Supporting Information

Synthesis and Structure-Activity Relationship Study of 1-Phenyl-1-(quinazolin-4-yl)ethanols as Anticancer Agents

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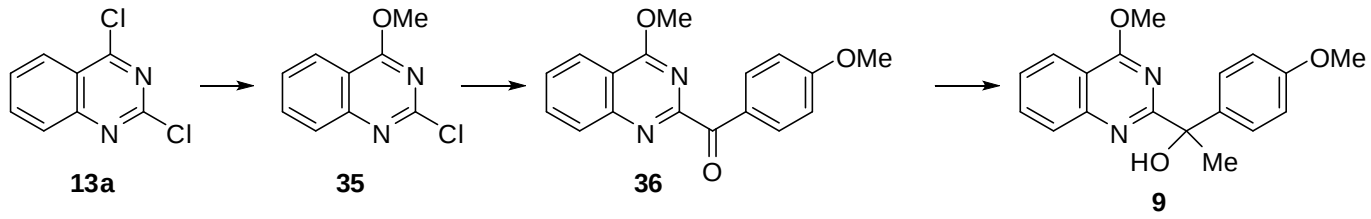
1. Scheme S-1



Scheme S-1: Synthesis of Derivative **9**

2. Figure S-1

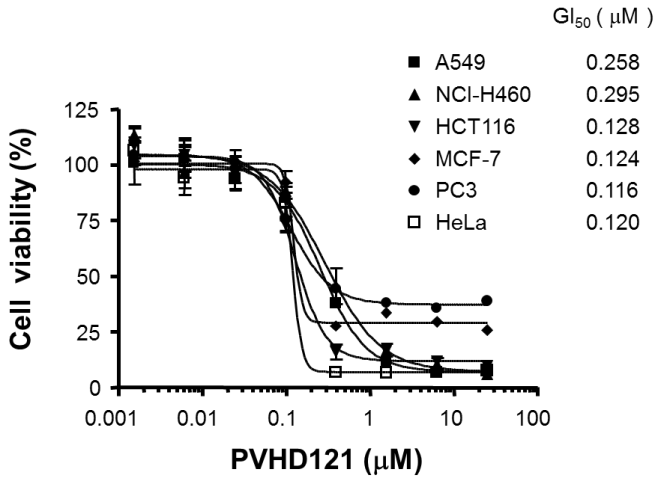


Figure S-1: Spectrum of anti-proliferative activity against various solid tumor-derived cell lines

