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SUPPLEMENTARY MATERIAL TO

Design of novel quinazoline-chalcone hybrids as potent epidermal growth factor receptor inhibitors

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Table SI The influence of the dropping time and temperature of $POCl_3$ 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%

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

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

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

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

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

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

Table SV The influence of different reation time on the yield of intermediates **8a-8c**.

No.	Synthesized Intermediate	Addition Temperature (°C)	Yield
1		10	45%
2	8a	0	60%
3		-10	50%
4		10	47%
5	8b	0	62%
6		-10	50%
10		10	42%
11	8c	0	56%
12		-10	43%

Table SVI The influence of different reation temperture on the yield of target compounds **9a-9d**.

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

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

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

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

Yield 92%, white solid, m. p. 103.4-105.6°C. ^{1}H 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), v, cm^{-1}: 3256.35 (N-H), 2753.22 (CH_3), 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. ^{1}H 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), v, cm^{-1}: 3255.32 (N-H), 2753.03 (CH_3), 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. ^{1}H 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), v, cm^{-1}: 3223.05(N-H), 2838.37(CH_3), 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℃. ^{1}H 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), v, cm^{-1}: 3266.25 (N-H), 2865.31 (CH_3), 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℃. ^{1}H 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), v, cm^{-1}: 3245.21 (N-H), 2945.98 (CH_3), 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℃. ^{1}H 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), v, cm^{-1}: 3261.76 (N-H), 2821.38 (CH_3), 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℃. ^{1}H 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), v, cm^{-1}: 3015.64 (N-H), 2837.02 (CH_3), 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℃. ^{1}H 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), v, cm^{-1}: 3274.08 (N-H), 2927.72 (CH_3), 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℃. ^{1}H 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), v, 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℃. ^{1}H 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), v, cm^{-1}: 3625.24 (-OH), 3304.96 (N-H), 2795.30 (CH_3), 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℃. ^{1}H 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), v, cm^{-1}: 3625.20 (-OH), 3338.02 (N-H), 2836.80 (CH_3), 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. ^{1}H-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), v, cm^{-1}: 3622.50 (-OH), 3337.01 (N-H), 2837.69 (CH_3), 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. ^{1}H 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), v, cm^{-1}: 3634.86 (-OH), 3313.96 (N-H), 2843.21 (CH_3), 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. ^{1}H 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), v, cm^{-1}: 3658.18 (-OH), 3345.18 (N-H), 2859.71 (CH_3), 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. ^{1}H 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), v, cm^{-1}: 3648.79 (-OH), 3324.36 (N-H), 2814.29 (CH_3), 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. ^{1}H 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), v, cm^{-1}: 3653.90 (-OH), 3358.63 (N-H), 2819.13 (CH_3), 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. ^{1}H NMR (400 MHz, $CDCl_3$) 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), v, cm^{-1}: 3335.22 (N-H), 2872.03 (CH_3), 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. ^{1}H NMR (400 MHz, $CDCl_3$) 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), v, cm^{-1}: 3354.21 (N-H), 2834.25 (CH_3), 1645.33 (C=O), 1580.72 (C=C), 1339.81 (C-N), 1259.90 (C-O-C), 779.21 (C-Cl).

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

Yield 56%, white solid, m. p. 151.9 - 154.6°C. ^{1}H 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), v, cm^{-1}: 3333.21 (N-H), 2863.28 (CH_3), 1671.70 (C=O), 1518.66 (C=C), 1335.54 (C-N), 1264.23 (C-O-C), 777.21 (C-Cl).

*N-{4-[(2E)-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℃. ^{1}H NMR (400 MHz, $CDCl_3$) 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), *v*, cm^{-1}: 3359.01 (N-H), 2833.91 (CH_3), 1648.58 (C=O), 1569.69 (C=C_{Ar}), 1525.58 (C=N), 1398.31 (C-N), 1205.56 (C-O-C). ^{13}C 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 $C_{33}H_{28}N_4O_4$: 544.61 (100%); found: 545.26 $[M+H]^+$ (100%).

*N-{4-[(2E)-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℃. ^{1}H NMR (400 MHz, $CDCl_3$) 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), *v*, cm^{-1}: 3357.00 (N-H), 2824.79 (CH_3), 1632.97 (C=O), 1568.47 (C=C_{Ar}), 1543.06 (C=N), 1398.90 (C-N), 1206.84 (C-O-C). ^{13}C 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 $C_{34}H_{30}N_4O_4$: 558.64 (100%); found: 559.28 $[M+H]^+$ (100%).

*N-{4-[(2E)-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℃. ^{1}H NMR (400 MHz, $CDCl_3$) 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), *v*, cm^{-1}: 3315.60 (N-H), 2971.93 (CH_3), 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). ^{13}C 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 $C_{34}H_{30}N_4O_5$: 574.64 (100%); found: 575.26 $[M+H]^+$ (100%).

*N-{4-[(2E)-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℃. ^{1}H NMR (400 MHz, $CDCl_3$) 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), *v*, cm^{-1}: 3356.13 (N-H), 3081.78 (CH_3), 1648.28 (C=O), 1568.00 (C=C_{Ar}), 1511.29 (C=C), 1471.31 (C=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 $C_{34}H_{30}N_4O_5$: 574.64 (100%); found: 575.27 $[M+H]^+$ (100%).

*N-{4-[(2E)-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. ^{1}H 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), *v*, cm^{-1}: 3362.08 (N-H), 2915.42 (CH_3), 1631.59 (C=O), 1569.52 (C=C_{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 $C_{35}H_{32}N_4O_4$: 572.66 (100%); found: 573.25 $[M+H]^+$ (100%).

*N-{4-[(2E)-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. ^{1}H 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), *v*, cm^{-1}: 3357.92 (N-H), 2833.33 (CH_3), 1631.84 (C=O), 1570.15 (C=C_{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 $C_{33}H_{28}N_4O_5$: 560.61 (100%); found: 561.27 $[M+H]^+$ (100%).

*N-{4-[(2E)-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. ^{1}H NMR (400 MHz, 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), *v*, cm^{-1}: 3359.45 (N-H), 1650.47 (C=O), 1572.11 (C=C_{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 $C_{33}H_{27}FN_4O_5$: 578.60 (100%); found: 579.23 $[M+H]^+$ (100%).

*N-{4-[(2E)-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. ^{1}H 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), *v*, cm^{-1}: 3358.21 (N-H), 2836.70 (CH_3), 1649.02 (C=O), 1570.39(C=C_{Ar}), 1541.06 (C=N), 1401.01 (C-N), 1234.63 (C-O-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 $C_{34}H_{30}N_4O_6$: 590.64 (100%); found: 591.27 $[M+H]^+$ (100%).

*N-{4-[(2E)-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℃. ^{1}H NMR (400 MHz, 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), v, cm^{-1}: 3319.12 (N-H), 2972.56 (CH_3), 1642.89 (C=O), 1570.77 (C=C_{Ar}), 1514.69 (C=N), 1429.55 (C-C), 1392.01 (C-N), 1276.98 (C-O-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 $C_{35}H_{32}N_4O_5$: 588.66 (100%); found: 589.28 $[M+H]^+$ (100%).

*N-{4-[(2E)-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℃. ^{1}H 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), v, cm^{-1}: 3365.25 (N-H), 2835.28 (CH_3), 1650.55 (C=O), 1572.46 (C=C_{Ar}), 1541.55 (C=N), 1401.62 (C-N), 1202.72 (C-O-C), 784.76 (C-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 $C_{34}H_{29}ClN_4O_5$: 609.08 (100%); found: 632.26 $[M+Na]^+$ (100%).

*N-{4-[(2E)-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℃. ^{1}H 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), v, cm^{-1}: 3352.98 (N-H), 2833.62 (CH_3), 1642.29 (C=O), 1586.70 (C=C_{Ar}), 1541.09(C=N), 1393.64 (C-N), 1215.32 (C-O-C), 984.60 (C-F), 752.12 (C-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 $C_{33}H_{26}ClFN_4O_5$: 613.04 (100%); found: 613.25 $[M]^+$ (100%).

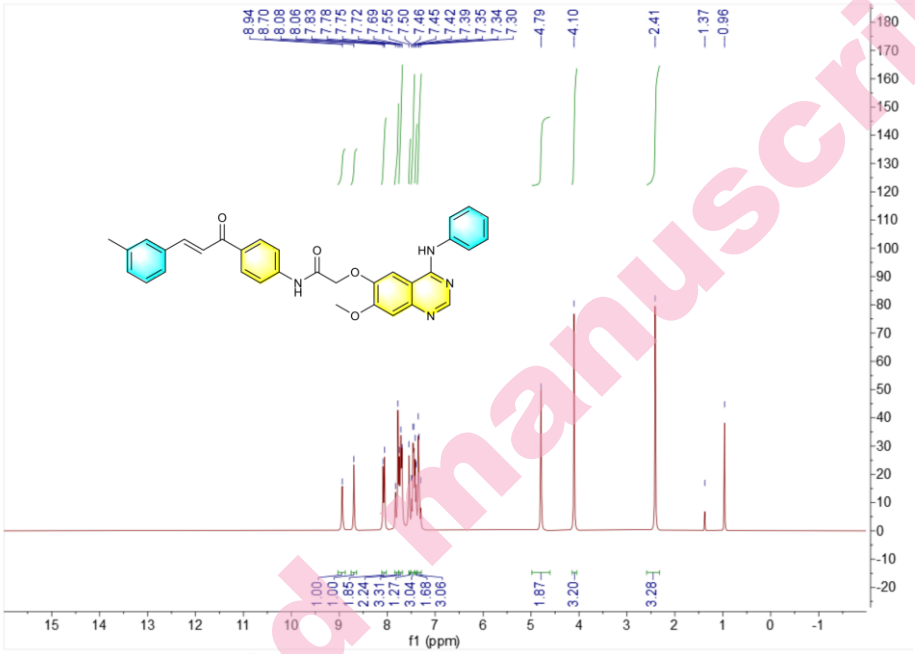

Figure. S1. ^{1}H NMR spectrum of target compound **9a**.

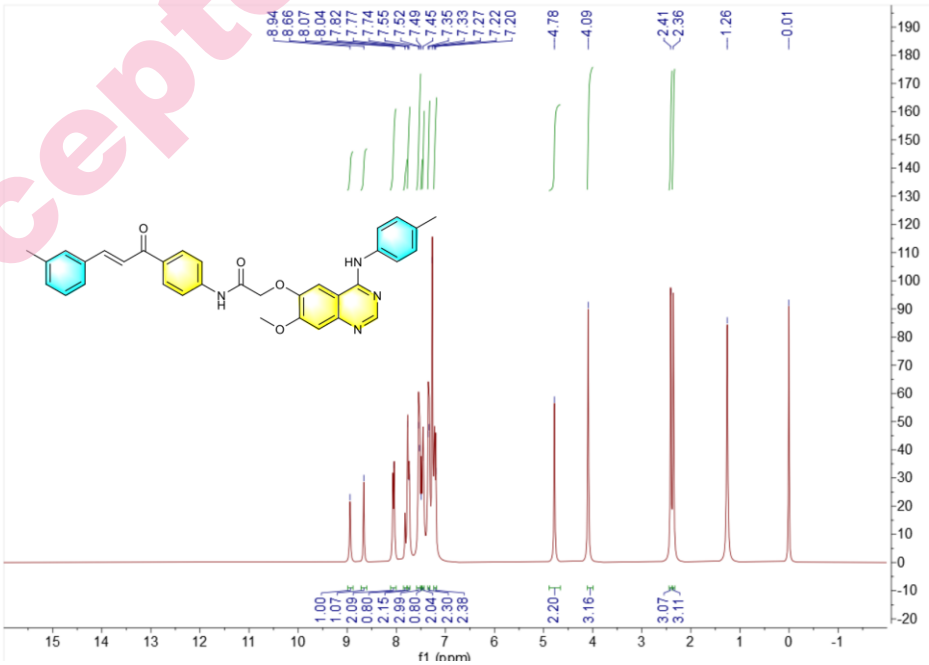

Figure. S2. ^{1}H NMR spectrum of target compound **9b**.

