* = 1.0 Hz, 2H), 7.74 (d, *J* = 2.0 Hz, 1H), 7.05-6.97 (m, 2H), 4.26 (s, 2H), 3.81 (s, 3H); IR (KBr), ν, cm⁻¹: 3333.21 (N-H), 2863.28 (CH₃), 1671.70 (C=O), 1518.66 (C=C), 1335.54 (C-N), 1264.23 (C-O-C), 777.21 (C-Cl).

N-{4-[(2*E*)-3-(3-methylphenyl)-1-oxoprop-2-en-1-yl]phenyl}-2-[(7-methoxy-4-(phenylamino)quinazolin-6-yl]oxy}acetamide(**9a**).

Yield 40%, white solid, m. p. 121.7 - 123.9°C. ¹H NMR (400 MHz, CDCl₃) δ 8.94 (s, 1H), 8.70 (s, 1H), 8.07 (d, *J* = 8.4 Hz, 2H), 7.80 (d, *J* = 8.1 Hz, 2H), 7.72 (t, *J* = 9.2 Hz, 3H), 7.55 (s, 1H), 7.50 - 7.43 (m, 3H), 7.41 (d, *J* = 7.8 Hz, 2H), 7.34 (d, *J* = 4.4 Hz, 3H), 4.79 (s, 2H), 4.10 (s, 3H), 2.41 (s, 3H); IR (KBr), ν, cm⁻¹: 3359.01 (N-H), 2833.91 (CH₃), 1648.58 (C=O), 1569.69 (C=C_{Ar}), 1525.58 (C=N), 1398.31 (C-N), 1205.56 (C-O-C). ¹³C NMR (101 MHz, DMSO) δ 188.03, 167.12, 157.02, 154.84, 153.78, 147.89, 147.80, 144.12, 143.26, 139.76, 138.63, 135.14, 133.25, 131.73, 130.42, 129.54, 129.25, 128.93, 128.81, 126.75, 124.00, 123.02, 122.25, 122.16, 119.42, 109.18, 108.09, 104.77, 68.89, 56.43, 56.35, 21.34. ESI-MS (m/z): calculated for C₃₃H₂₈N₄O₄: 544.61 (100%); found: 545.26 [M+H]⁺ (100%).

N-{4-[(2*E*)-3-(3-methylphenyl)-1-oxoprop-2-en-1-yl]phenyl}-2-[(7-methoxy-4-(4-methylphenyl)amino)quinazolin-6-yl]oxy}acetamide(**9b**).

Yield 41%, light-yellow solid, m. p. 135.1 - 138.7°C. ¹H NMR (400 MHz, CDCl₃) δ 8.94 (s, 1H), 8.66 (s, 1H), 8.06 (d, *J* = 8.1 Hz, 2H), 7.82 (s, 1H), 7.75 (d, *J* = 8.7 Hz, 2H), 7.53 (d, *J* = 6.4 Hz, 3H), 7.49 (s, 1H), 7.45 (s, 2H), 7.34 (d, *J* = 6.2 Hz, 2H), 7.21 (d, *J* = 8.1 Hz, 2H), 4.78 (s, 2H), 4.09 (s, 3H), 2.41 (s, 3H), 2.36 (s, 3H); IR (KBr), ν, cm⁻¹: 3357.00 (N-H), 2824.79 (CH₃), 1632.97 (C=O), 1568.47 (C=C_{Ar}), 1543.06 (C=N), 1398.90 (C-N), 1206.84 (C-O-C). ¹³C NMR (101 MHz, DMSO) δ 188.02, 167.12, 157.12, 154.78, 153.80, 147.76, 144.12, 143.28, 138.64, 137.09, 135.15, 133.22, 133.14, 131.75, 130.42, 129.54, 129.38, 129.28, 126.80, 123.22, 122.17, 119.39, 109.08, 108.00, 104.73, 68.83, 56.43, 21.35, 21.01. ESI-MS (m/z): calculated for C₃₄H₃₀N₄O₄: 558.64 (100%); found: 559.28 [M+H]⁺ (100%).

N-{4-[(2*E*)-3-(3-methylphenyl)-1-oxoprop-2-en-1-yl]phenyl}-2-[(7-methoxy-4-[(3-methoxyphenyl)amino]quinazolin-6-yl]oxy}acetamide(**9c**).

Yield 45%, light-yellow solid, m. p. 118.4 - 121.7°C. ¹H NMR (400 MHz, CDCl₃) δ 8.90 (s, 1H), 8.69 (s, 1H), 8.04 (d, *J* = 8.4 Hz, 2H), 7.74 (d, *J* = 8.6 Hz, 2H), 7.64 (d, *J* = 8.7 Hz, 1H), 7.53 (s, 1H), 7.47 - 7.39 (m, 4H), 7.32 (d, *J* = 4.6 Hz, 2H), 7.29 (s, 1H), 7.22 (s, 1H), 6.71 (dd, *J* = 8.0, 1.9 Hz, 1H), 4.78 (s, 2H), 4.09 (s, 3H), 3.82 (d, *J* = 1.1 Hz, 3H), 2.40 (s, 3H); IR (KBr), ν, cm⁻¹: 3315.60 (N-H), 2971.93 (CH₃), 1627.83 (C=O), 1577.82 (C=C_{Ar}), 1541.91 (C=N), 1492.97 (C=C), 1390.77 (C-N), 1212.12 (C-O-C). ¹³C NMR (101 MHz, DMSO) δ 188.02, 167.11, 159.87, 156.95, 154.87, 153.71, 147.90, 147.81, 147.78, 144.12, 143.26, 140.98, 138.63, 135.14, 133.24, 131.73, 130.49, 130.42, 129.65, 129.54, 129.26, 126.77, 122.16, 119.41, 115.11, 109.23, 109.16, 108.75, 108.11, 104.80, 68.93, 56.44, 55.55, 21.34. ESI-MS (m/z): calculated for C₃₄H₃₀N₄O₅: 574.64 (100%); found: 575.26 [M+H]⁺ (100%).

N-{4-[(2*E*)-3-(3-methylphenyl)-1-oxoprop-2-en-1-yl]phenyl}-2-[(7-methoxy-4-[(4-methoxyphenyl)amino]quinazolin-6-yl]oxy}acetamide(**9d**).

Yield 50%, light-yellow solid, m. p. 137.6 - 140.1°C. ¹H NMR (400 MHz, CDCl₃) δ 8.94 (s, 1H), 8.62 (s, 1H), 8.01 (d, *J* = 8.4 Hz, 2H), 7.82 - 7.67 (m, 4H), 7.54 - 7.44 (m, 4H), 7.29 (d, *J* = 3.5 Hz, 2H), 7.23 (d, *J* = 7.7 Hz, 1H), 6.90 (d, *J* = 8.5 Hz, 2H), 4.75 (s, 2H), 4.06 (s, 3H),

3.79 (s, 3H), 2.40 (s, 3H); IR (KBr), ν , cm^{-1} : 3356.13 (N-H), 3081.78 (CH_3), 1648.28 ($\text{C}=\text{O}$), 1568.00 ($\text{C}=\text{C}_{\text{Ar}}$), 1511.29 ($\text{C}=\text{C}$), 1471.31 ($\text{C}=\text{N}$), 1434.25 (C-C), 1338.63 (C-N), 1237.37 (C-O-C). ^{13}C NMR (101 MHz, DMSO) δ 188.02, 167.14, 157.28, 156.27, 154.67, 153.94, 147.68, 144.12, 143.28, 138.63, 135.14, 133.22, 132.48, 131.73, 130.42, 129.54, 129.26, 126.77, 125.11, 122.16, 119.39, 114.15, 108.99, 108.04, 104.70, 68.79, 56.38, 55.67, 21.34. ESI-MS (m/z): calculated for $\text{C}_{34}\text{H}_{30}\text{N}_4\text{O}_5$: 574.64 (100%); found: 575.27 $[\text{M}+\text{H}]^+$ (100%).

N-{4-[(2*E*)-3-(3-methylphenyl)-1-oxoprop-2-en-1-yl]phenyl}-2-({4-[(2,4-dimethylphenyl)amino]-7-methoxyquinazolin-6-yl}oxy)acetamide(**9e**).

Yield 46%, light-yellow solid, m. p. 138.7 - 141.7°C. ^1H NMR (400 MHz, CDCl_3) δ 8.92 (s, 1H), 8.59 (s, 1H), 8.05 (d, J = 8.2 Hz, 1H), 7.96 (d, J = 8.2 Hz, 2H), 7.84 - 7.73 (m, 1H), 7.70 (d, J = 8.7 Hz, 2H), 7.47 (d, J = 9.9 Hz, 1H), 7.37 (d, J = 7.8 Hz, 2H), 7.31 (d, J = 4.8 Hz, 2H), 7.16 - 7.02 (m, 3H), 4.71 (s, 2H), 4.08 (s, 3H), 2.59 (s, 3H), 2.35 (s, 3H), 2.25 (s, 3H); IR (KBr), ν , cm^{-1} : 3362.08 (N-H), 2915.42 (CH_3), 1631.59 ($\text{C}=\text{O}$), 1569.52 ($\text{C}=\text{C}_{\text{Ar}}$), 1541.96 (C=N), 1400.31 (C-N), 1205.93 (C-O-C). ^{13}C NMR (101 MHz, DMSO) δ 188.00, 186.31, 167.14, 167.08, 158.31, 154.61, 154.36, 154.18, 154.09, 147.67, 147.49, 144.11, 141.99, 138.64, 138.53, 135.81, 135.55, 135.18, 135.15, 135.08, 129.21, 127.24, 126.43, 122.64, 119.33, 113.20, 112.92, 108.76, 107.93, 104.53, 68.50, 56.37, 21.36, 21.07, 18.39. ESI-MS (m/z): calculated for $\text{C}_{35}\text{H}_{32}\text{N}_4\text{O}_4$: 572.66 (100%); found: 573.25 $[\text{M}+\text{H}]^+$ (100%).

N-{4-[(2*E*)-3-(3-methoxyphenyl)-1-oxoprop-2-en-1-yl]phenyl}-2-([7-methoxy-4-(phenylamino)quinazolin-6-yl]oxy)acetamide(**9f**).

Yield 40%, white solid, m. p. 127.4 - 130.9°C. ^1H NMR (400 MHz, CDCl_3) δ 8.93 (s, 1H), 8.68 (s, 1H), 8.01 (d, J = 8.2 Hz, 2H), 7.78 (s, 1H), 7.73 (s, 2H), 7.70 (s, 2H), 7.68 (s, 1H), 7.50 (s, 1H), 7.45 (s, 2H), 7.37 (s, 2H), 7.16 (d, J = 9.4 Hz, 2H), 7.01 - 6.92 (m, 1H), 4.76 (s, 2H), 4.07 (s, 3H), 3.86 (s, 3H); IR (KBr), ν , cm^{-1} : 3357.92 (N-H), 2833.33 (CH_3), 1631.84 ($\text{C}=\text{O}$), 1570.15 ($\text{C}=\text{C}_{\text{Ar}}$), 1533.30 (C=N), 1397.94 (C-N), 1206.27 (C-O-C). ^{13}C NMR (101 MHz, DMSO) δ 188.05, 167.10, 160.13, 159.88, 156.98, 154.91, 153.66, 147.84, 143.99, 143.30, 140.94, 136.64, 133.18, 130.48, 130.40, 130.00, 129.67, 122.65, 122.15, 119.40, 119.28, 117.11, 115.15, 113.78, 109.22, 108.79, 104.82, 68.91, 56.46, 55.56. ESI-MS (m/z): calculated for $\text{C}_{33}\text{H}_{28}\text{N}_4\text{O}_5$: 560.61 (100%); found: 561.27 $[\text{M}+\text{H}]^+$ (100%).

N-{4-[(2*E*)-3-(3-methoxyphenyl)-1-oxoprop-2-en-1-yl]phenyl}-2-({4-[(2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl}oxy)acetamide(**9g**).