3. Figure S-2

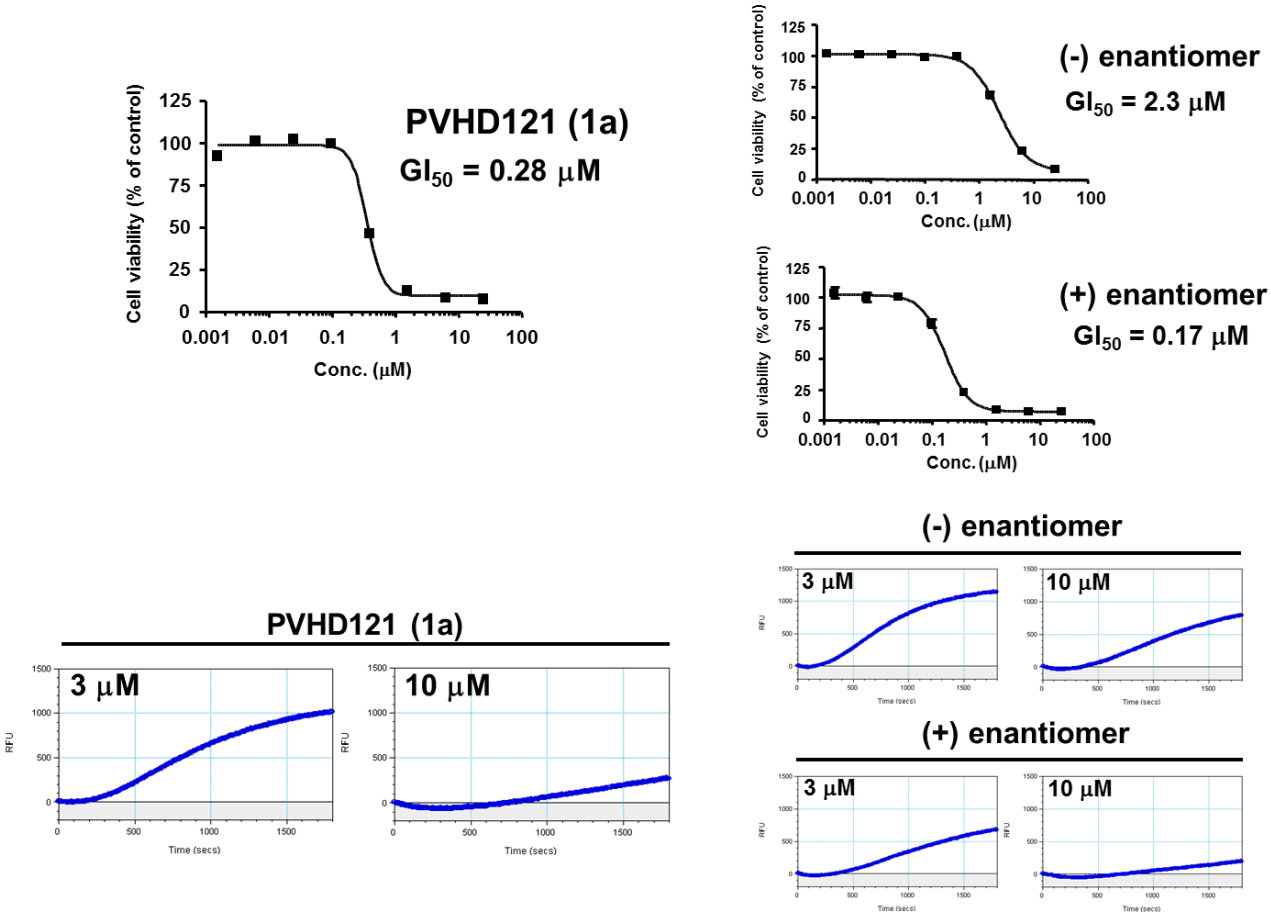


Figure S-2: A549 cell proliferation assay and *in vitro* tubulin polymerization assay for enantiomers separated from the racemic mixture (**1a**)