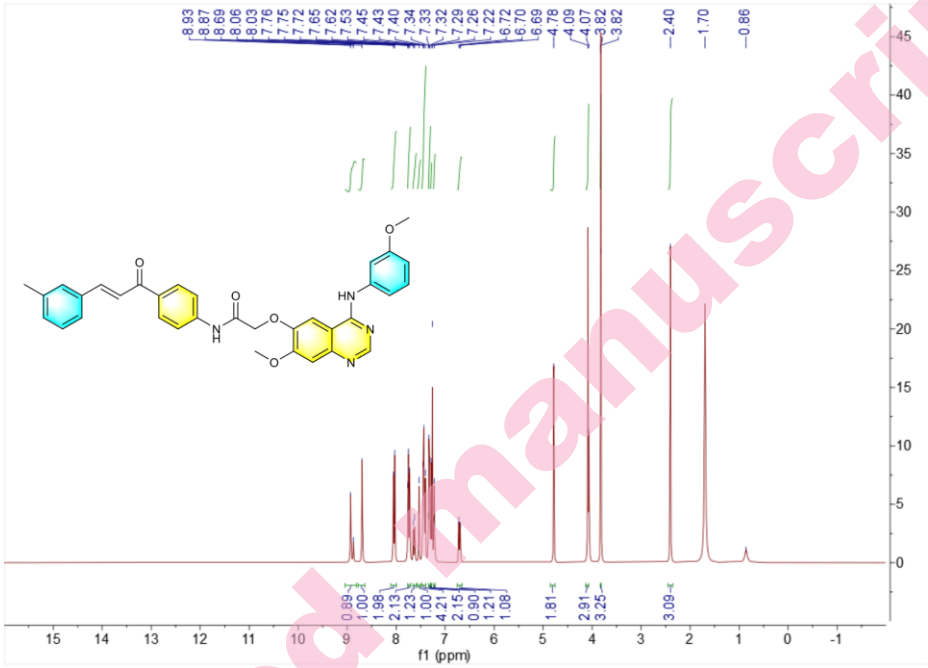

Figure. S3. ^{1}H NMR spectrum of target compound **9c**.

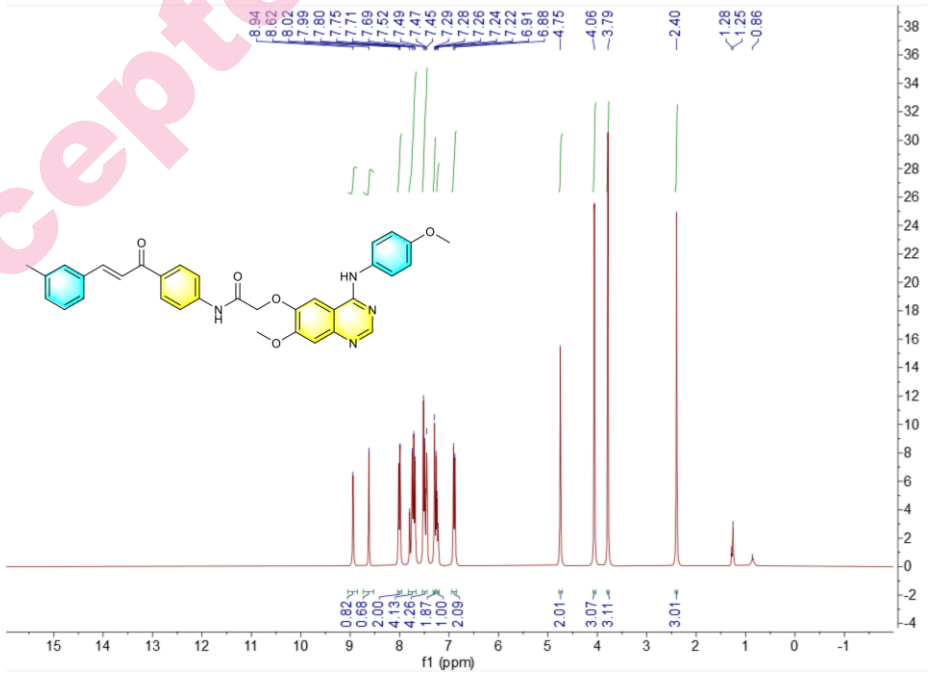

Figure. S4. ^{1}H NMR spectrum of target compound **9d**.

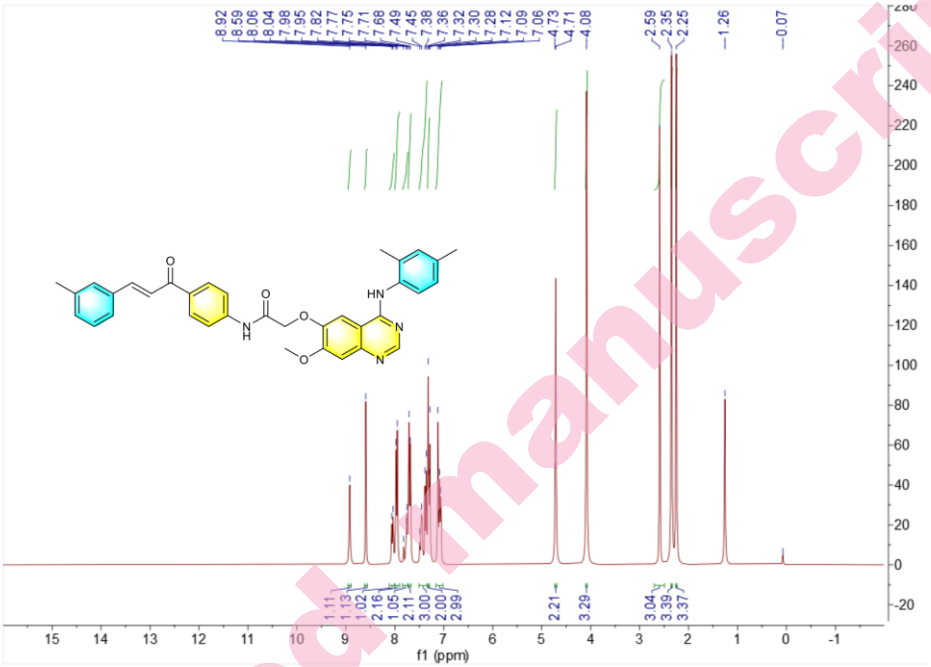

Figure. S5. ^{1}H NMR spectrum of target compound **9e**.

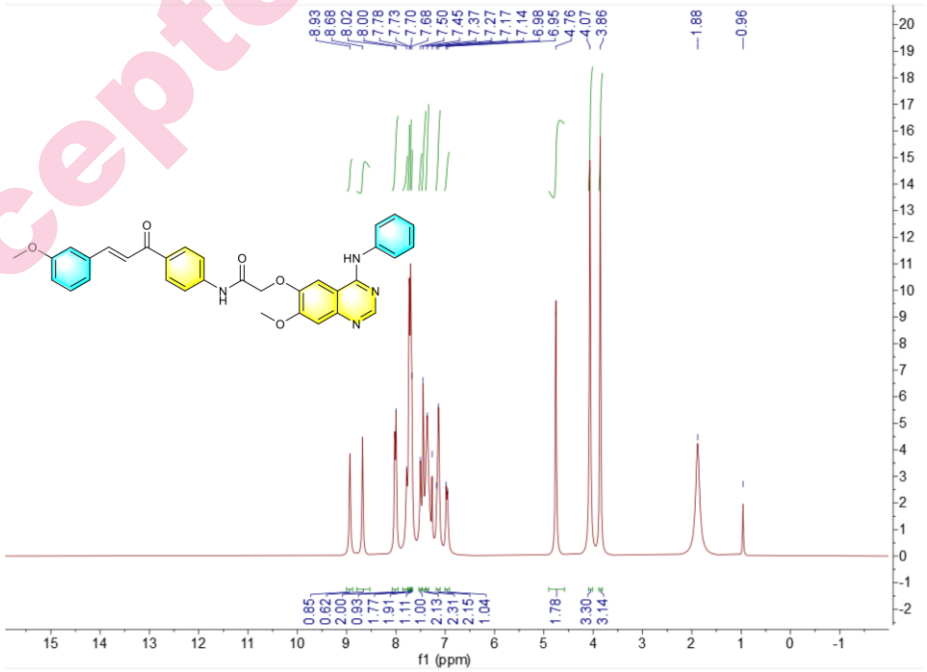

Figure. S6. ^{1}H NMR spectrum of target compound **9f**.

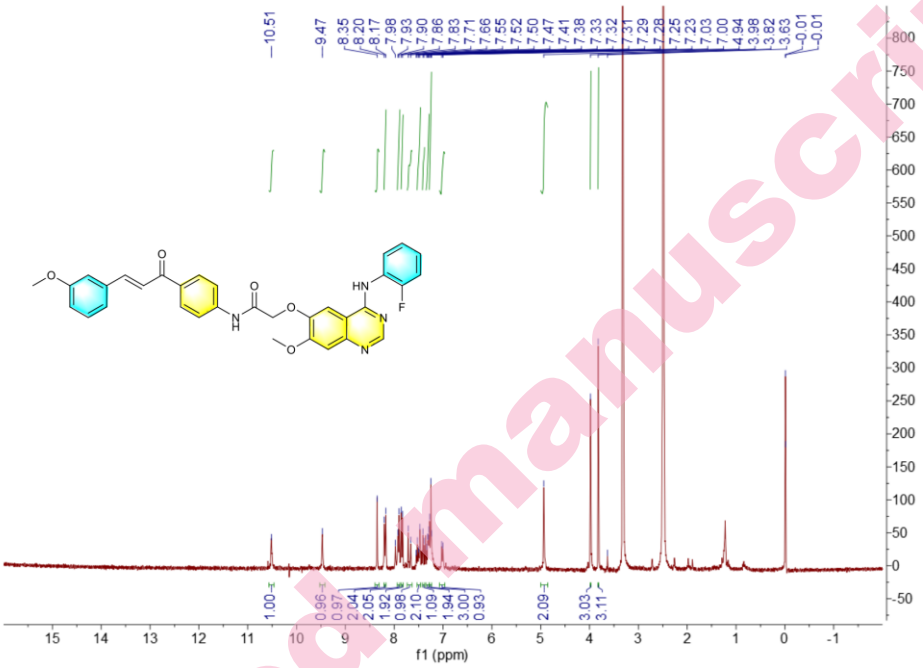

Figure. S7. ^{1}H NMR spectrum of target compound **9g**.