Yield 46%, light-yellow solid, m. p. 158.9 - 160.3°C. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.51 (s, 1H), 9.47 (s, 1H), 8.35 (s, 1H), 8.19 (d, J = 8.4 Hz, 2H), 7.91 (d, J = 7.6 Hz, 2H), 7.85 (d, J = 8.3 Hz, 2H), 7.70 (d, J = 9.7 Hz, 1H), 7.53 - 7.46 (m, 2H), 7.40 (d, J = 8.6 Hz, 1H), 7.31 (dd, J = 7.4, 4.8 Hz, 2H), 7.26 (d, J = 8.0 Hz, 3H), 7.02 (d, J = 8.1 Hz, 1H), 4.94 (s, 2H), 3.98 (s, 3H), 3.82 (s, 3H); IR (KBr), ν , cm^{-1} : 3359.45 (N-H), 1650.47 ($\text{C}=\text{O}$), 1572.11 ($\text{C}=\text{C}_{\text{Ar}}$), 1542.58 (C=N), 1397.92 (C-N), 1215.02 (C-O-C), 979.34 (C-F). ^{13}C NMR (101 MHz, DMSO) δ 188.06, 167.12, 160.13, 157.02, 154.85, 153.77, 147.87, 147.81, 143.99, 143.30, 139.74, 136.64, 133.18, 130.47, 130.40, 130.00, 128.94, 124.02, 123.02, 122.65, 122.14, 119.40, 117.10, 113.78, 109.16, 108.09, 104.78, 68.88, 56.44, 55.79. ESI-MS (m/z): calculated for $\text{C}_{33}\text{H}_{27}\text{FN}_4\text{O}_5$: 578.60 (100%); found: 579.23 $[\text{M}+\text{H}]^+$ (100%).

N-{4-[(2*E*)-3-(3-Methoxyphenyl)-1-oxoprop-2-en-1-yl]phenyl}-2-({7-methoxy-4-[(4-methoxyphenyl)amino]quinazolin-6-yl}oxy)acetamide(**9h**).

Yield 49%, light-yellow solid, m. p. 140.3 - 143.7°C. ^1H NMR (400 MHz, CDCl_3) δ 8.94 (s, 1H), 8.62 (s, 1H), 8.01 (d, J = 8.3 Hz, 2H), 7.80 - 7.68 (m, 3H), 7.58 - 7.44 (m, 4H), 7.41 (s,

1H), 7.35 (d, $J = 7.8$ Hz, 1H), 7.23 (d, $J = 7.7$ Hz, 1H), 7.14 (s, 1H), 6.91 (d, $J = 8.6$ Hz, 2H), 4.75 (s, 2H), 4.07 (s, 3H), 3.86 (s, 3H), 3.80 (s, 3H); IR (KBr), ν , cm^{-1} : 3358.21 (N-H), 2836.70 (CH_3), 1649.02 ($\text{C}=\text{O}$), 1570.39 ($\text{C}=\text{C}_{\text{Ar}}$), 1541.06 ($\text{C}=\text{N}$), 1401.01 ($\text{C}-\text{N}$), 1234.63 ($\text{C}-\text{O}-\text{C}$). ^{13}C NMR (101 MHz, DMSO) δ 188.05, 167.16, 160.13, 157.27, 156.26, 154.67, 153.94, 147.68, 143.98, 143.34, 136.64, 133.16, 132.50, 130.47, 130.39, 125.10, 122.65, 122.14, 119.38, 117.09, 114.15, 113.78, 109.00, 108.05, 104.70, 68.78, 56.38, 55.78, 55.67. ESI-MS (m/z): calculated for $\text{C}_{34}\text{H}_{30}\text{N}_4\text{O}_6$: 590.64 (100%); found: 591.27 $[\text{M}+\text{H}]^+$ (100%).

N-{4-[(2*E*)-3-(3-Methoxyphenyl)-1-oxoprop-2-en-1-yl]phenyl}-2-({4-[(2,4-dimethylphenyl)amino]-7-methoxyquinazolin-6-yl}oxy)acetamide(**9i**).

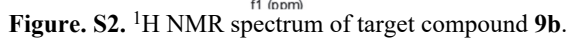
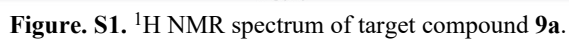
Yield 46%, light-yellow solid, m. p. 132.5 - 135.6°C. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.49 (s, 1H), 9.27 (s, 1H), 8.26 (s, 1H), 8.20 (d, $J = 8.5$ Hz, 2H), 7.90 (d, $J = 9.7$ Hz, 2H), 7.83 (d, $J = 8.5$ Hz, 2H), 7.49 - 7.31 (m, 3H), 7.21 (s, 1H), 7.18 - 7.06 (m, 3H), 7.02 (d, $J = 8.5$ Hz, 2H), 4.92 (s, 2H), 3.96 (d, $J = 3.9$ Hz, 3H), 3.82 (d, $J = 1.2$ Hz, 3H), 2.29 (s, 3H), 2.09 (s, 3H); IR (KBr), ν , cm^{-1} : 3319.12 (N-H), 2972.56 (CH_3), 1642.89 ($\text{C}=\text{O}$), 1570.77 ($\text{C}=\text{C}_{\text{Ar}}$), 1514.69 ($\text{C}=\text{N}$), 1429.55 ($\text{C}-\text{C}$), 1392.01 ($\text{C}-\text{N}$), 1276.98 ($\text{C}-\text{O}-\text{C}$). ^{13}C NMR (101 MHz, DMSO) δ 188.03, 167.14, 160.13, 158.32, 154.63, 154.16, 147.68, 147.42, 143.97, 143.39, 136.64, 135.82, 135.18, 135.07, 133.10, 131.46, 130.47, 130.40, 128.12, 127.24, 122.65, 122.15, 119.33, 117.10, 113.78, 108.75, 107.88, 104.55, 68.50, 56.38, 55.79, 21.07, 18.39. ESI-MS (m/z): calculated for $\text{C}_{35}\text{H}_{32}\text{N}_4\text{O}_5$: 588.66 (100%); found: 589.28 $[\text{M}+\text{H}]^+$ (100%).

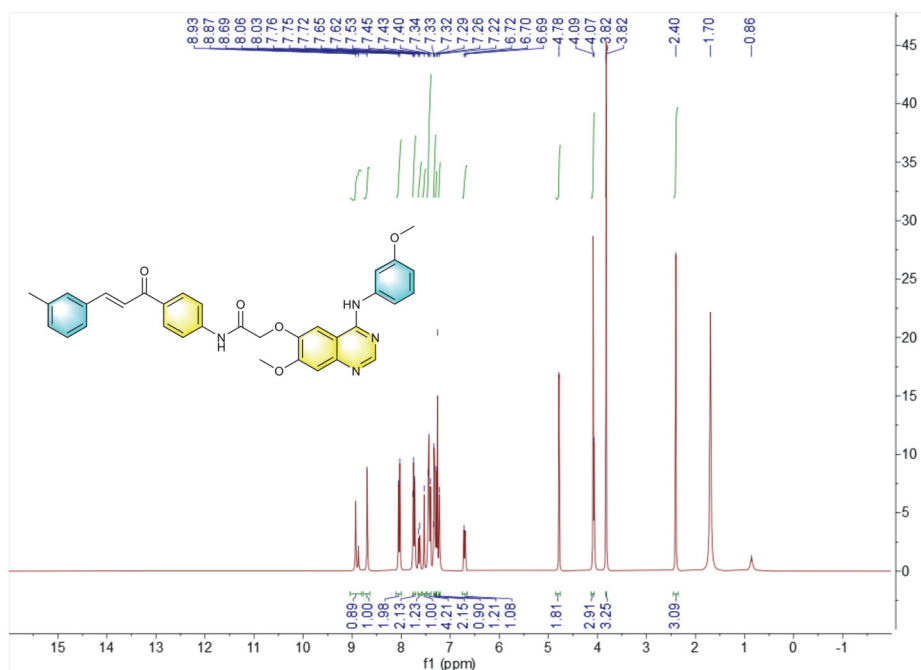
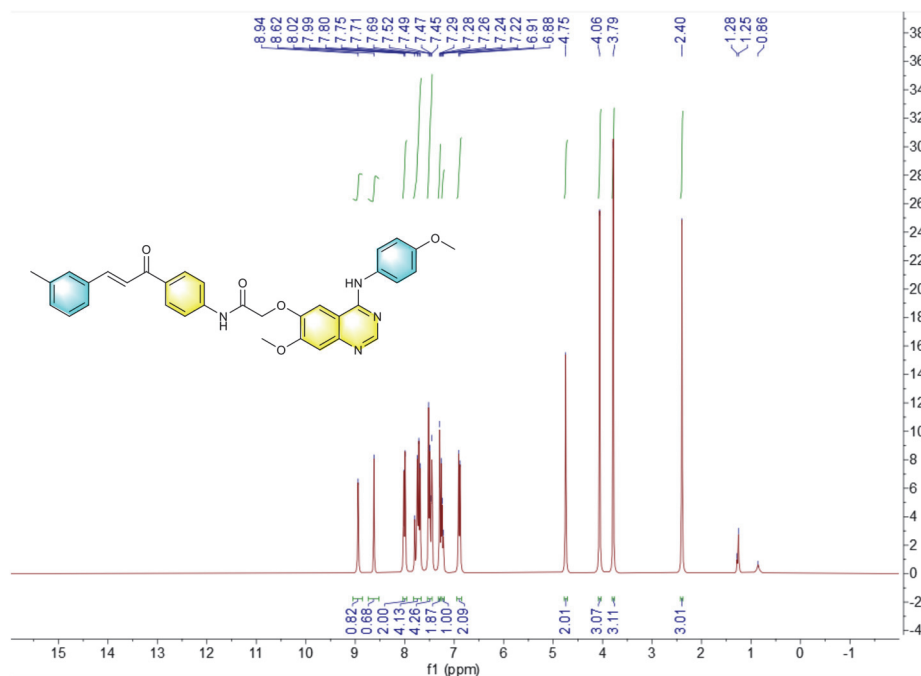
N-{4-[(2*E*)-3-(3-Methoxyphenyl)-1-oxoprop-2-en-1-yl]phenyl}-2-({4-[(4-chloro-2-methylphenyl)amino]-7-methoxyquinazolin-6-yl}oxy)acetamide(**9j**).

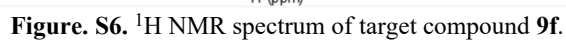
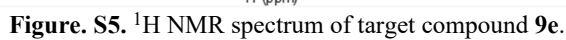
Yield 51%, light-yellow solid, m. p. 149.5 - 152.1°C. ^1H NMR (400 MHz, CDCl_3) δ 8.93 (s, 1H), 8.60 (s, 1H), 8.04 (d, $J = 8.4$ Hz, 2H), 7.85 - 7.67 (m, 3H), 7.49 - 7.43 (m, 1H), 7.33 (d, $J = 6.9$ Hz, 3H), 7.16 (s, 2H), 7.06 - 6.91 (m, 3H), 4.78 (s, 2H), 4.10 (s, 3H), 3.87 (s, 3H), 2.28 (s, 3H); IR (KBr), ν , cm^{-1} : 3365.25 (N-H), 2835.28 (CH_3), 1650.55 ($\text{C}=\text{O}$), 1572.46 ($\text{C}=\text{C}_{\text{Ar}}$), 1541.55 ($\text{C}=\text{N}$), 1401.62 ($\text{C}-\text{N}$), 1202.72 ($\text{C}-\text{O}-\text{C}$), 784.76 ($\text{C}-\text{Cl}$). ^{13}C NMR (101 MHz, DMSO) δ 188.03, 167.11, 160.13, 158.29, 154.74, 154.09, 147.77, 147.48, 143.98, 143.38, 138.32, 136.64, 134.01, 133.11, 130.47, 130.40, 130.15, 122.65, 122.15, 119.33, 117.32, 117.10, 113.78, 113.41, 113.19, 108.70, 107.92, 104.48, 68.49, 56.41, 55.79, 18.48. ESI-MS (m/z): calculated for $\text{C}_{34}\text{H}_{29}\text{ClN}_4\text{O}_5$: 609.08 (100%); found: 632.26 $[\text{M}+\text{Na}]^+$ (100%).