4. Figure S-3

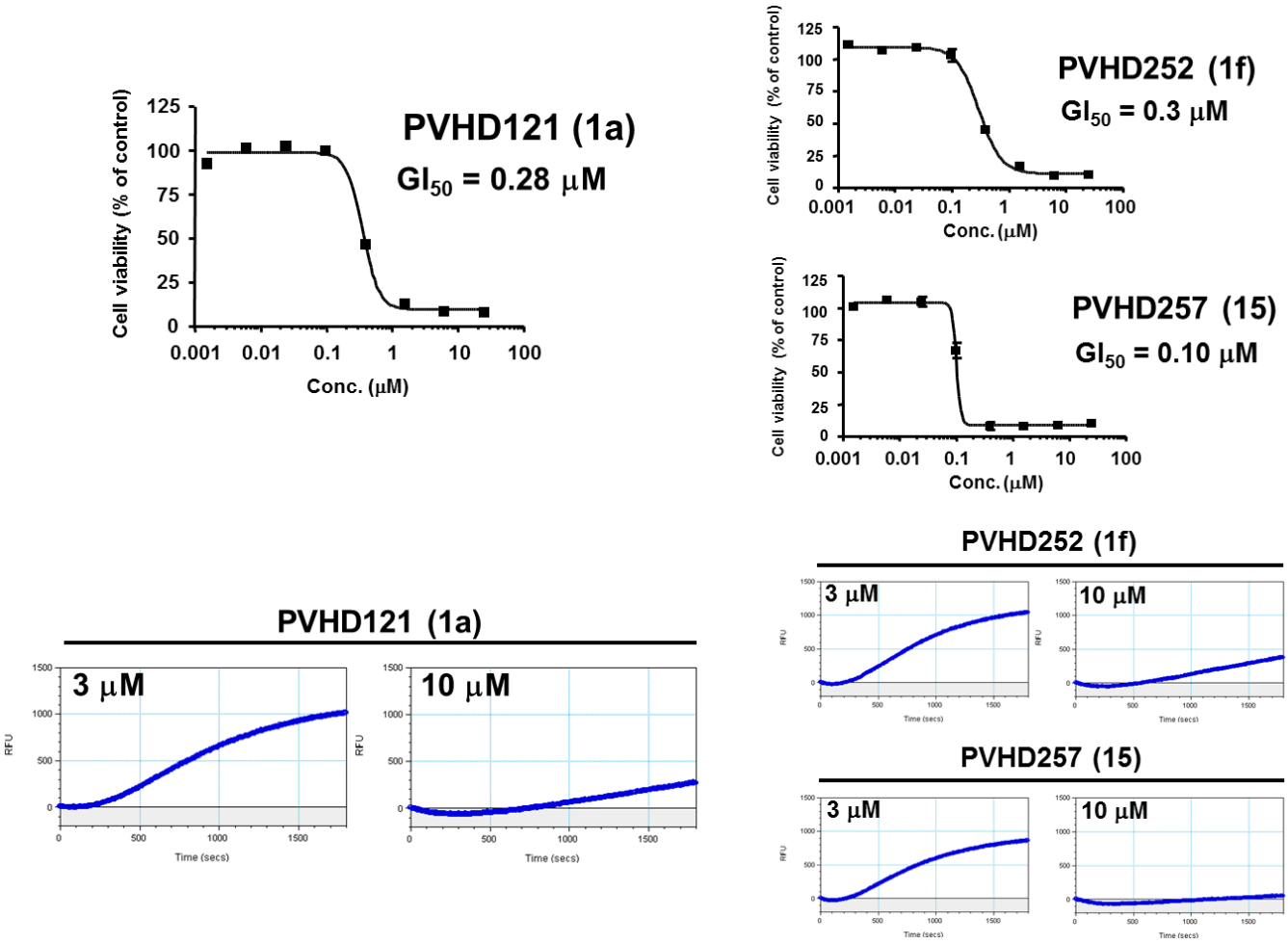


Figure S-3: A549 cell proliferation assay and *in vitro* tubulin polymerization assay for derivatives (**1a**, **1f**, **15**)

5. Experimental

General Information

The ^{1}H-NMR spectra and ^{13}C-NMR spectra were recorded on JEOL ECA-500 NMR Spectrometer or on JEOL ECA-300 NMR Spectrometer using TMS and $CDCl_3$ as internal standards.

IR spectra were recorded on SHIMADZU IR Prestige-21 or JASCO FT-IR 4100 spectrometer.

MS data were measured using 3-nitrobenzyl alcohol as a matrix on JEOL MStation JMS-700 (FAB).

Optical resolution and enantiomeric excess analysis were performed on Hitachi HPLC LaChrom Elite using DICEL CHIRALCEL OD, 10 X 250 mm, DICEL CHIRALCEL OD-H, 4.6 X 150 mm, respectively.

Chemicals were supplied by WAKO Pure Chemical Industries, Ltd., Kanto Chemical Co. INC, Tokyo Chemical Industry Co., LTD., or Sigma-Aldrich, and were used without purification as commercially available.

Column chromatography was performed on Merck Silica Gel 60 using chloroform or ethyl acetate and *n*- hexane as eluents.

TLC experiments were carried out on Merck Silica Gel 60-F_{254} plates.

◆Chemistry

(i) Synthesis of Keto Compounds

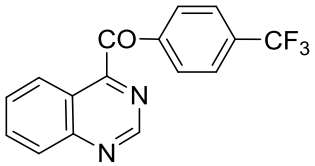
General procedure for NHC-catalyzed aroylation

To a mixture of the 4-chloroquinazoline (329 mg, 2 mmol), aromatic aldehyde (1.5 mmol), and 1,3-dimethylimidazolium iodide (23 mg, 0.1 mmol) in THF (20 ml), NaH (60% in oil, 100 mg, 2.5 mmol) was added with stirring under argon atmosphere. The reaction mixture was then refluxed for the indicated time and poured into ice water. Subsequently, the products were extracted with ethyl acetate and washed with brine; the solvent was then evaporated. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate) to obtain 4-aroylquinazolines.

For the spectrum date and synthesis of **4a**-**4c, 4e, 10b**, and **11b**: see ref. S1

For the spectrum date and synthesis of **4i**: see ref. S2.

4-(4-Trifluoromethylbenzoyl)quinazoline **(4d)**

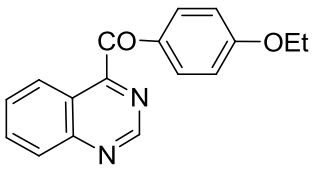


Yield ; 68%

^{1}H-NMR (500 MHz, $CDCl_3$) δ: 9.44 (1H, s), 8.18 (1H, d, *J* = 8.5 Hz), 8.09 (1H, d, *J* = 8.5 Hz), 8.04-7.99 (3H, m), 7.71-7.68 (1H, m), 7.19 (2H, t, *J* = 8.5 Hz).