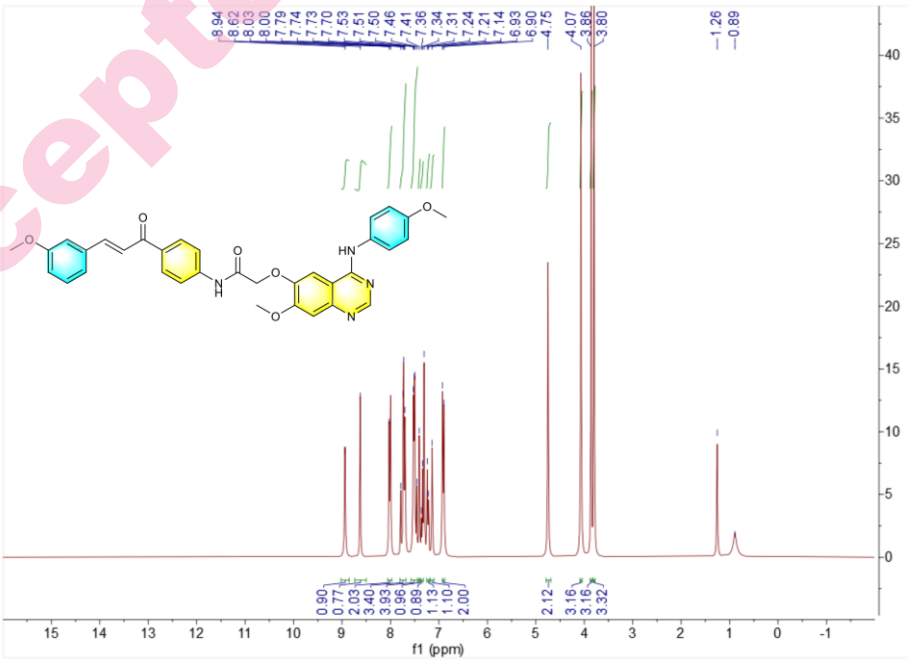

Figure. S8. ^{1}H NMR spectrum of target compound **9h**.

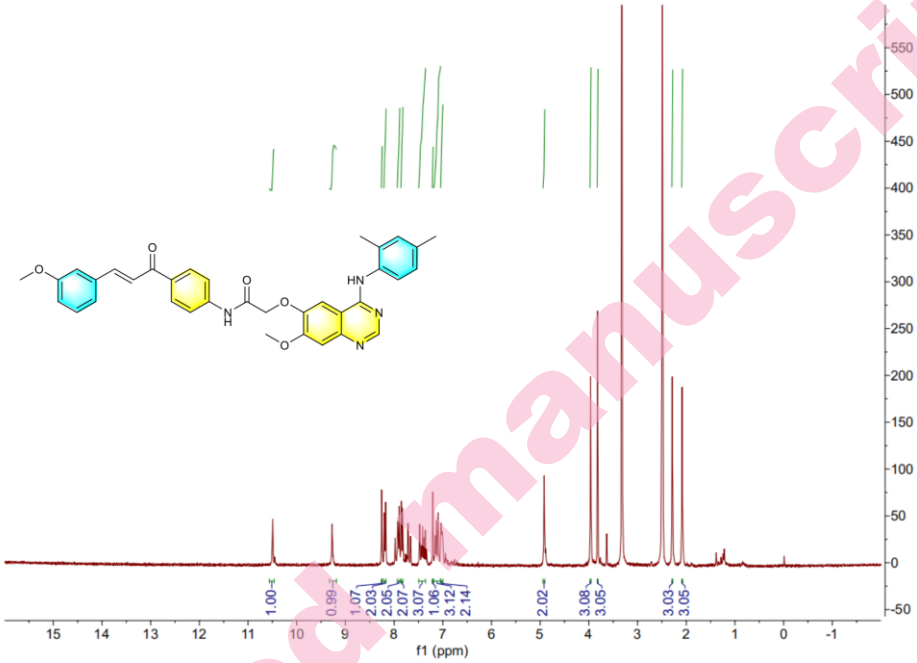

Figure. S9. ^{1}H NMR spectrum of target compound **9i**.

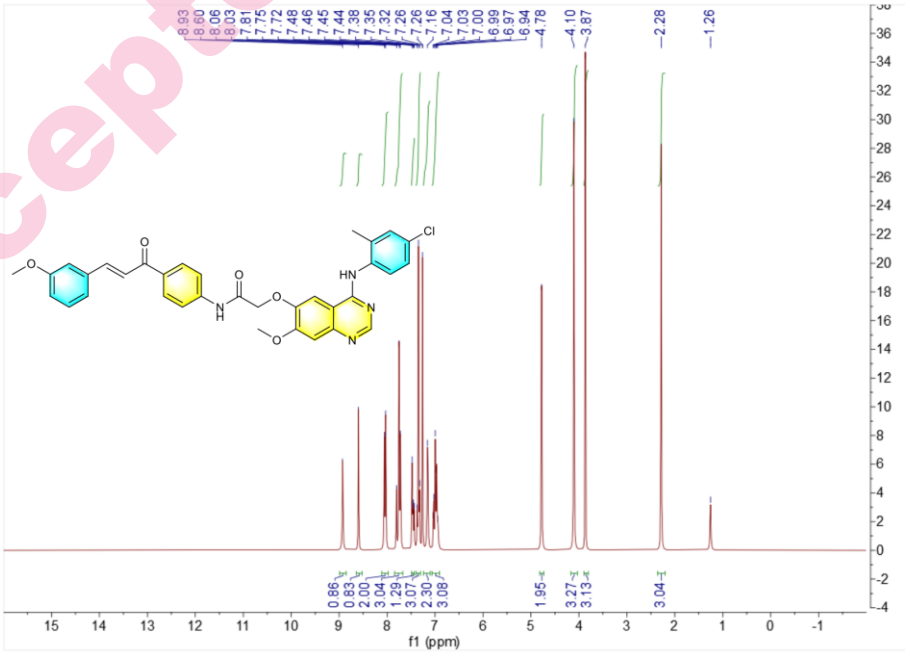

Figure. S10. ^{1}H NMR spectrum of target compound **9j**.

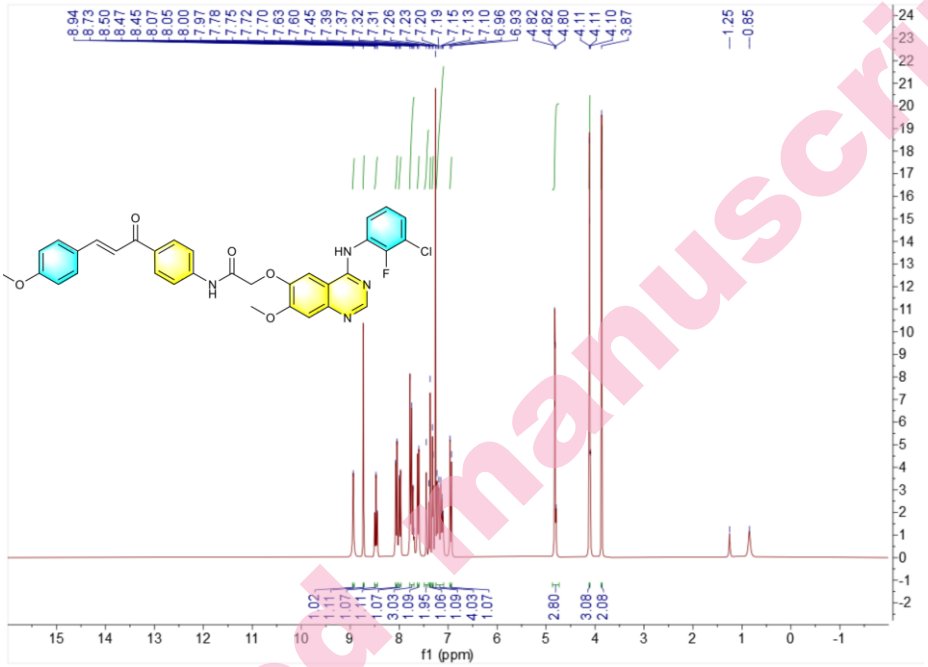

Figure. S11. ^{1}H NMR spectrum of target compound **9k**.

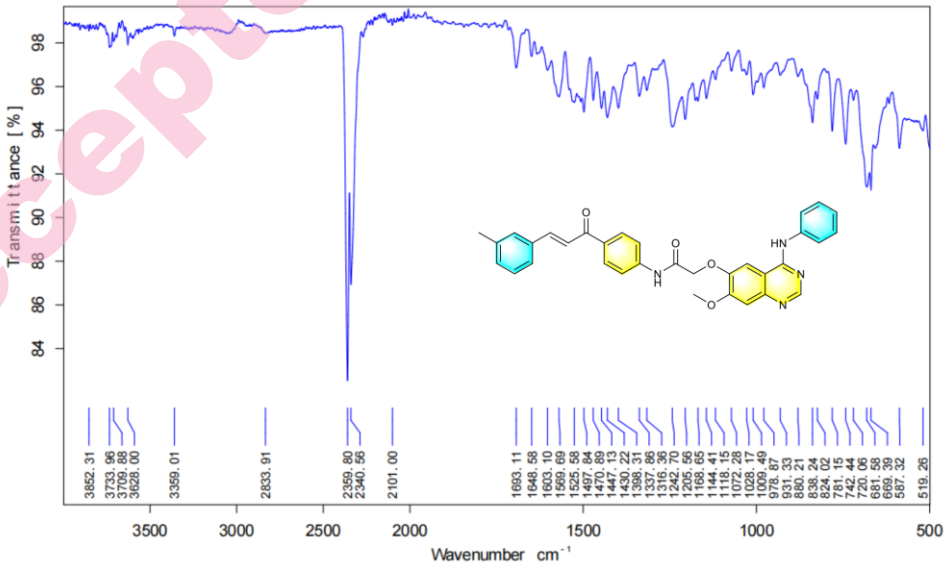

Figure. S12. IR spectrum of target compound **9a**.

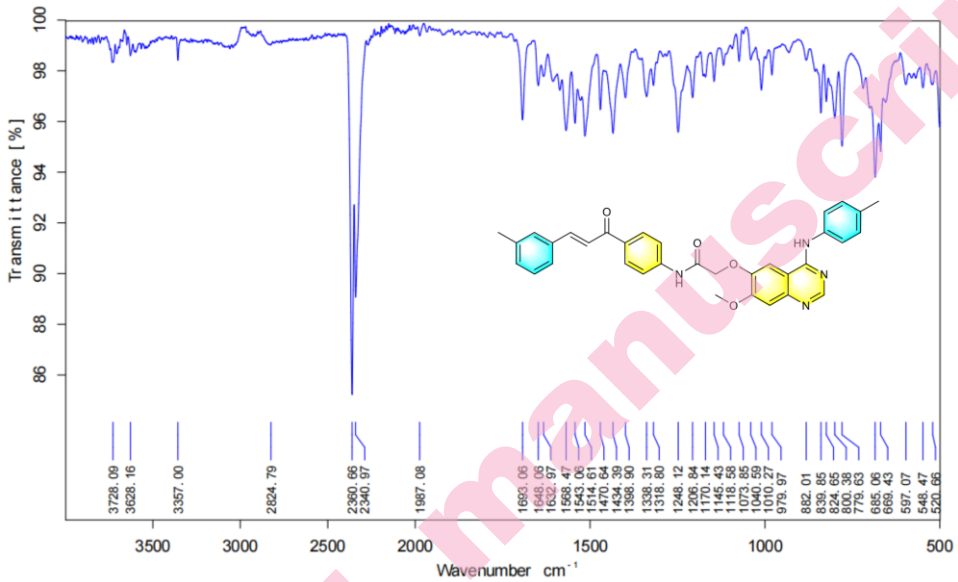

Figure. S13. IR spectrum of target compound **9b**.