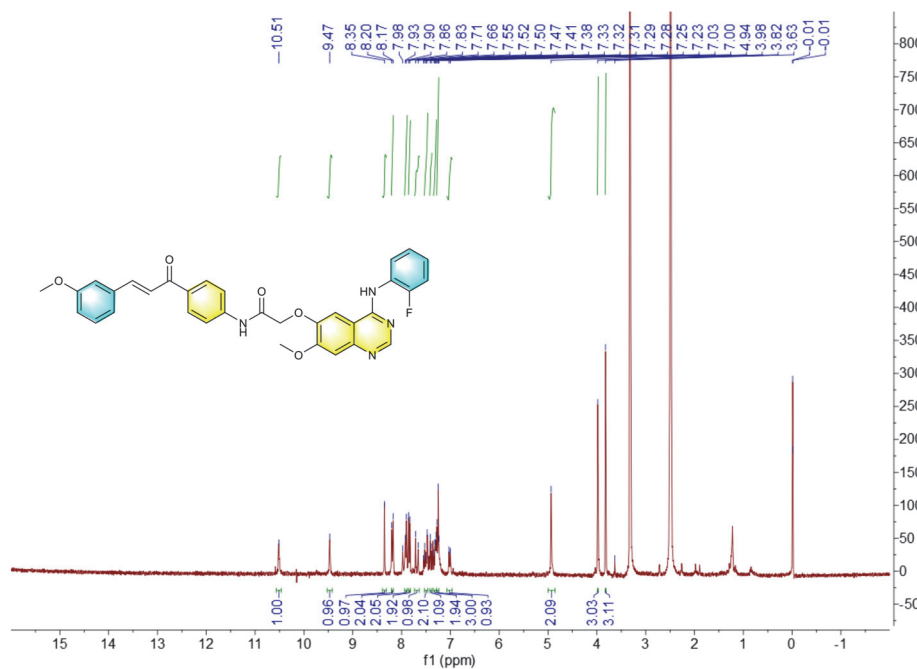
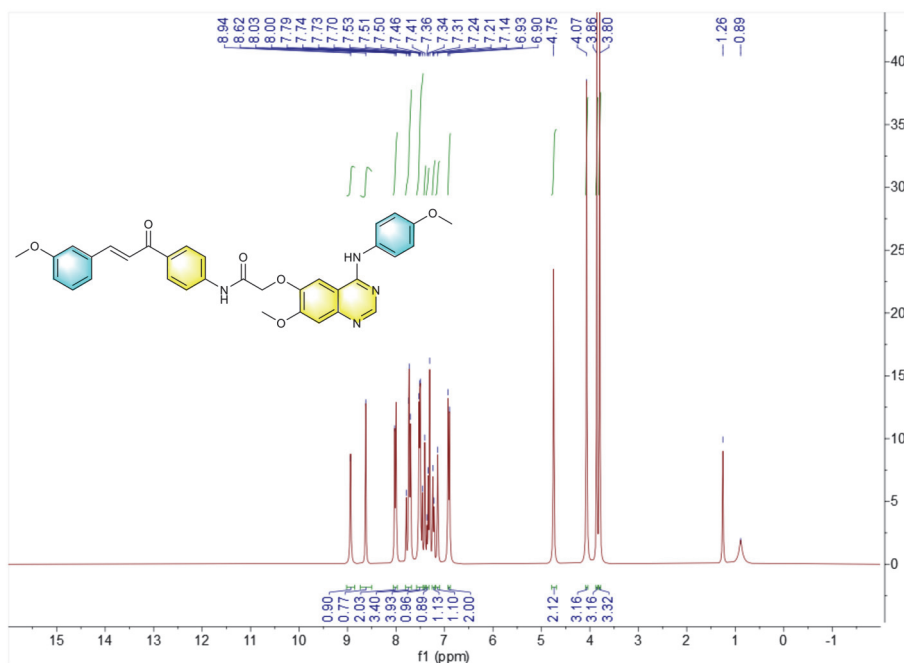
N-{4-[(2*E*)-3-(4-Methoxyphenyl)-1-oxoprop-2-en-1-yl]phenyl}-2-({4-[(3-chloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl}oxy)acetamide(**9k**).

Yield 33%, white solid, m. p. 118.4 - 121.9°C. ^1H NMR (400 MHz, CDCl_3) δ 8.94 (s, 1H), 8.73 (s, 1H), 8.46 (t, $J = 8.4$ Hz, 1H), 8.07 (d, $J = 8.2$ Hz, 1H), 8.00 (d, $J = 8.6$ Hz, 1H), 7.79 - 7.70 (m, 3H), 7.61 (d, $J = 8.6$ Hz, 1H), 7.45 (s, 2H), 7.37 (s, 1H), 7.32 (d, $J = 4.1$ Hz, 1H), 7.25 - 7.09 (m, 4H), 6.95 (d, $J = 8.7$ Hz, 1H), 4.82 (d, $J = 2.8$ Hz, 3H), 4.11 (d, $J = 2.5$ Hz, 3H), 3.87 (s, 2H); IR (KBr), ν , cm^{-1} : 3352.98 (N-H), 2833.62 (CH_3), 1642.29 ($\text{C}=\text{O}$), 1586.70 ($\text{C}=\text{C}_{\text{Ar}}$), 1541.09 ($\text{C}=\text{N}$), 1393.64 ($\text{C}-\text{N}$), 1215.32 ($\text{C}-\text{O}-\text{C}$), 984.60 ($\text{C}-\text{F}$), 752.12 ($\text{C}-\text{Cl}$). ^{13}C NMR (101 MHz, DMSO) δ 188.05, 167.10, 160.13, 158.59, 157.83, 156.14, 154.89, 153.88, 147.94, 147.67, 143.98, 143.37, 136.64, 133.13, 130.48, 130.40, 128.96, 127.65, 126.96, 124.88, 122.65, 122.14, 119.35, 117.10, 116.54, 116.34, 113.78, 108.89, 107.87, 104.41, 68.50, 56.43, 55.79. ESI-MS (m/z): calculated for $\text{C}_{33}\text{H}_{26}\text{ClFN}_4\text{O}_5$: 613.04 (100%); found: 613.25 $[\text{M}]^+$ (100%).



**Figure. S3.** ¹H NMR spectrum of target compound 9c.**Figure. S4.** ¹H NMR spectrum of target compound 9d.



**Figure. S7.** ^1H NMR spectrum of target compound **9g**.**Figure. S8.** ^1H NMR spectrum of target compound **9h**.

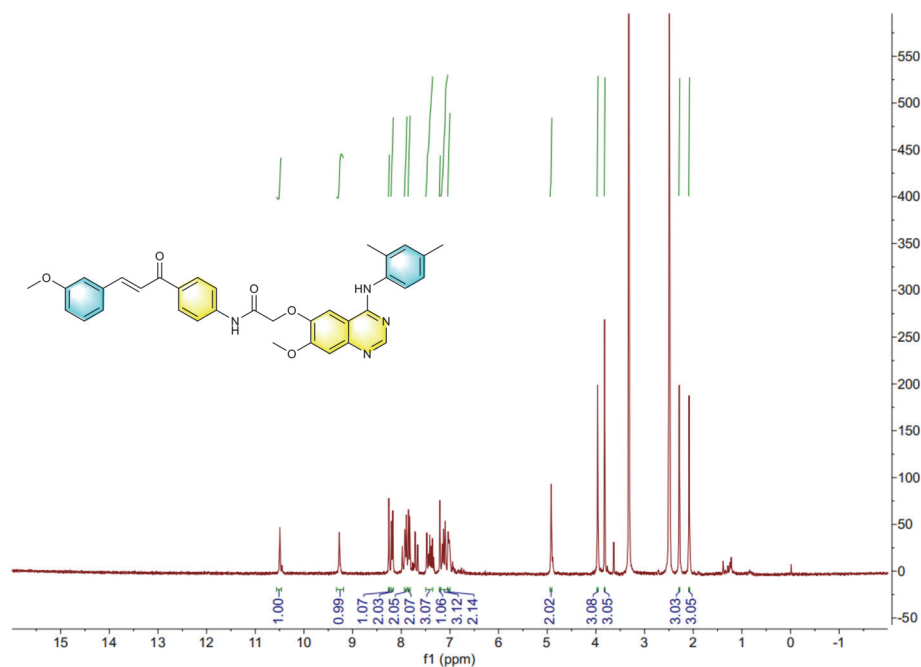


Figure. S9. ¹H NMR spectrum of target compound **9i**.

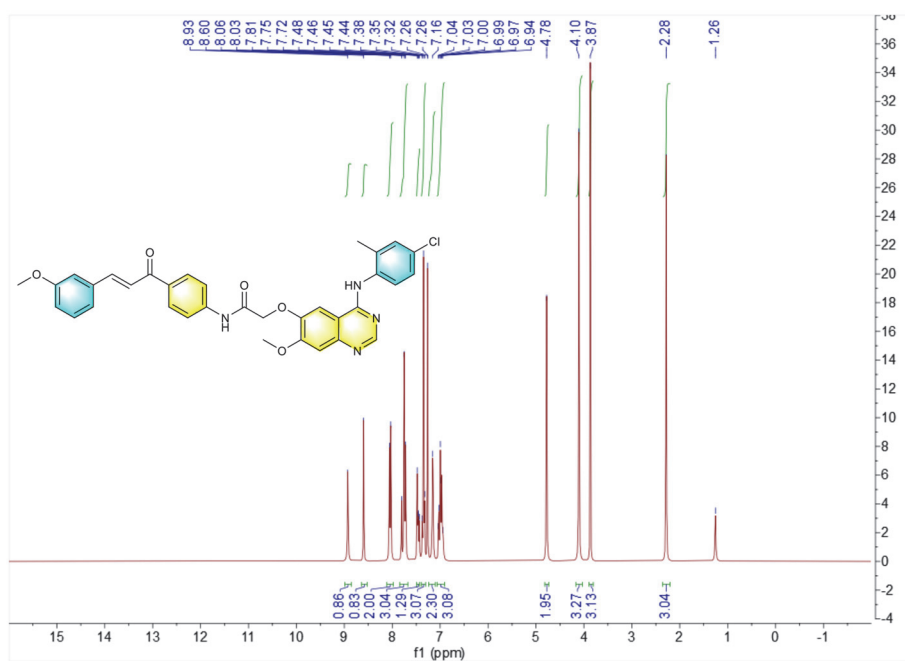
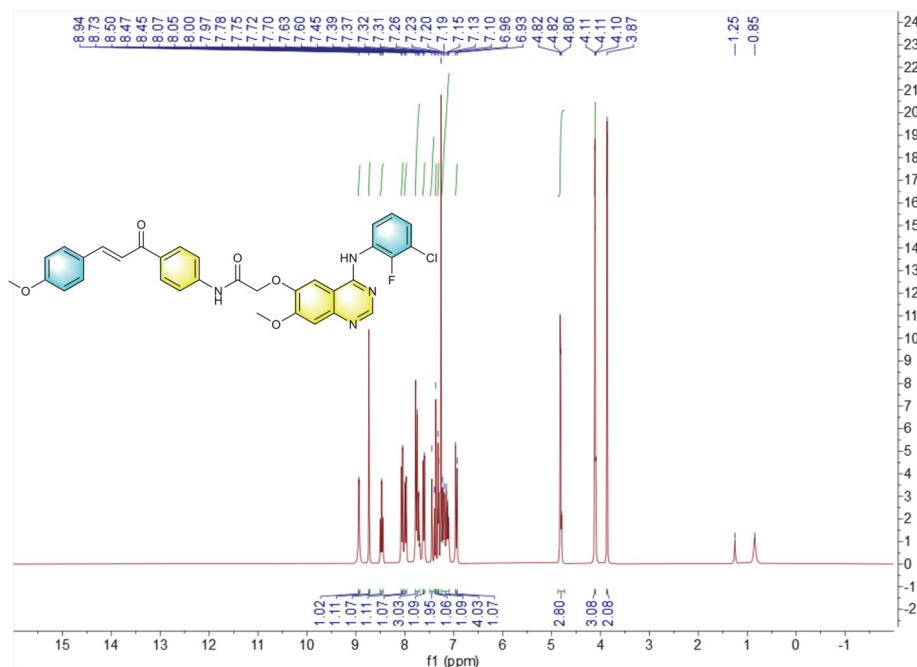
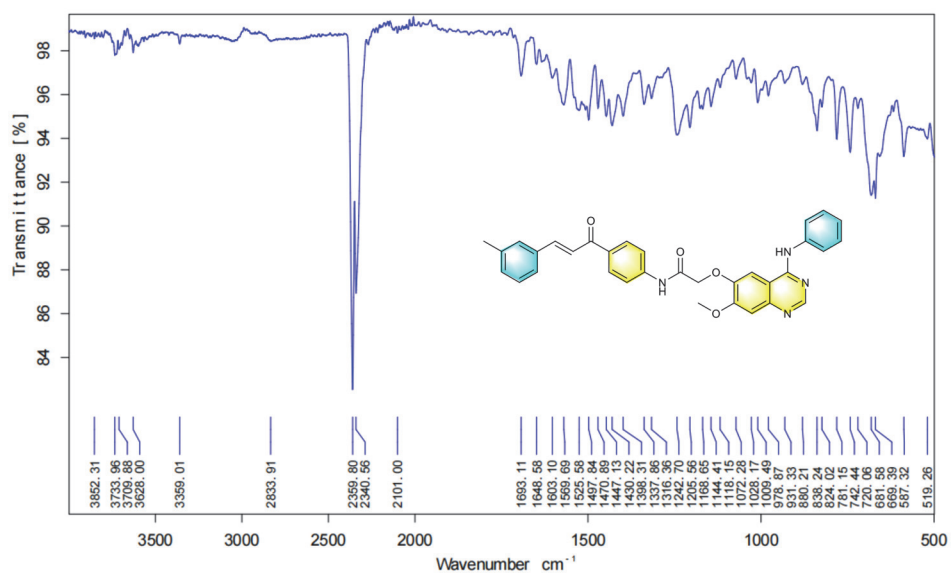


Figure. S10. ¹H NMR spectrum of target compound **9j**.