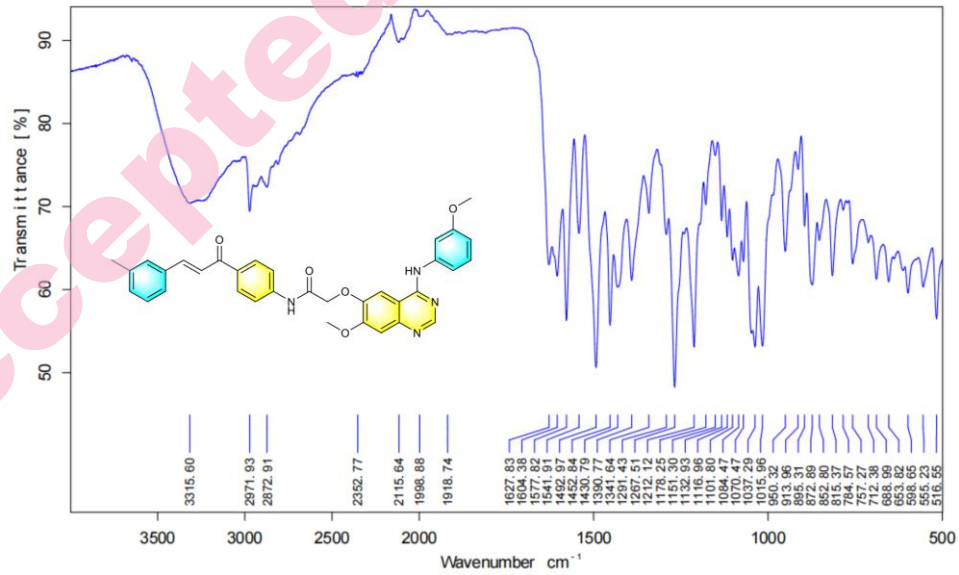

Figure. S14. IR spectrum of target compound **9c**.

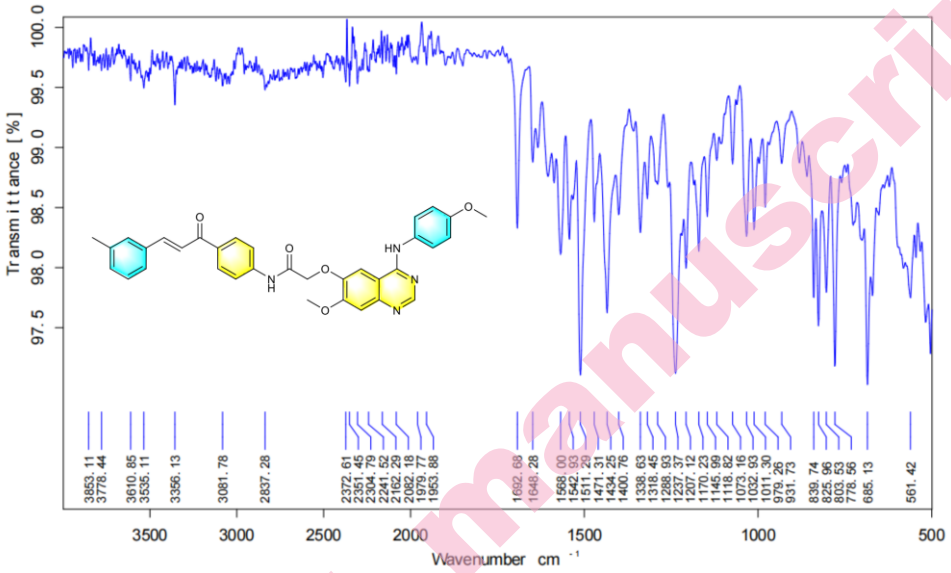

Figure. S15. IR spectrum of target compound **9d**.

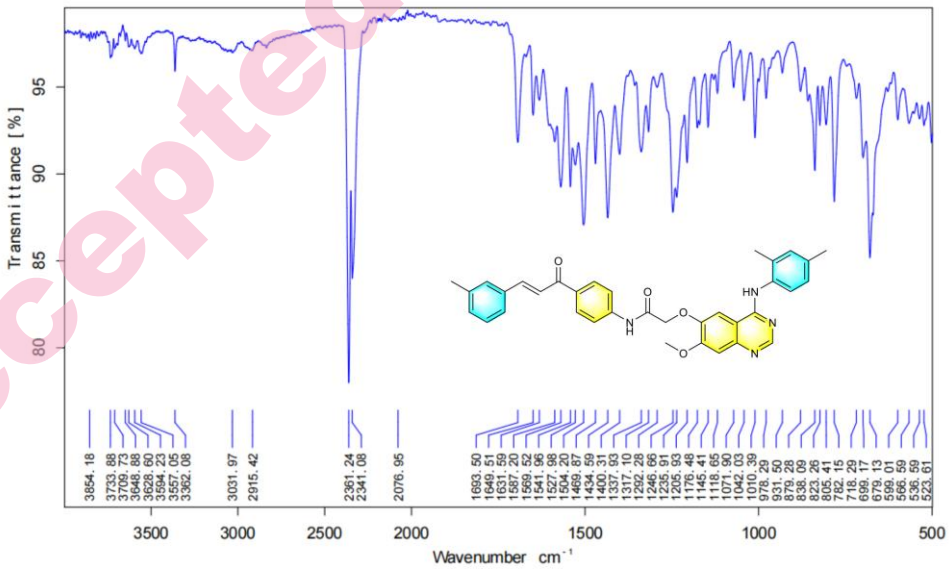

Figure. S16. IR spectrum of target compound **9e**.

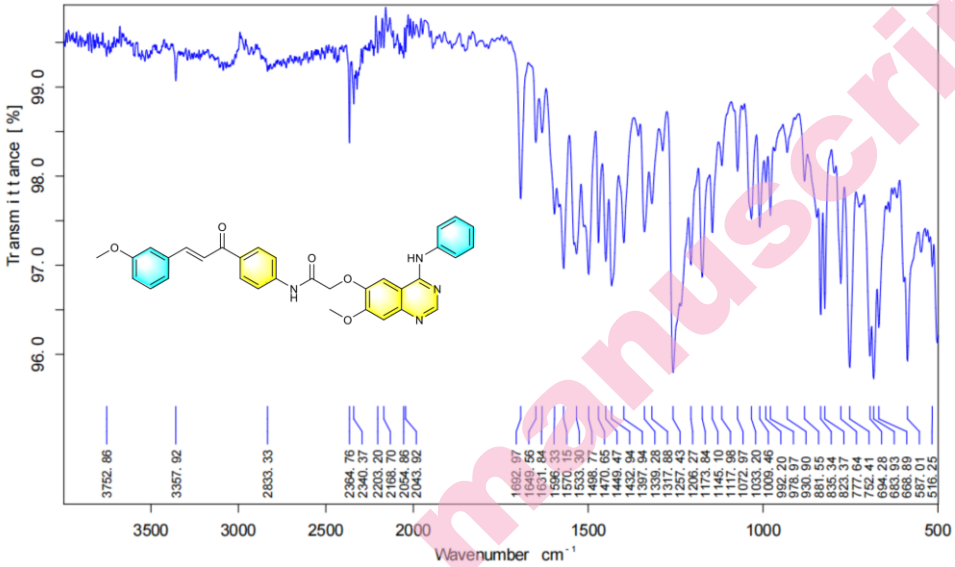

Figure. S17. IR spectrum of target compound **9f**.

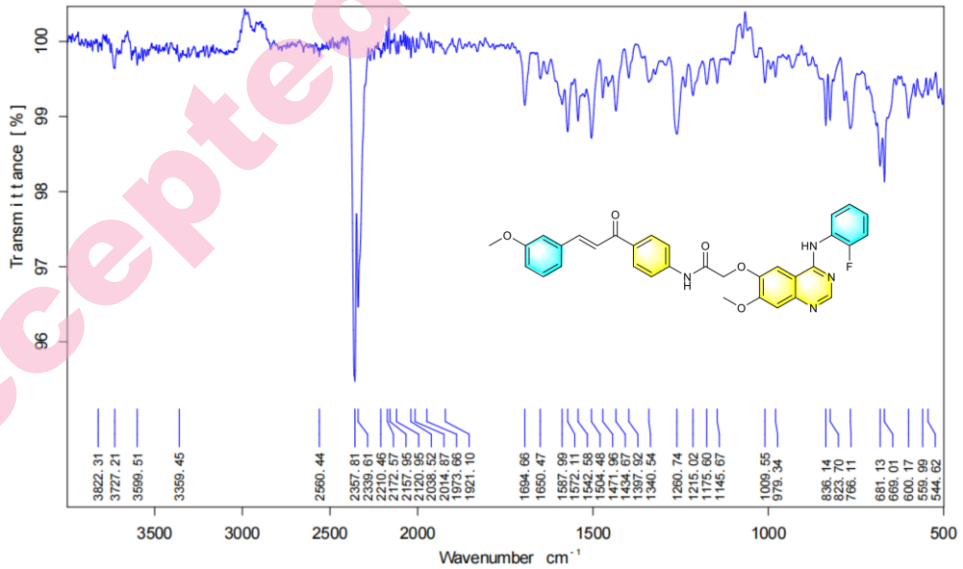

Figure. S18. IR spectrum of target compound **9g**.

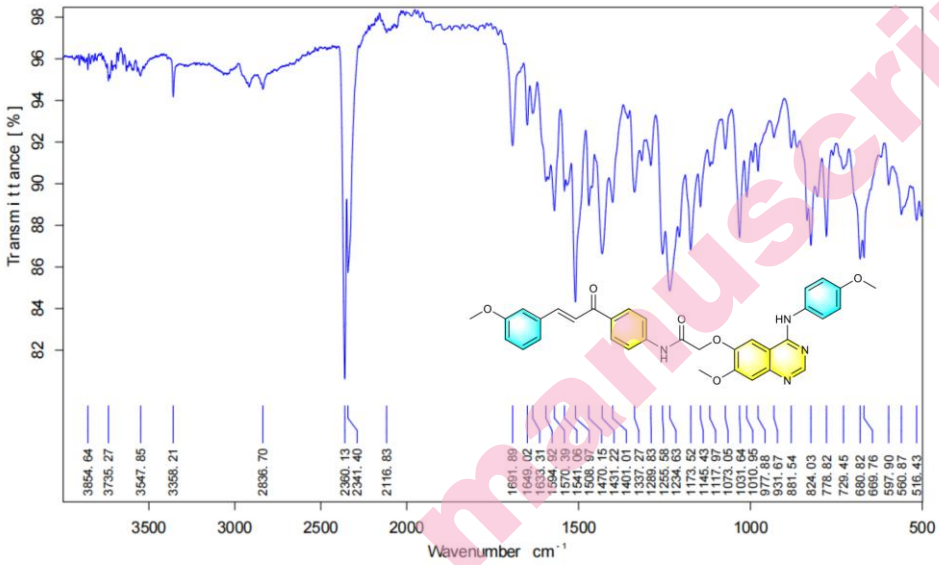

Figure. S19. IR spectrum of target compound **9h**.

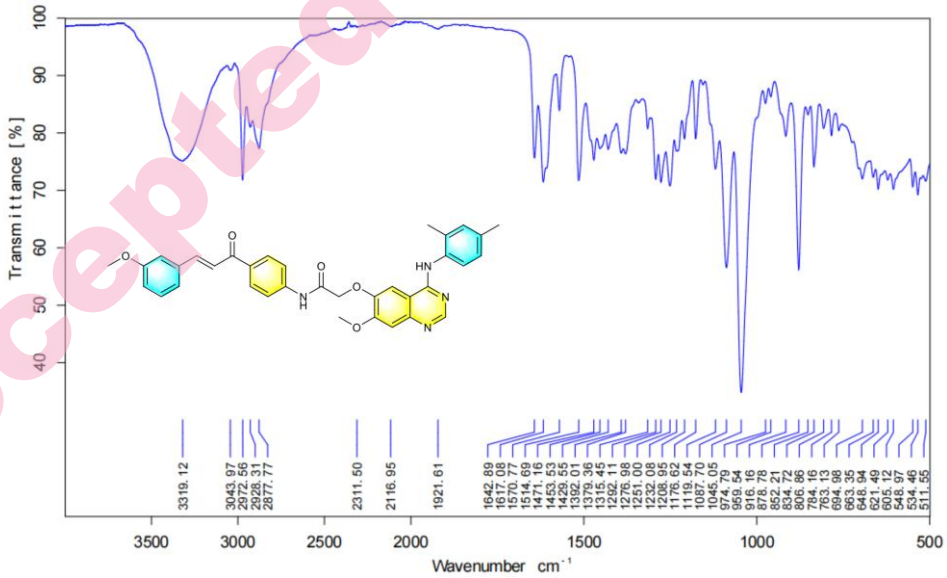

Figure. S20. IR spectrum of target compound **9i**.

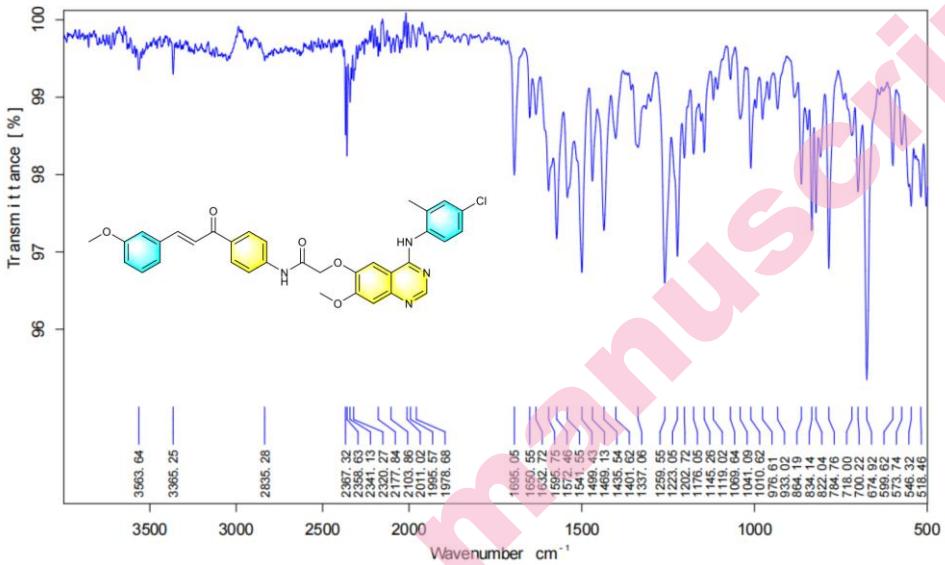

Figure. S21. IR spectrum of target compound **9j**.

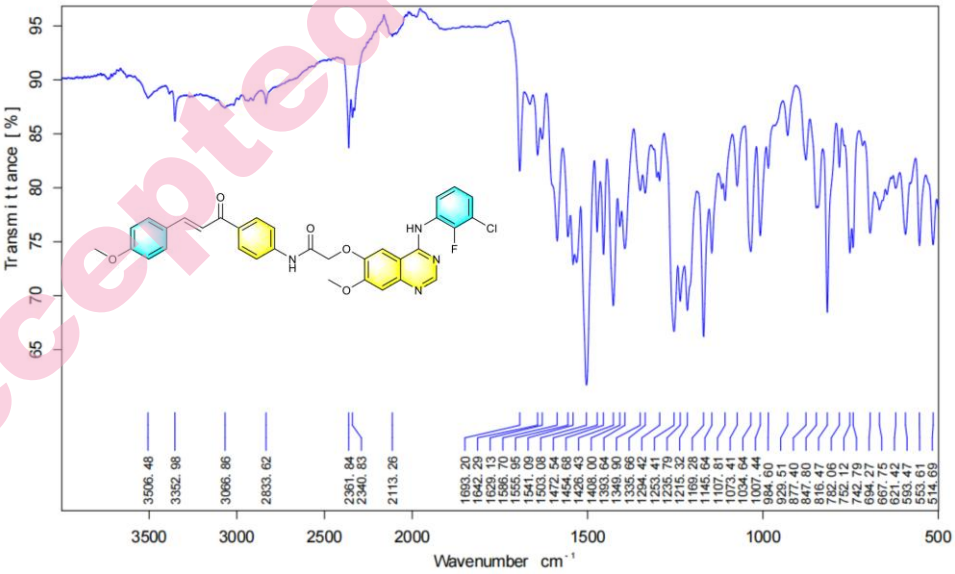

Figure. S22. IR spectrum of target compound **9k**.

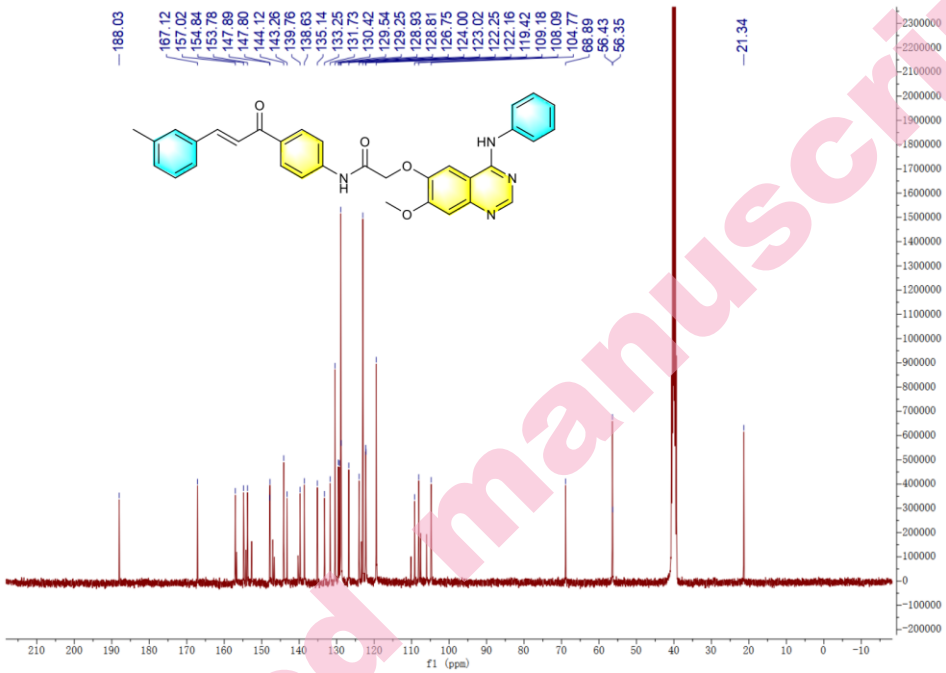

Figure. S23. ^{13}C NMR spectrum of target compound **9a**.

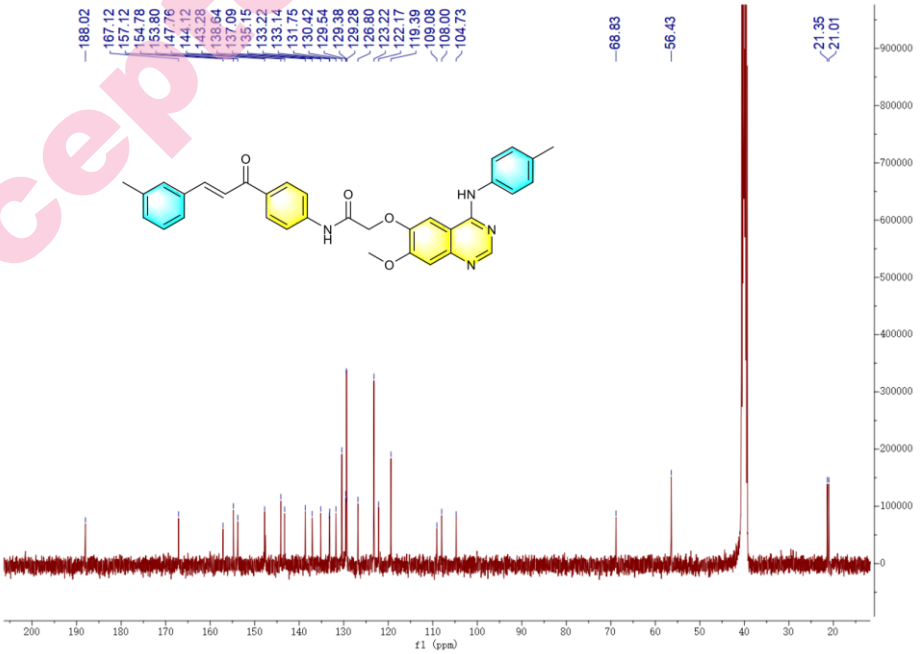

Figure. S24. ^{13}C NMR spectrum of target compound **9b**.

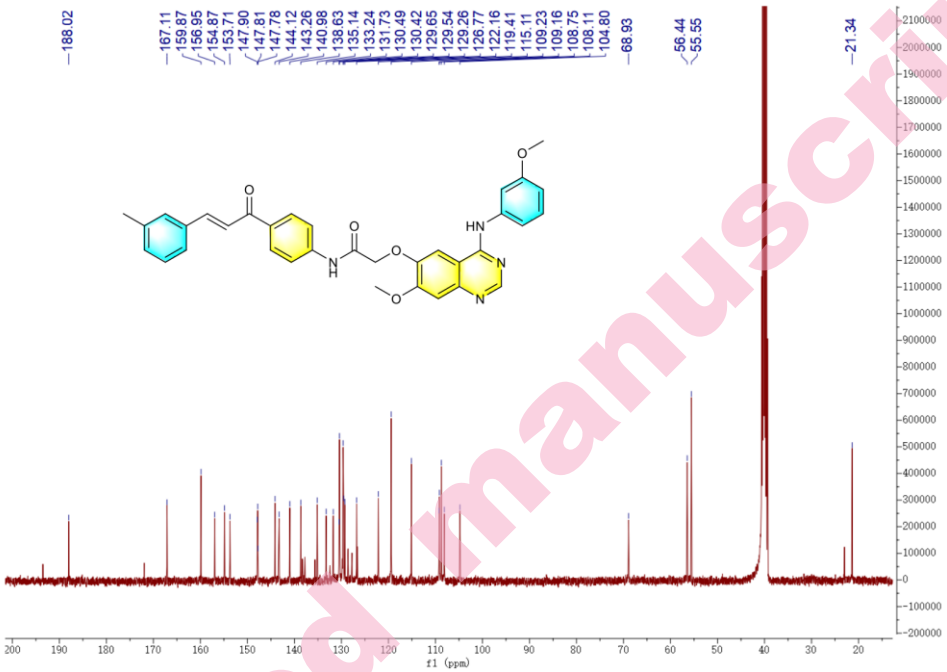

Figure. S25. ^{13}C NMR spectrum of target compound **9c**.