Figure. S11. ^1H NMR spectrum of target compound **9k**.Figure. S12. IR spectrum of target compound **9a**.

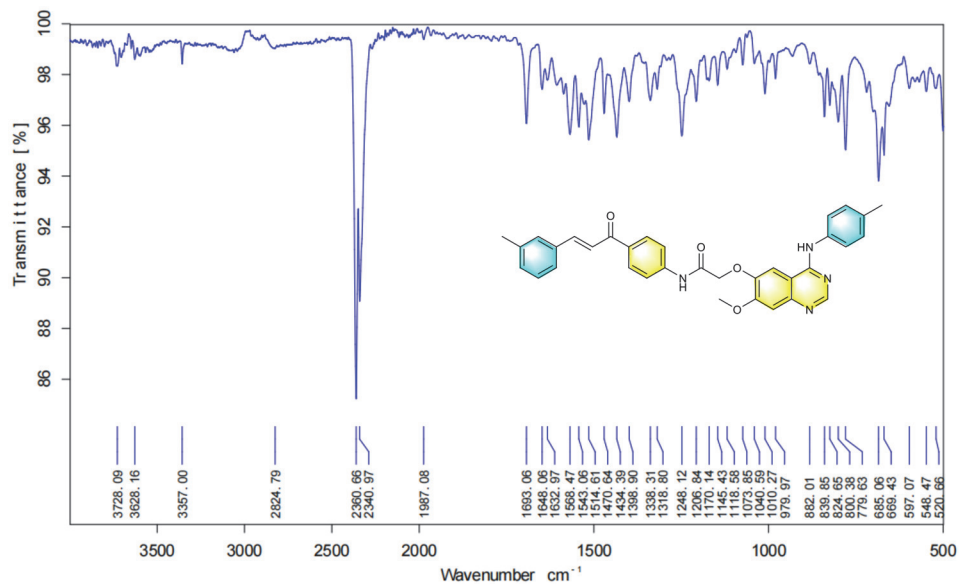


Figure. S13. IR spectrum of target compound 9b.

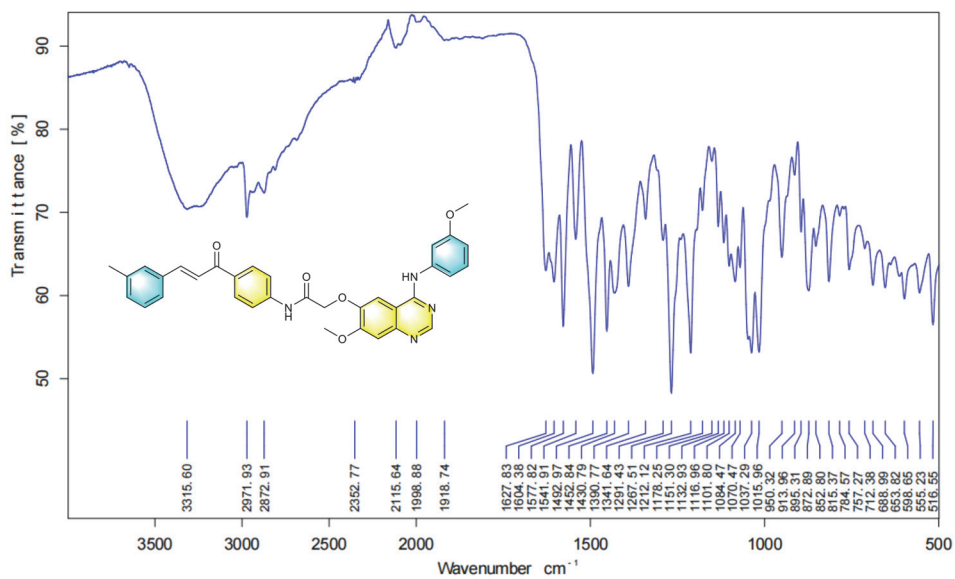


Figure. S14. IR spectrum of target compound 9c.

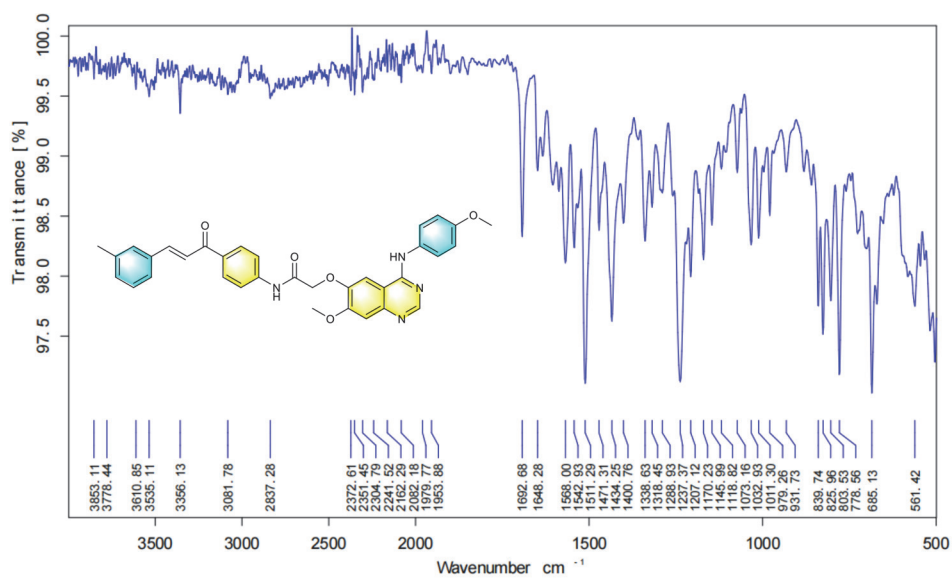


Figure. S15. IR spectrum of target compound 9d.

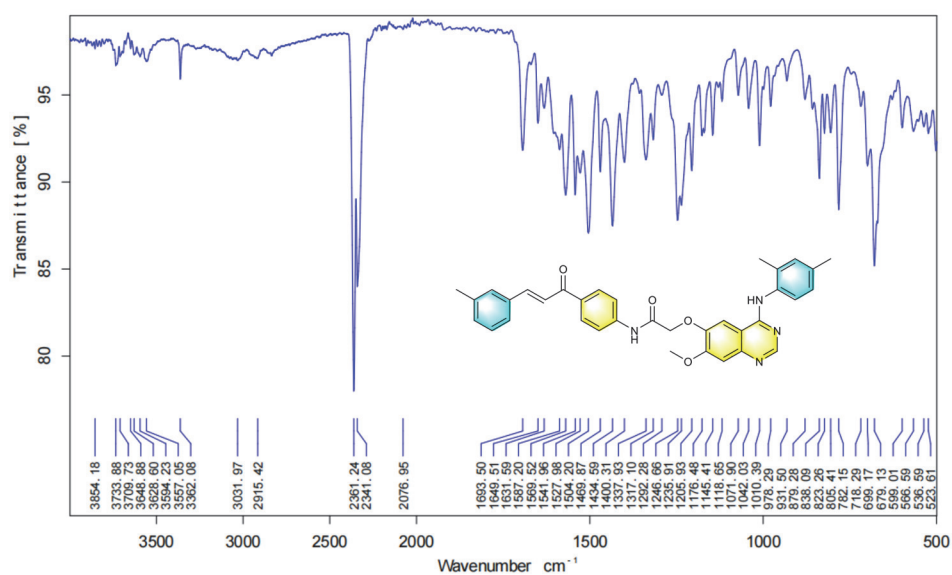
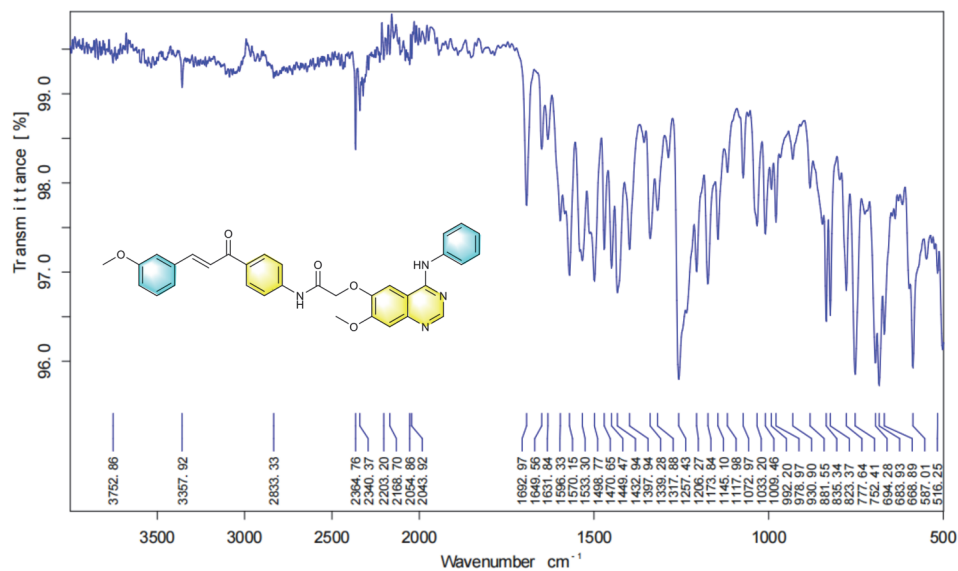
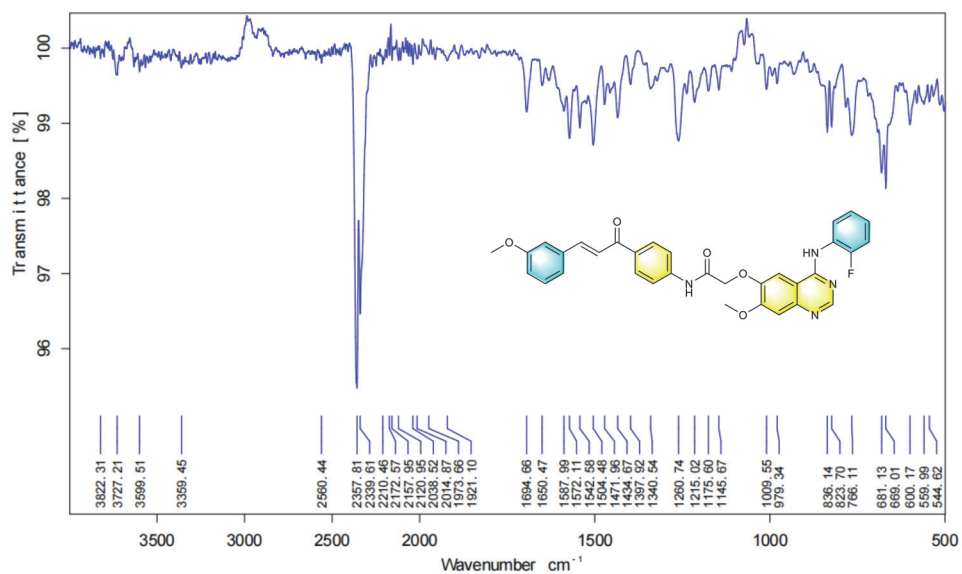


Figure. S16. IR spectrum of target compound 9e.