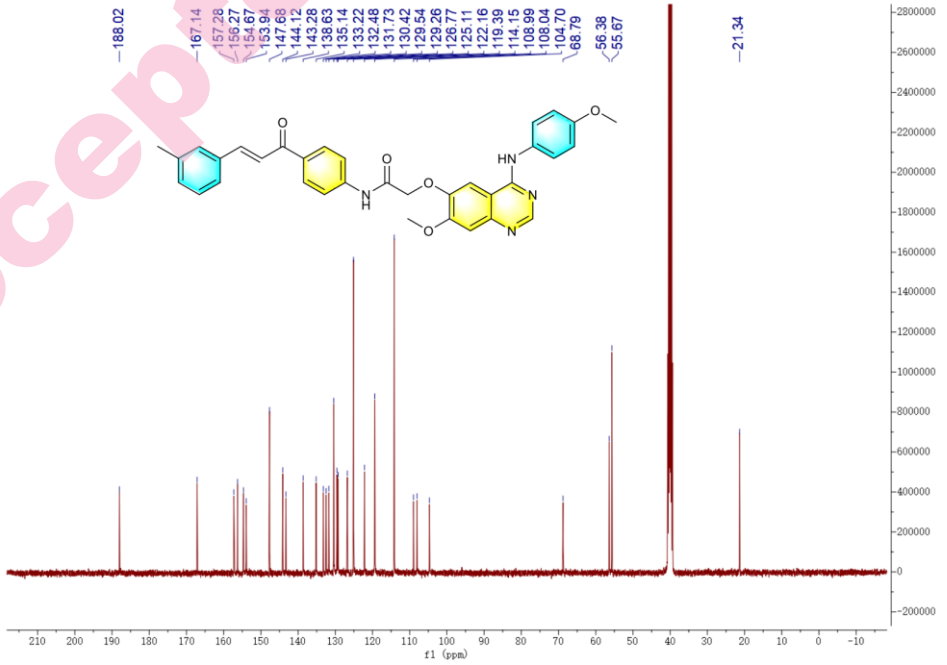

Figure. S26. ^{13}C NMR spectrum of target compound **9d**.

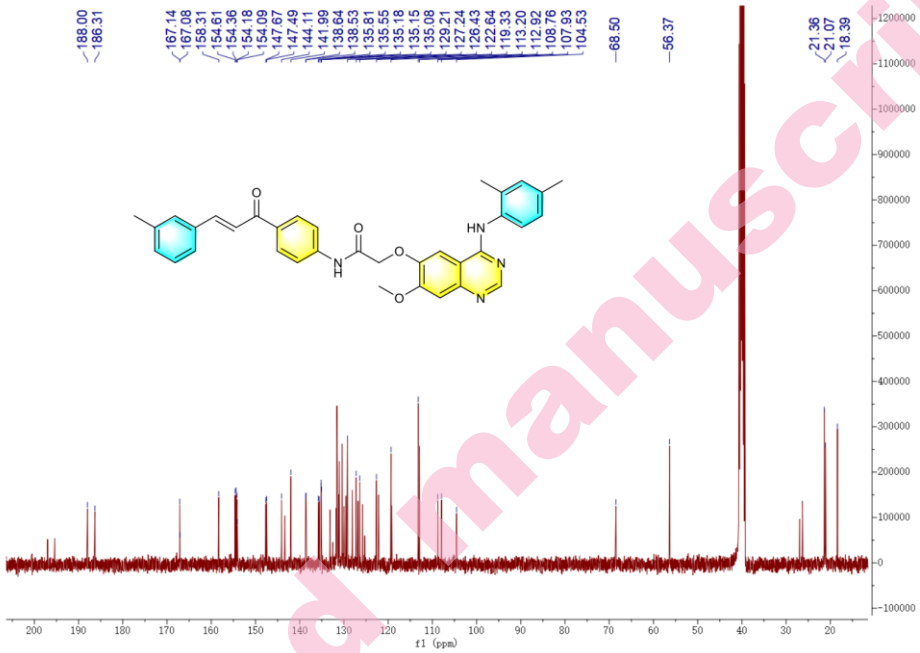

Figure. S27. ^{13}C NMR spectrum of target compound **9e**.

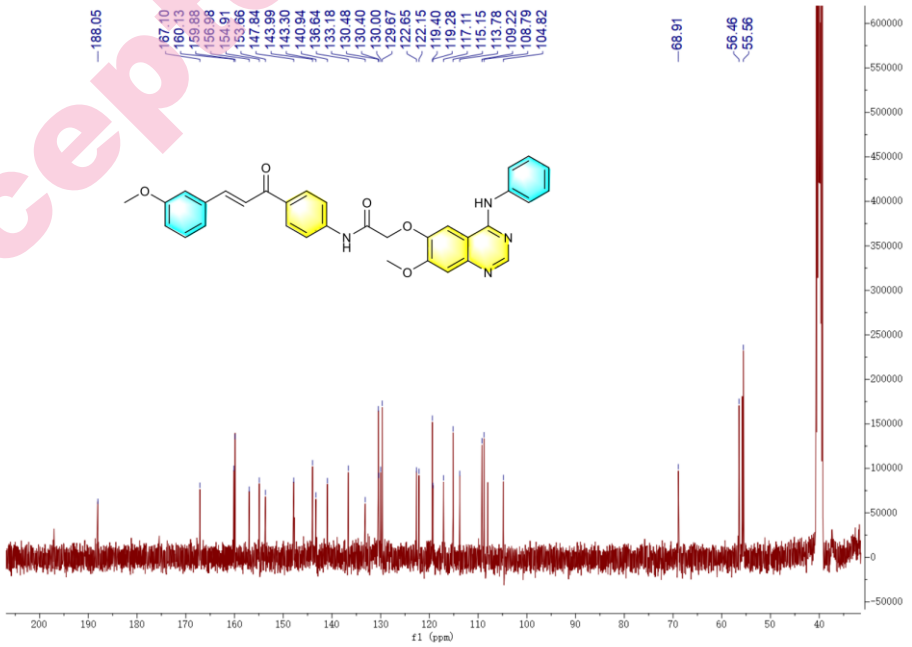

Figure. S28. ^{13}C NMR spectrum of target compound **9f**.

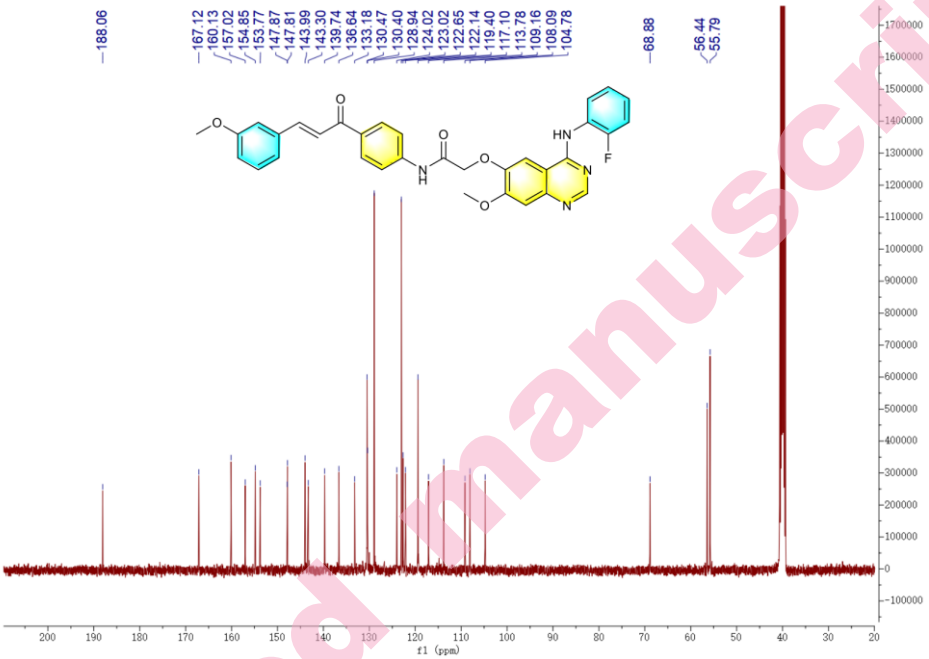

Figure. S29. ^{13}C NMR spectrum of target compound **9g**.

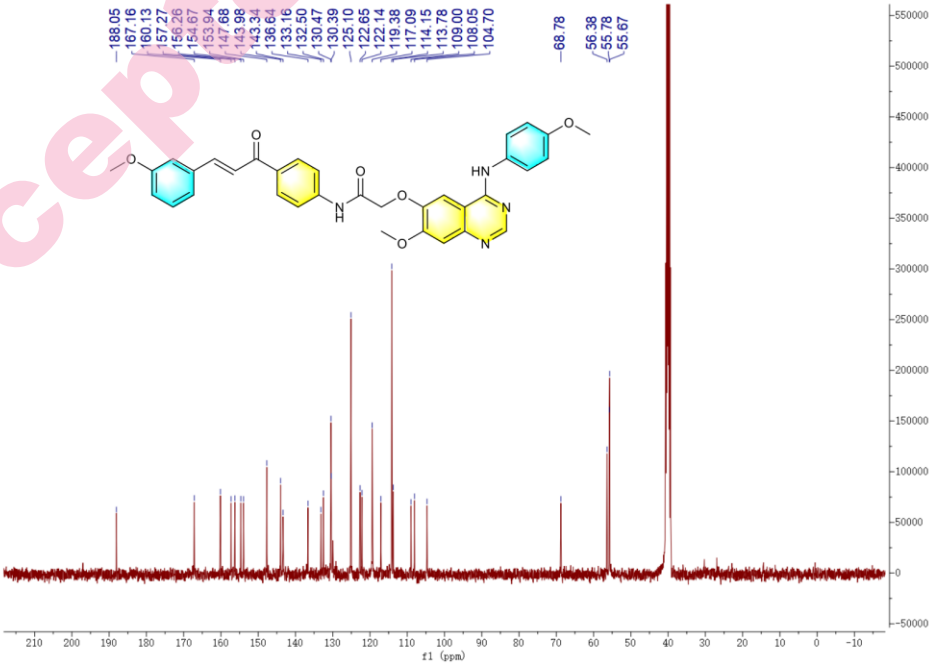

Figure. S30. ^{13}C NMR spectrum of target compound **9h**.

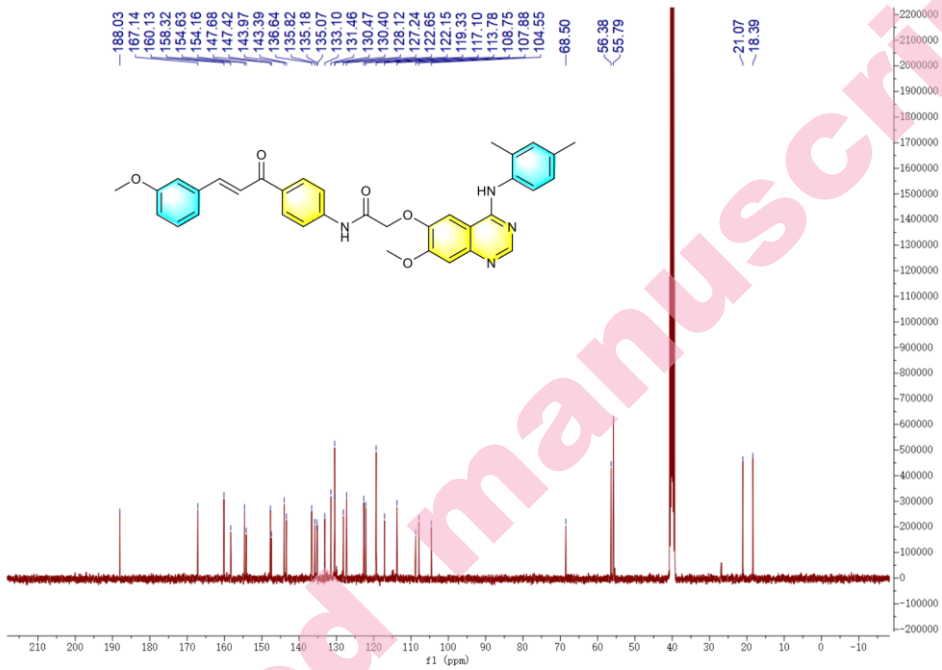

Figure. S31. ^{13}C NMR spectrum of target compound **9i**.

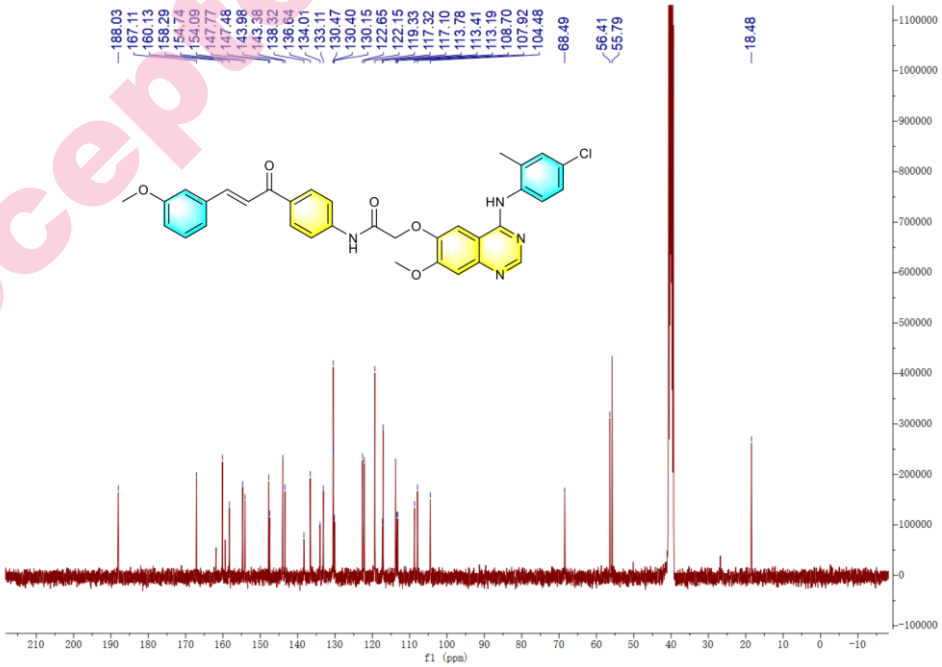

Figure. S32. ^{13}C NMR spectrum of target compound **9j**.

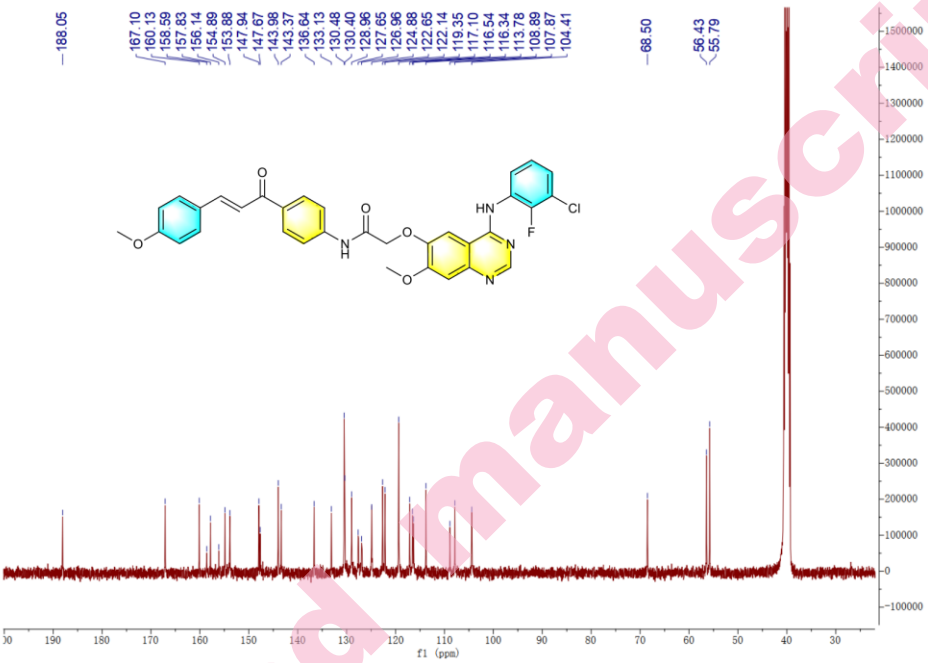

Figure. S33. ^{13}C NMR spectrum of target compound **9k**.

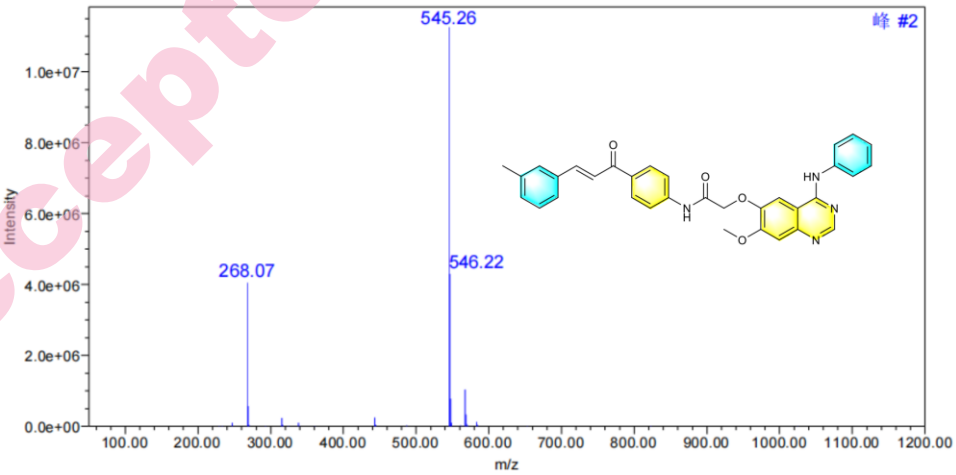

Figure. S34. MS spectrum of target compound **9a**.

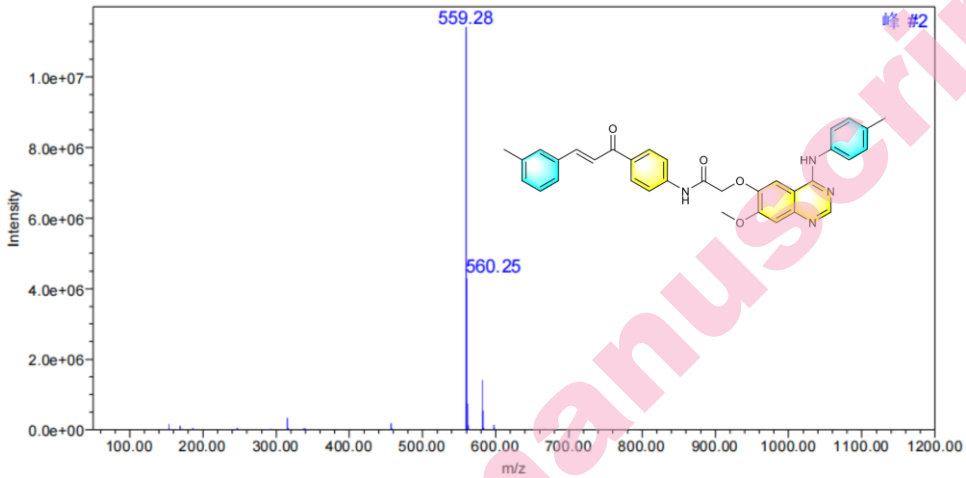

Figure. S35. MS spectrum of target compound **9b**.

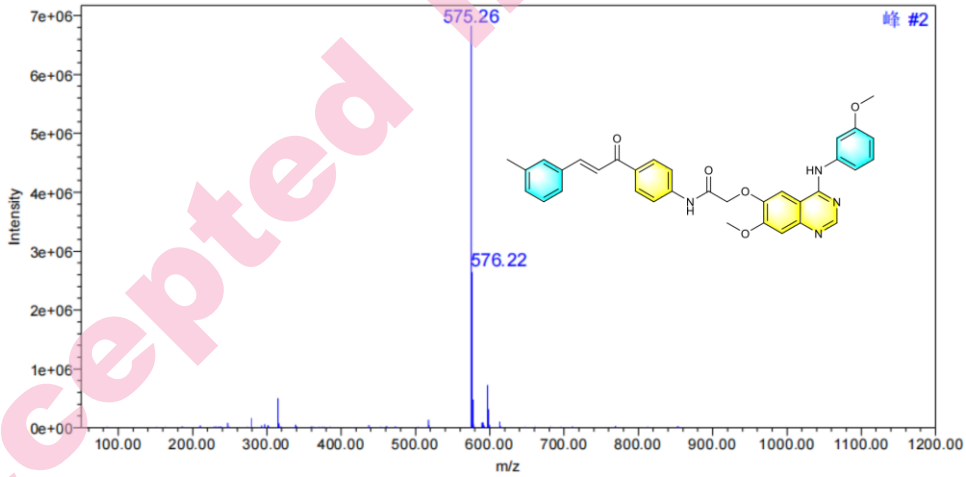

Figure. S36. MS spectrum of target compound **9c**.

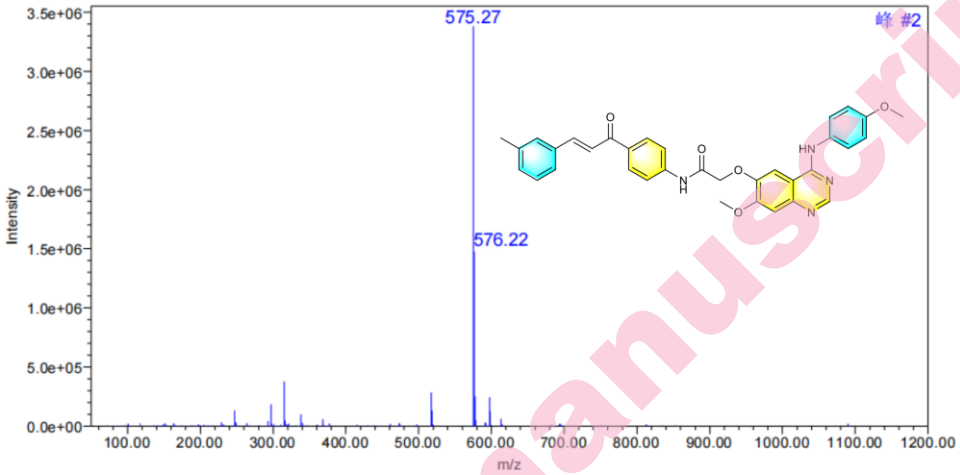

Figure. S37. MS spectrum of target compound **9d**.