Figure. S17. IR spectrum of target compound **9f**.Figure. S18. IR spectrum of target compound **9g**.

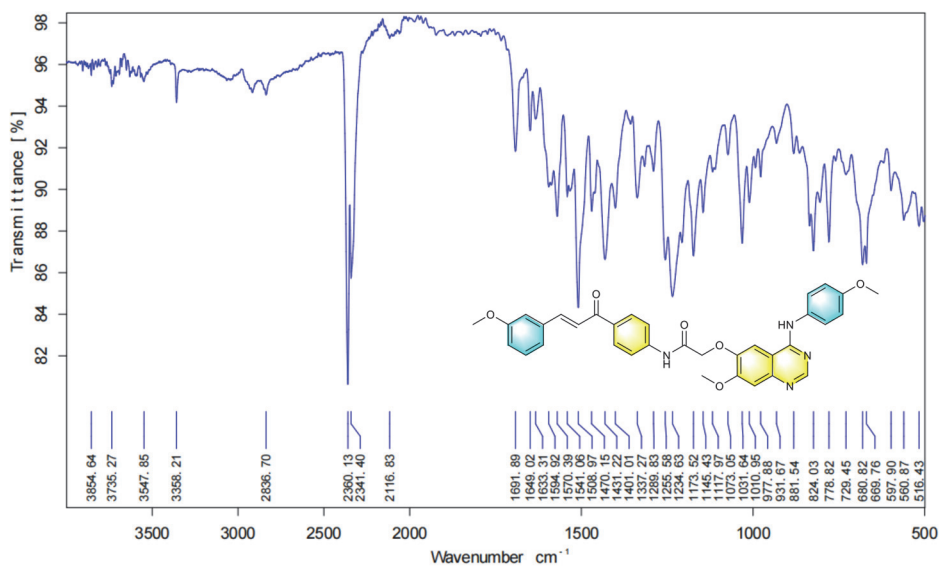


Figure. S19. IR spectrum of target compound 9h.

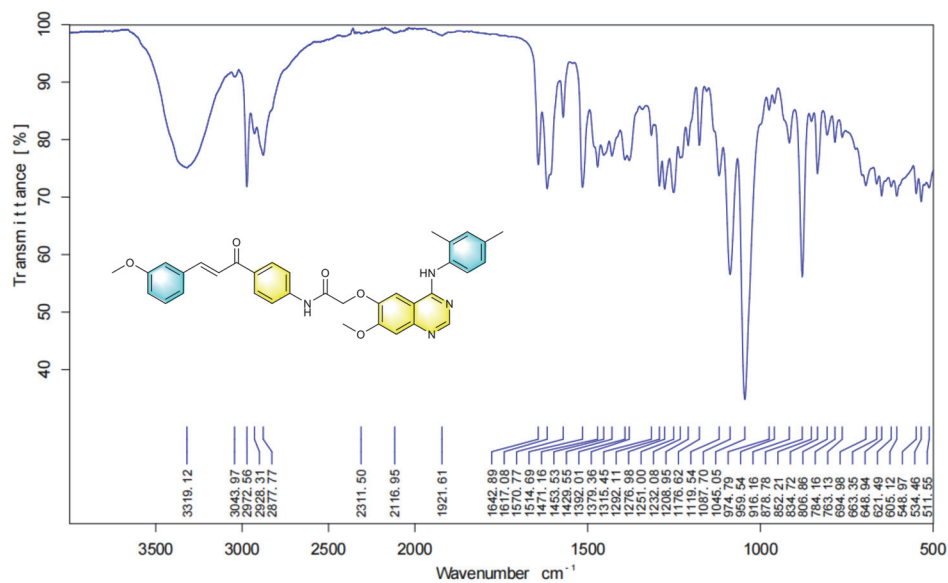


Figure. S20. IR spectrum of target compound 9i.

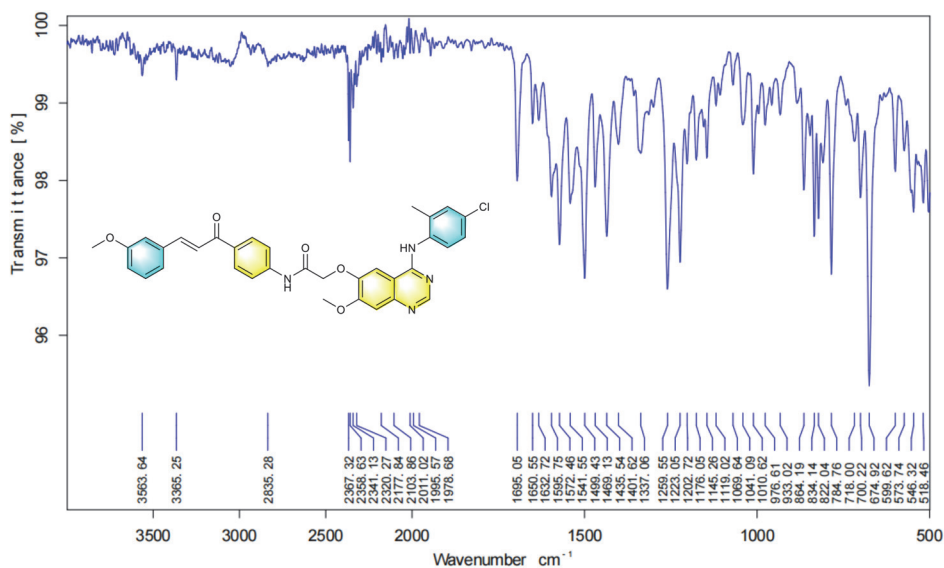


Figure. S21. IR spectrum of target compound 9j.

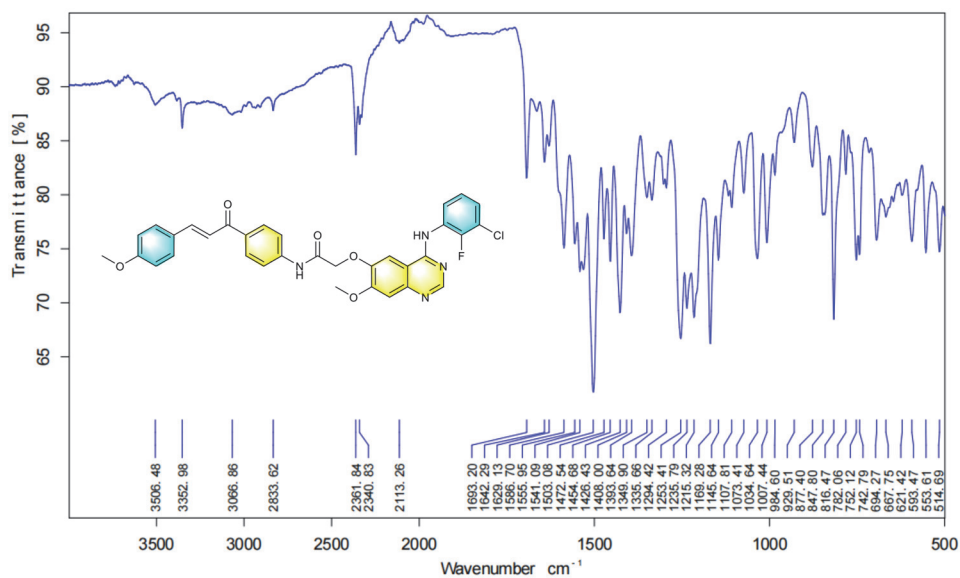


Figure. S22. IR spectrum of target compound 9k.

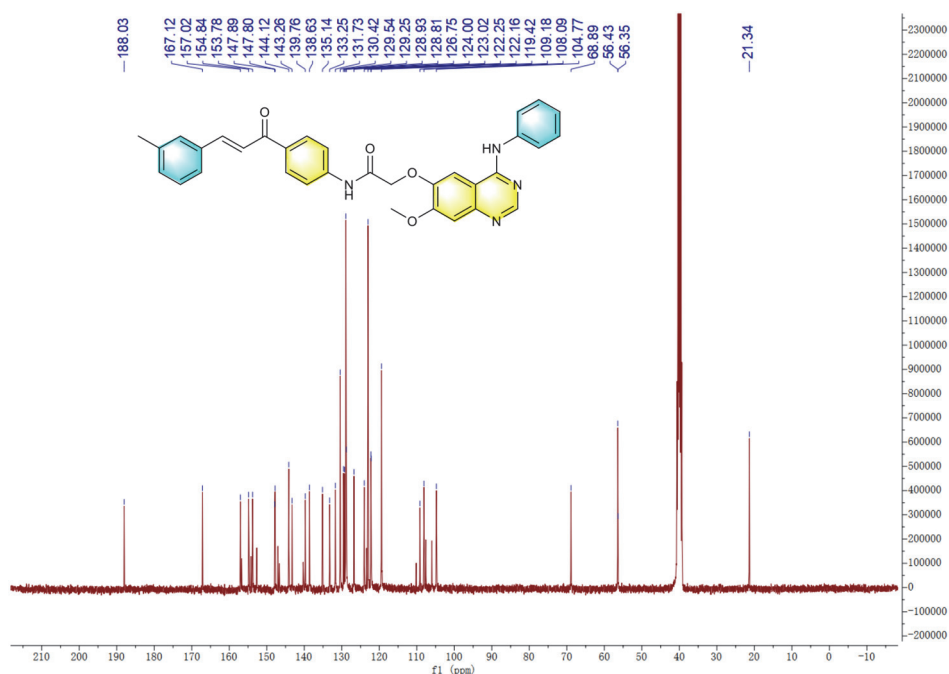


Figure. S23. ¹³C NMR spectrum of target compound **9a**.

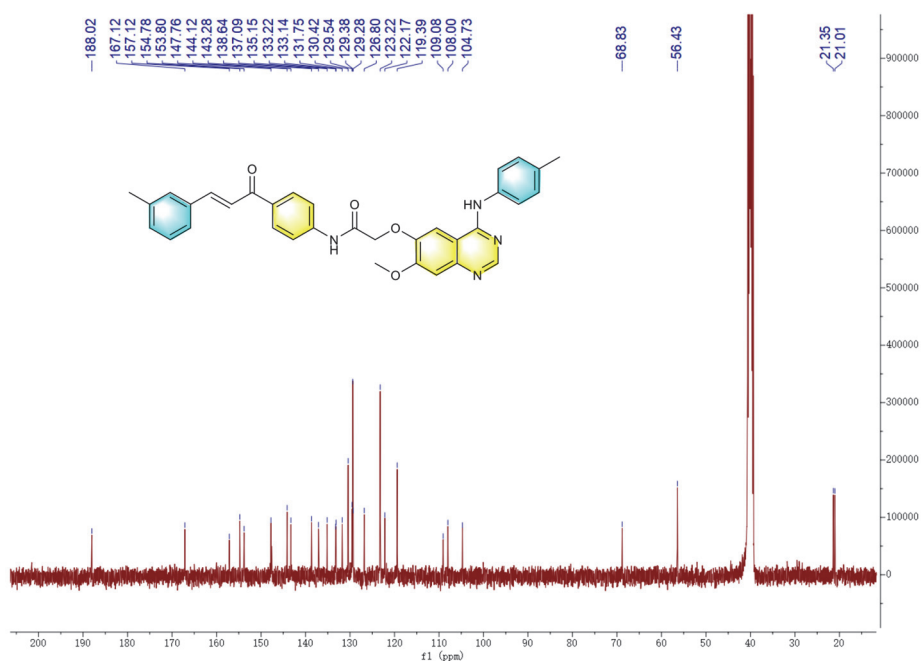


Figure. S24. ¹³C NMR spectrum of target compound **9b**.

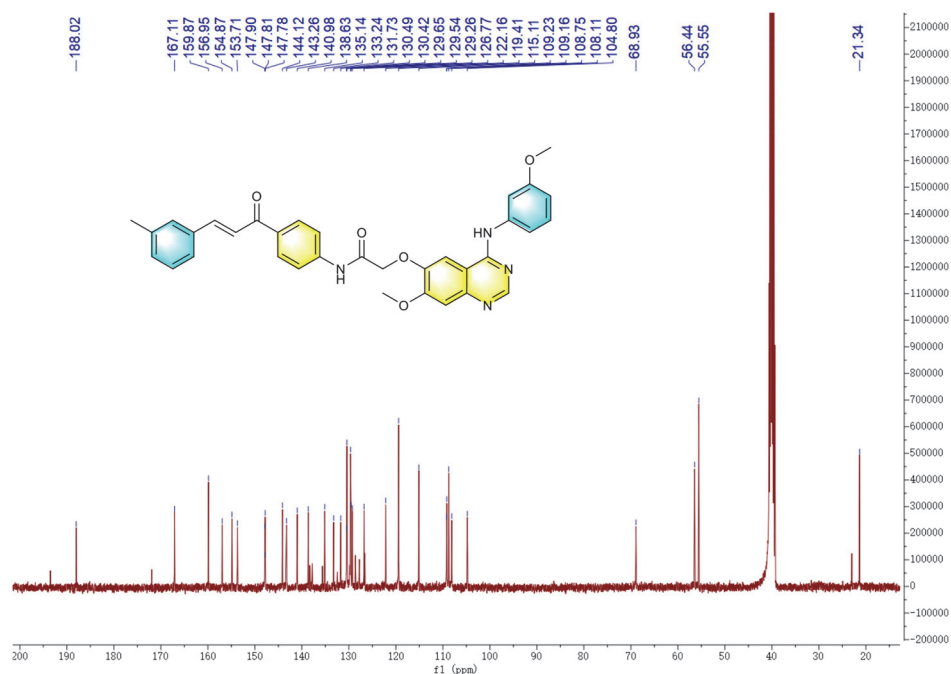


Figure. S25. ¹³C NMR spectrum of target compound 9c.

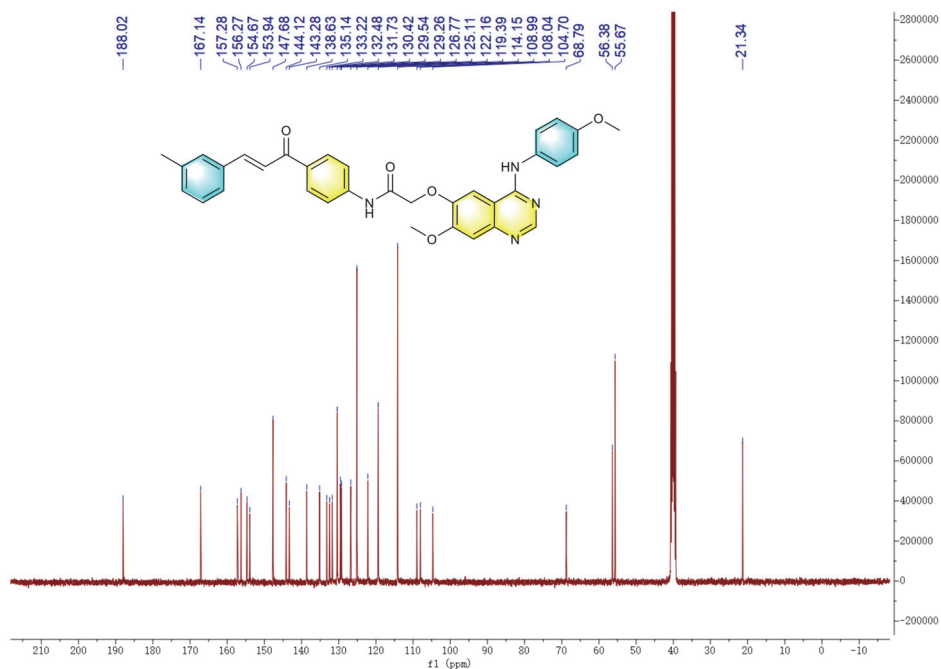
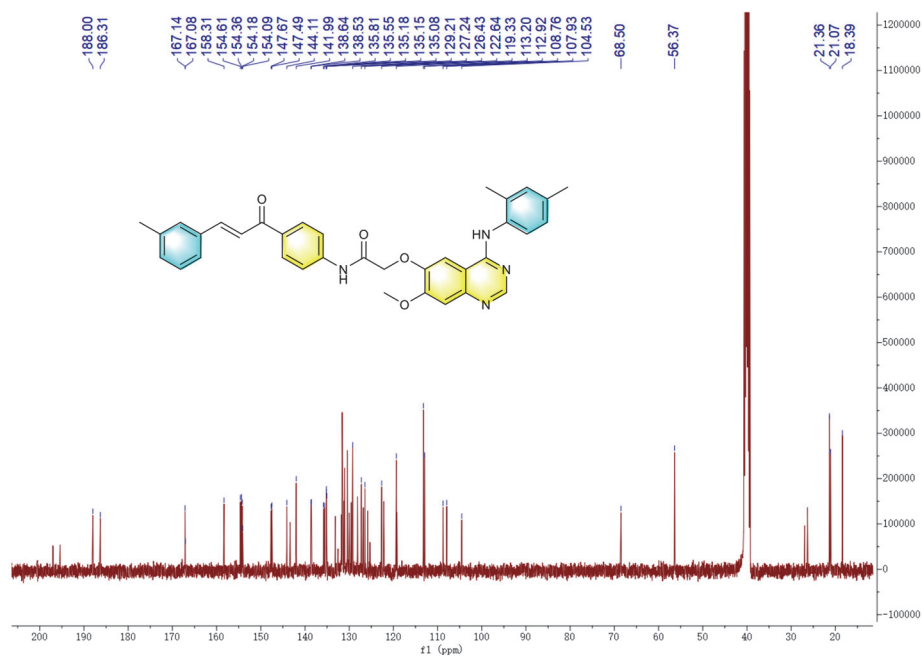
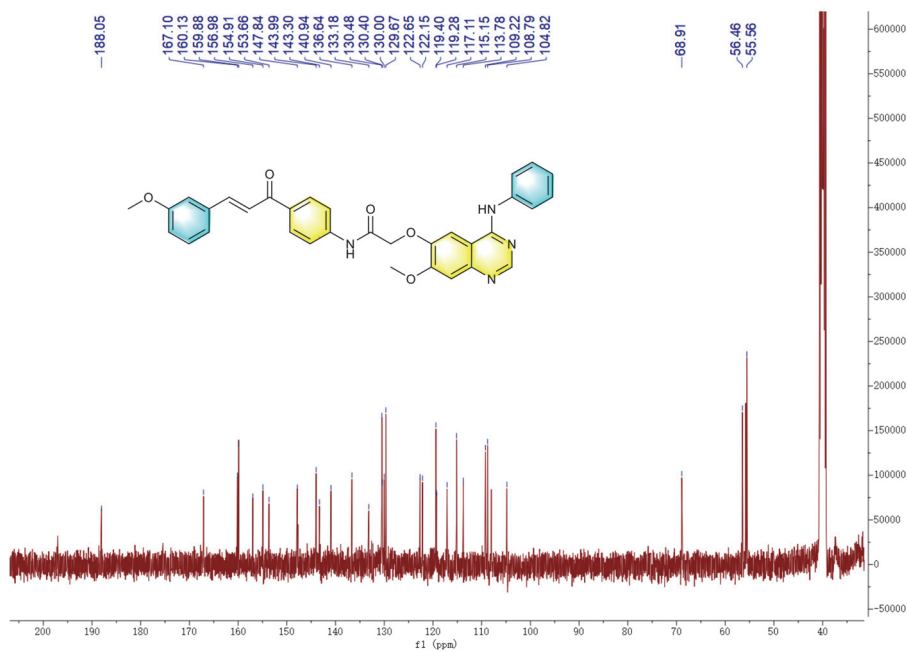


Figure. S26. ¹³C NMR spectrum of target compound 9d.

Figure. S27. ¹³C NMR spectrum of target compound 9e.Figure. S28. ¹³C NMR spectrum of target compound 9f.

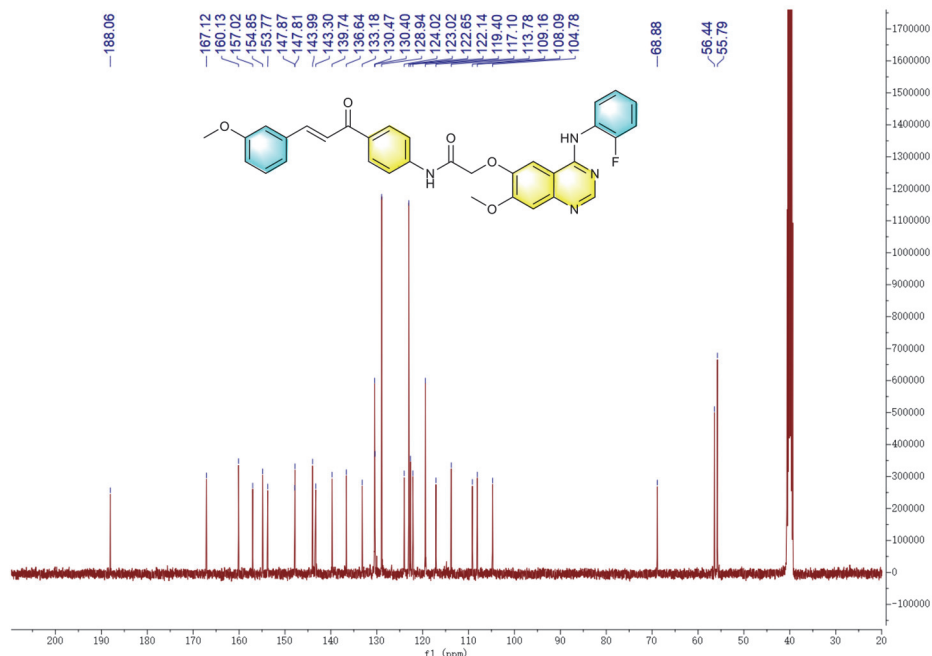


Figure. S29. ¹³C NMR spectrum of target compound 9g.

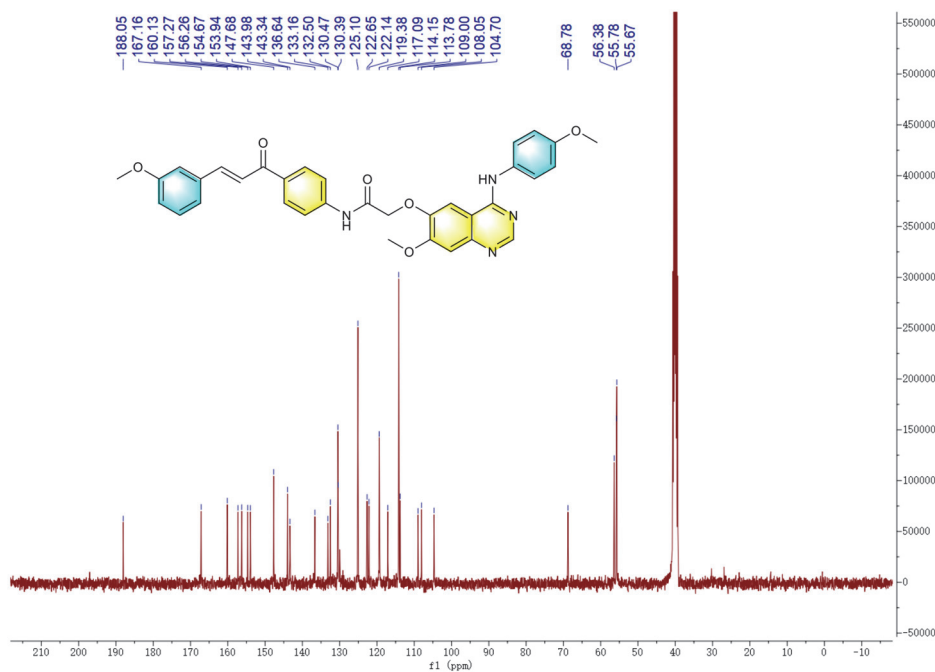


Figure. S30. ¹³C NMR spectrum of target compound 9h.