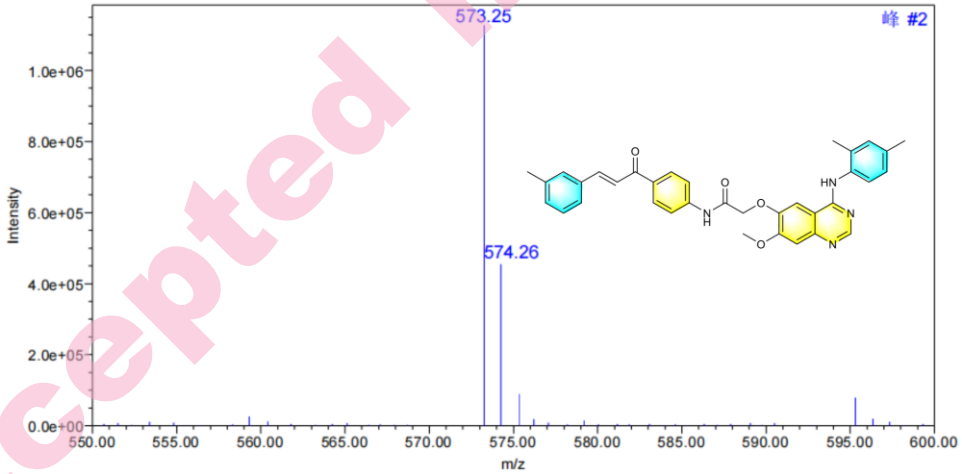

Figure. S38. MS spectrum of target compound **9e**.

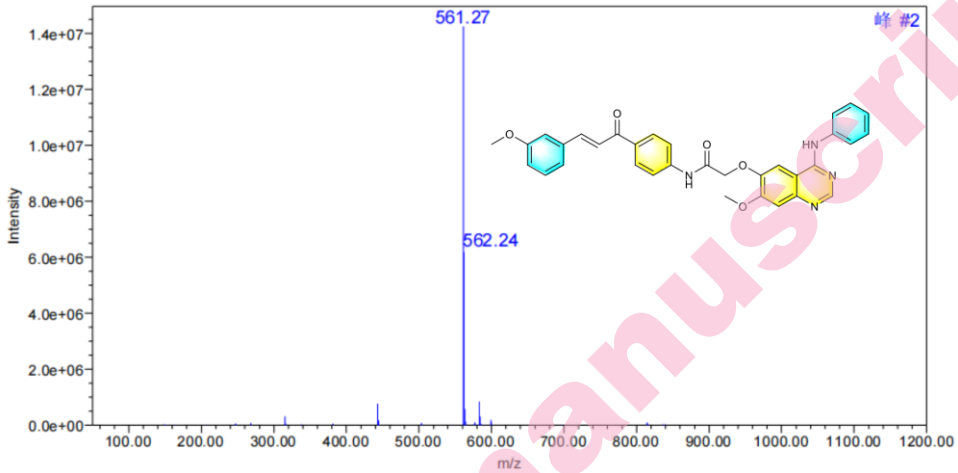

Figure. S39. MS spectrum of target compound **9f**.

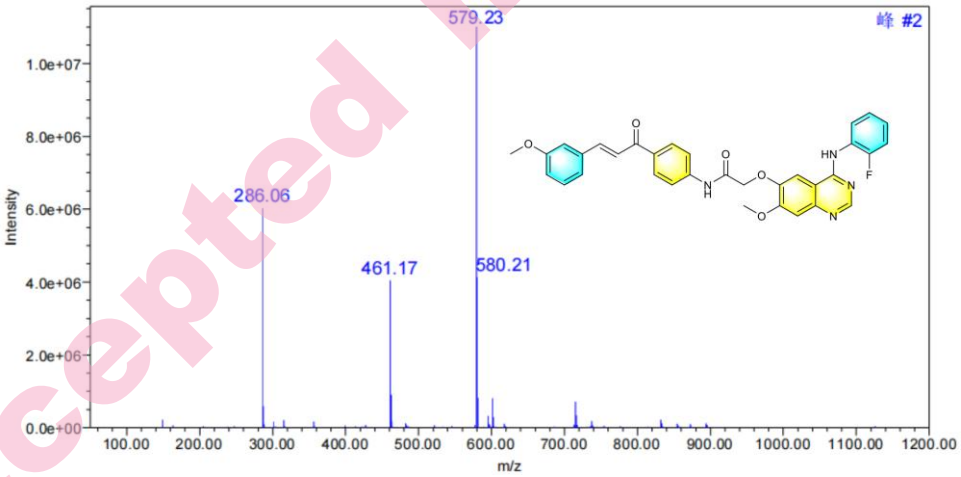

Figure. S40. MS spectrum of target compound **9g**.

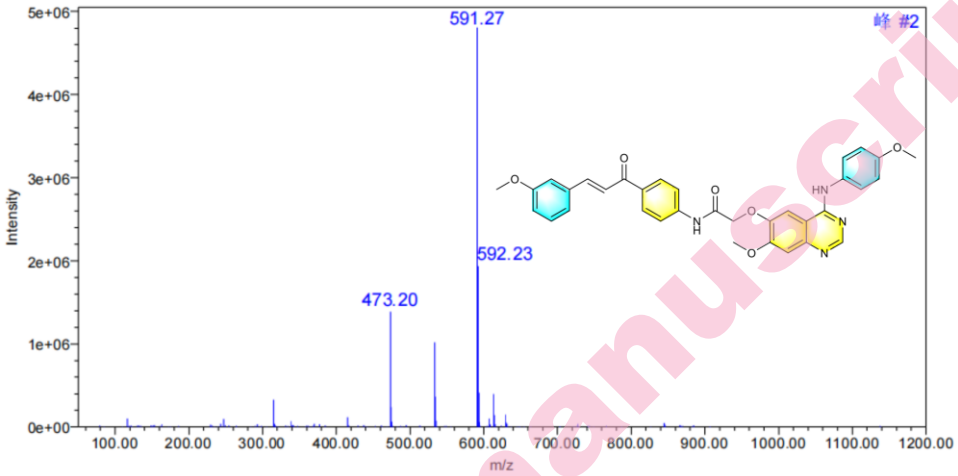

Figure. S41. MS spectrum of target compound **9h**.

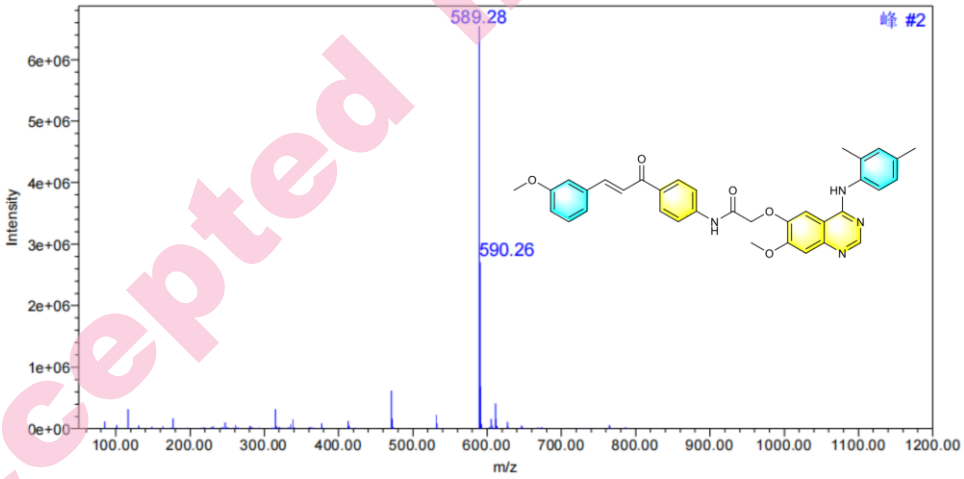

Figure. S42. MS spectrum of target compound **9i**.

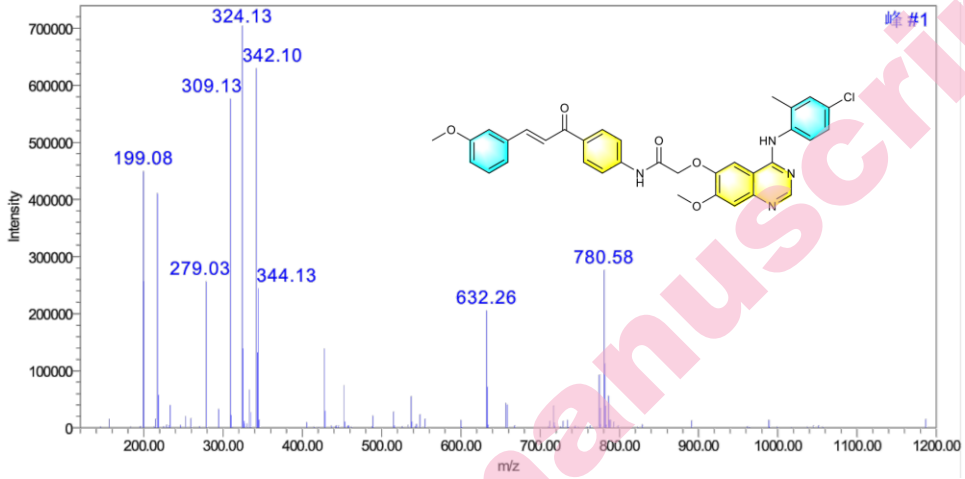

Figure. S43. MS spectrum of target compound **9j**.

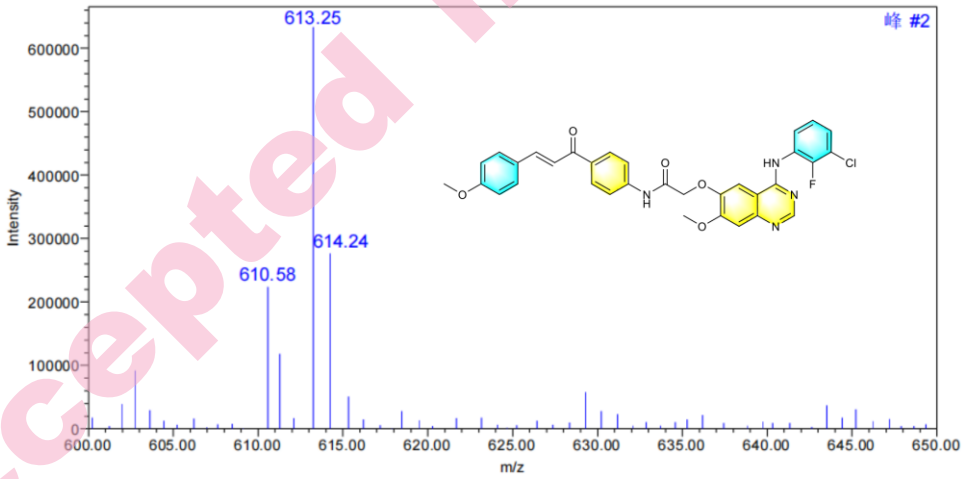

Figure. S44. MS spectrum of target compound **9k**.