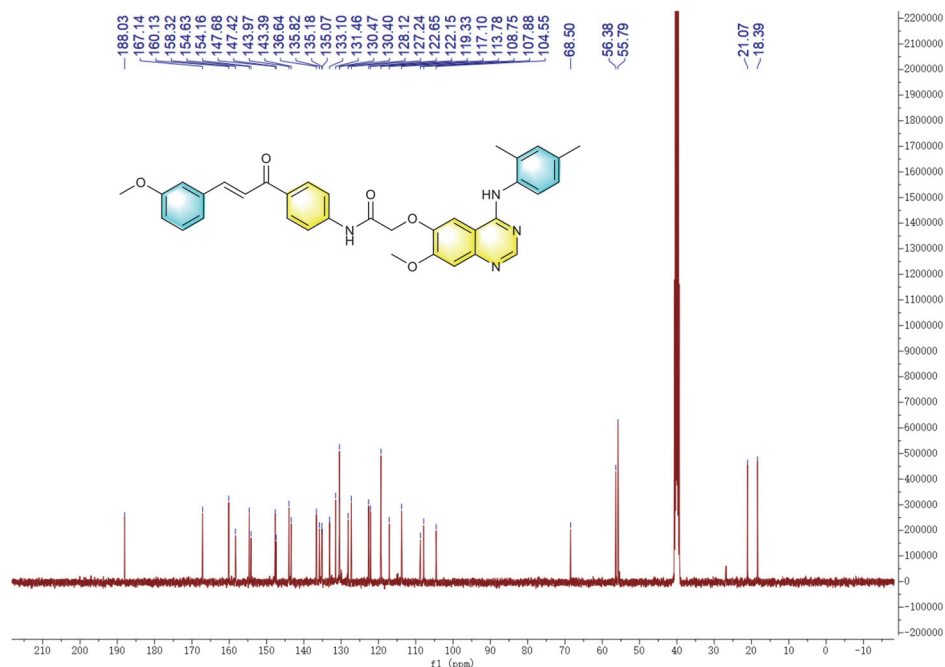


Figure. S31. ^{13}C NMR spectrum of target compound **9i**.

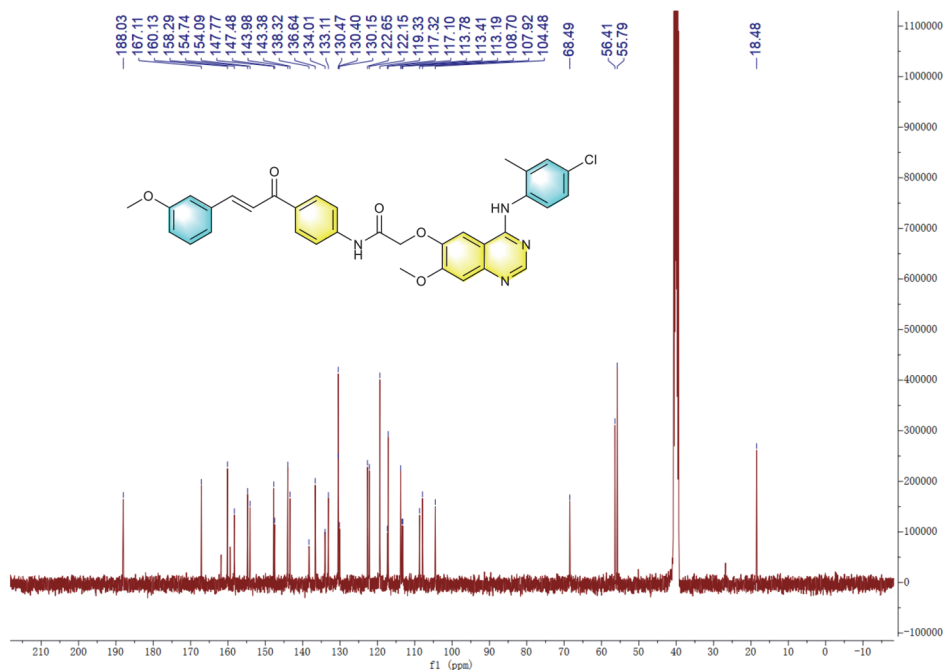


Figure. S32. ^{13}C NMR spectrum of target compound **9j**.

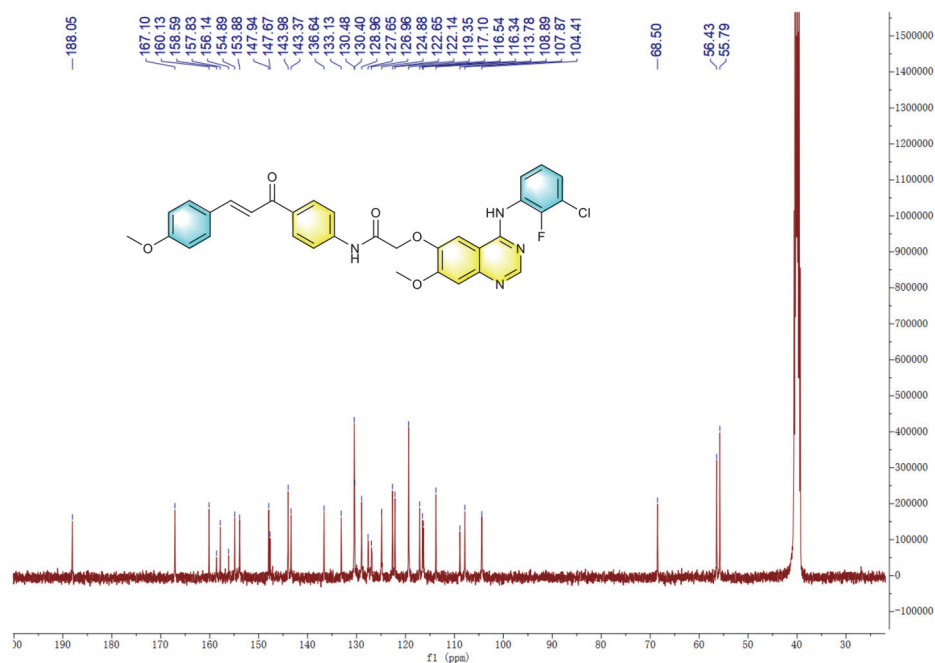


Figure. S33. ¹³C NMR spectrum of target compound 9k.

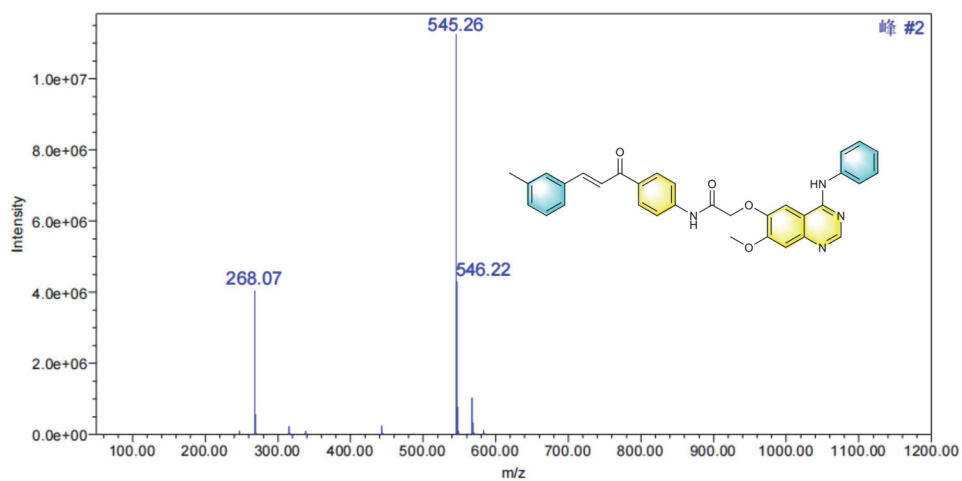


Figure. S34. MS spectrum of target compound 9a.

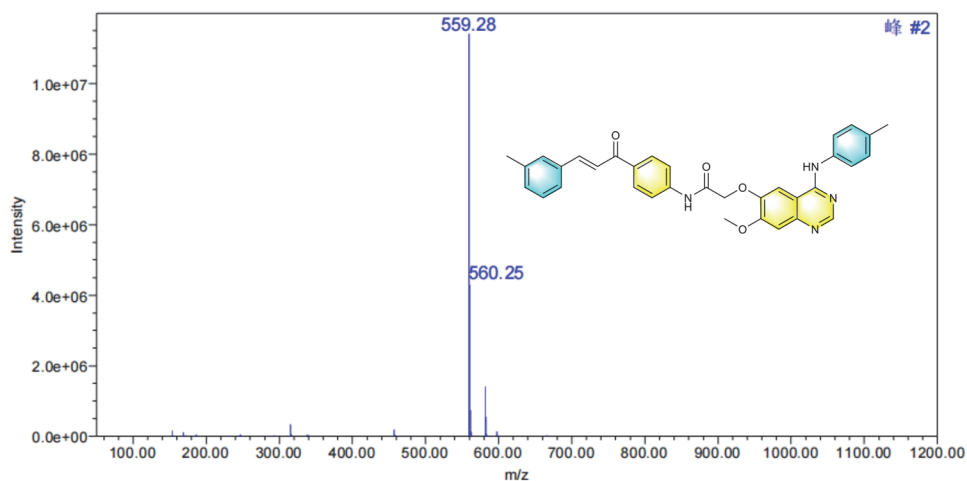


Figure. S35. MS spectrum of target compound **9b**.

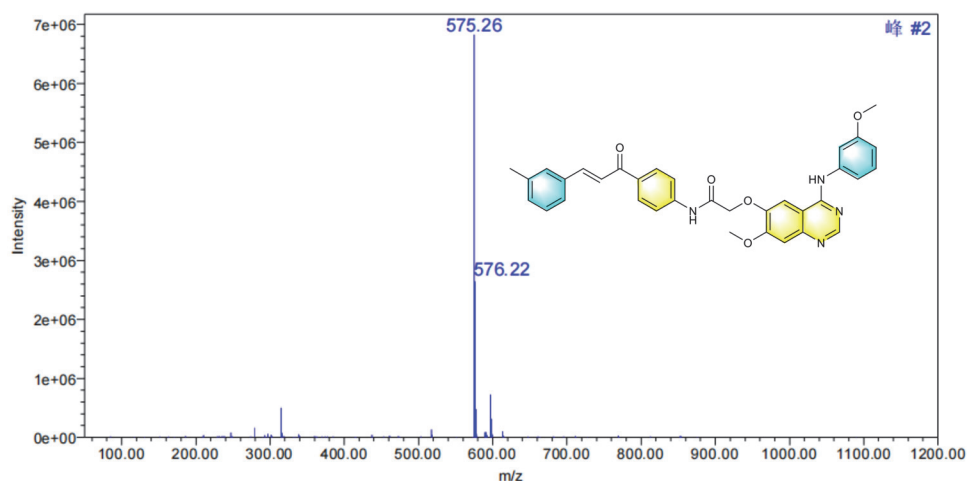


Figure. S36. MS spectrum of target compound **9c**.

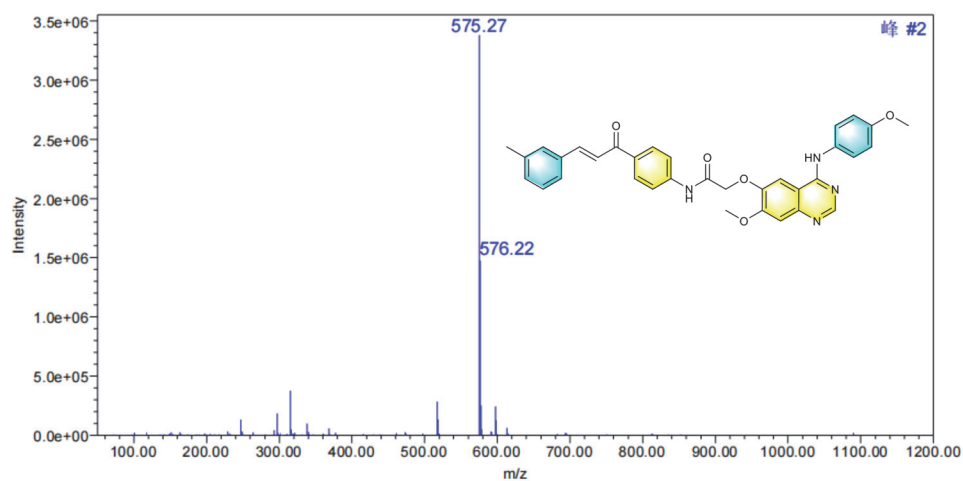


Figure. S37. MS spectrum of target compound **9d**.

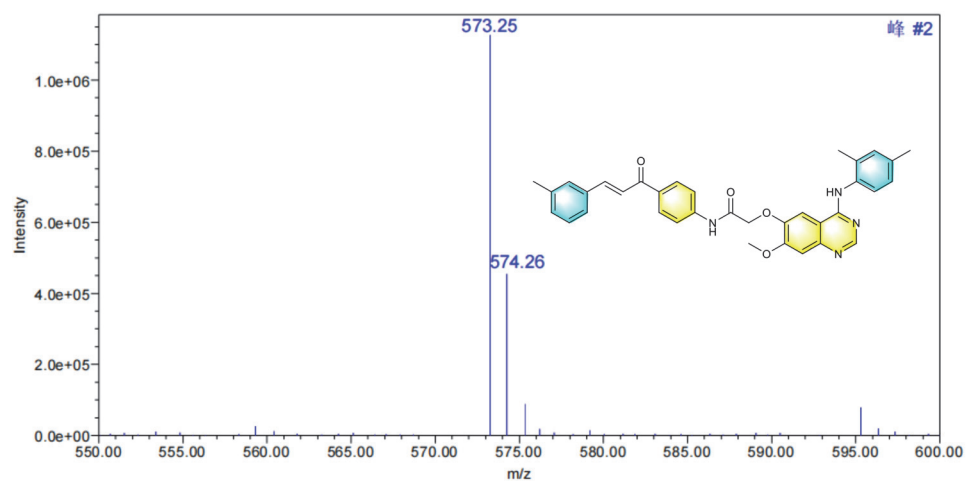
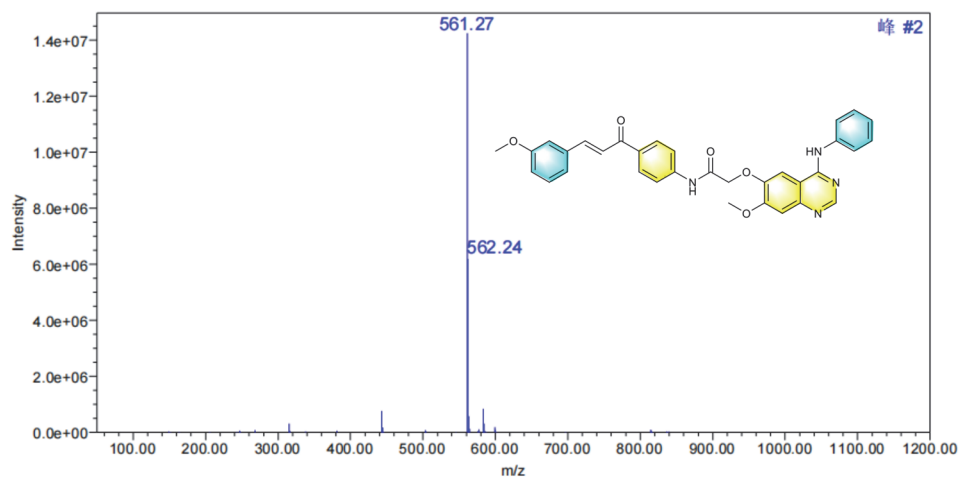
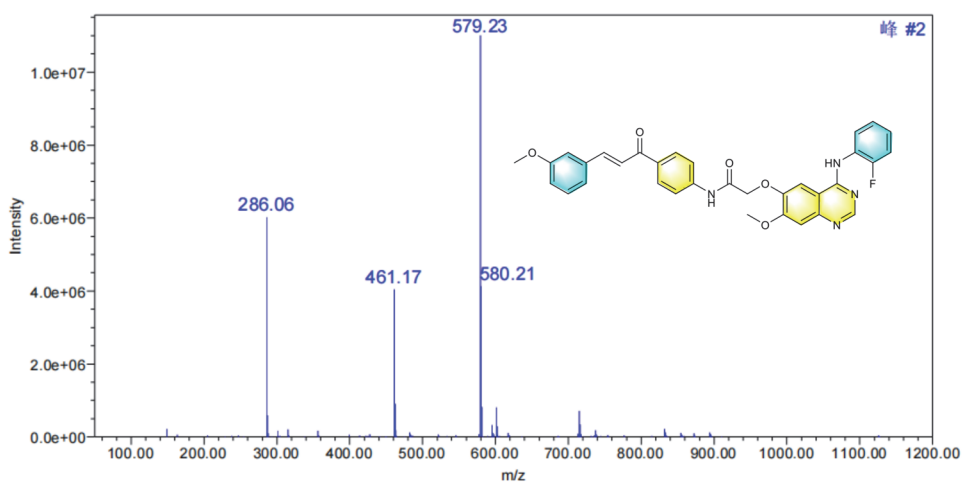


Figure. S38. MS spectrum of target compound **9e**.

**Figure. S39.** MS spectrum of target compound **9f**.**Figure. S40.** MS spectrum of target compound **9g**.

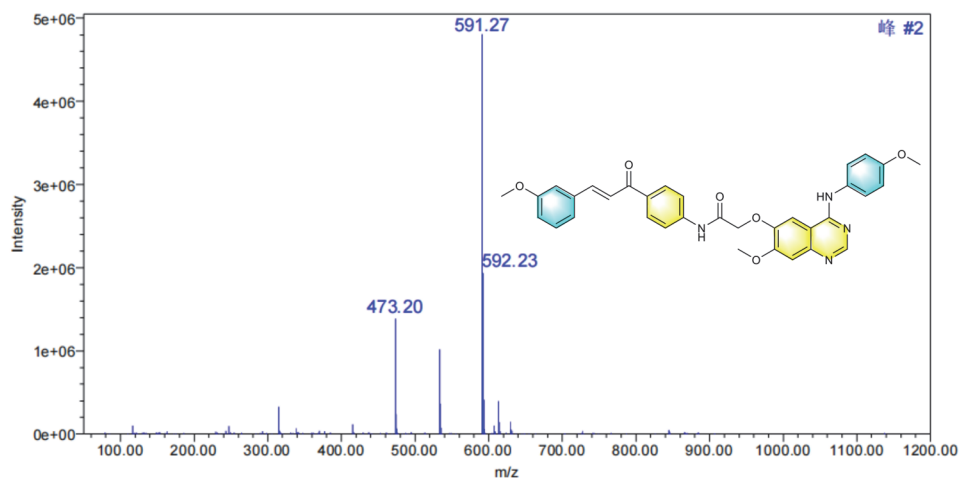


Figure. S41. MS spectrum of target compound **9h**.

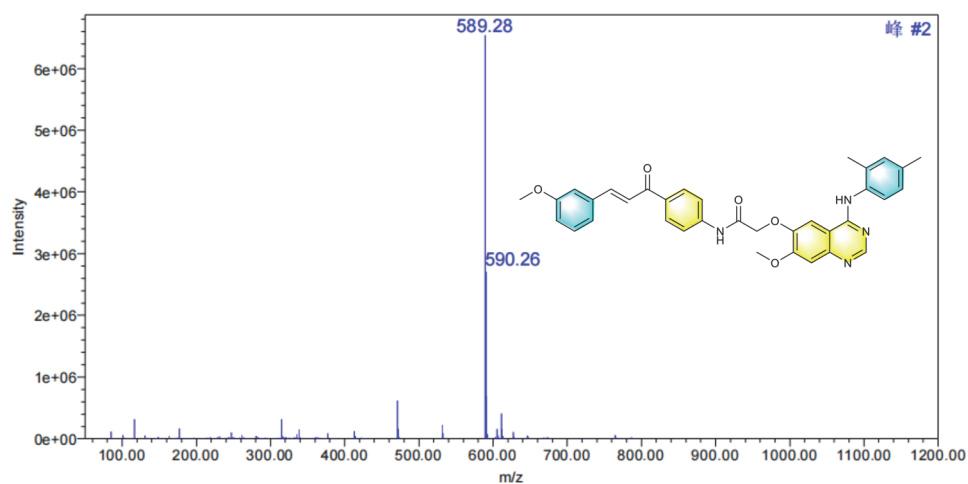


Figure. S42. MS spectrum of target compound **9i**.

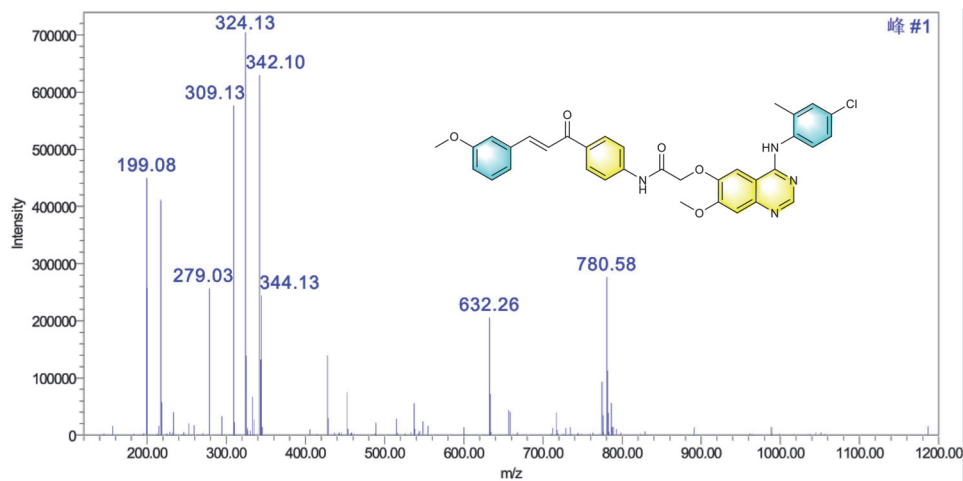


Figure. S43. MS spectrum of target compound **9j**.

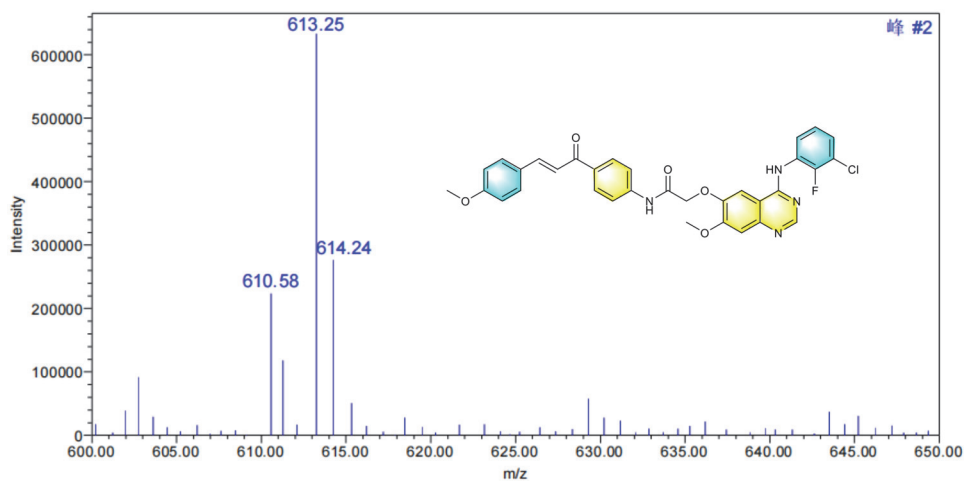


Figure. S44. MS spectrum of target compound **9k**.