FAB-Mass: 303 (M+1)

4-(4-Ethoxybenzoyl)quinazoline **(4f)**



Yield ; 61%

^{1}H-NMR (500 MHz, $CDCl_3$) δ: 9.42 (1H, s), 8.15 (1H, d, *J* = 8.5 Hz), 8.05 (1H, d, *J* = 8.5 Hz), 7.99-7.96 (1H, m), 7.93 (2H, d, *J* = 9.0 Hz), 7.66 (1H, t, *J* = 7.5 Hz), 6.95 (2H, d, *J* = 9.0 Hz), 4.12 (2H, q, *J* = 7.0 Hz), 1.45 (3H, t, *J* = 7.0 Hz).

FAB-Mass: 279 (M+1)

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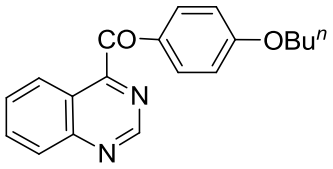
4-(4-*n*-Butoxybenzoyl)quinazoline **(4g)**

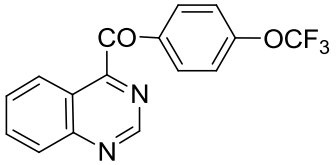


Yield ; 85%

^{1}H-NMR (500 MHz, $CDCl_3$) δ: 9.42 (1H, s), 8.15 (1H, d, *J* = 8.5 Hz), 8.05 (1H, d, *J* = 9.0 Hz), 7.99-7.96 (1H, m), 7.92 (2H, d, *J* = 9.0 Hz), 7.67-7.64 (1H, m), 6.95 (2H, d, *J* = 9.0 Hz), 4.05 (2H, t, *J* = 6.5 Hz), 1.82-1.77 (2H, m), 1.50 (2H, sextet, *J* = 7.5 Hz), 0.98 (3H, t, *J* = 7.5 Hz).

FAB-Mass: 307 (M+1)

4-(4-Trifluoromethoxybenzoyl)quinazoline **(4h)**

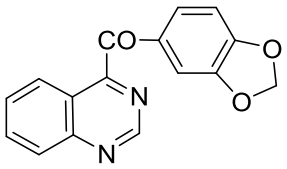


Yield ; 54%

^{1}H-NMR (500 MHz, $CDCl_3$) δ: 9.44 (1H, s), 8.19 (1H, d, *J* = 8.5 Hz), 8.13 (1H, d, *J* = 8.0 Hz), 8.06 (2H, d, *J* = 9.0 Hz), 8.03-7.99 (1H, m), 7.70 (1H, m), 7.34 (2H, dd, *J* = 9.0 Hz).

FAB-Mass: 319 (M+1)

4-(2,3-Methylenedioxybenzoyl) quinazoline **(4j)**

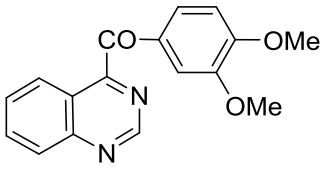


Yield ; 85%

^{1}H-NMR (500 MHz, $CDCl_3$) δ: 12.97 (1H, s), 8.15 (1H, d, *J* = 8.6), 8.03 (1H, d, *J* = 8.6), 7.99-7.96 (1H, m), 7.68-7.65 (1H, m), 7.53(1H, d, *J* = 1.5), 7.44 (1H, dd, *J* = 8.5, 1.5), 6.85 (1H, d, *J* = 8.5), 6.09 (2H, s).

FAB-Mass: 279 (M+1)

4-(3,4-Dimethoxybenzoyl)quinazoline **(4k)**

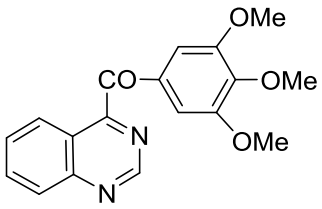


Yield ; 83%

^{1}H-NMR (500 MHz, $CDCl_3$) δ: 9.42 (1H,s), 8.16 (1H, d, *J* = 8.6), 8.05 (1H, d, *J* = 8.0), 8.00-7.96 (1H, m), 7.73 (1H, d, *J* = 2..0), 7.68-7.65 (1H, m), 7.35 (1H, dd, *J* = 8.6, 2.0), 6.86 (1H, d, *J* = 8.6), 3.98 (3H, s), 3.96 (3H, s).

FAB-Mass: 295 (M+1)

4-(3,4,5-Trimethoxybenzoyl)quinazoline **(4l)**

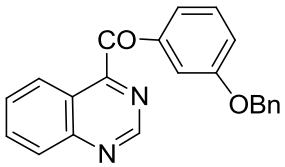


Yield ; 68%

^{1}H-NMR (500 MHz, $CDCl_3$) δ: 9.44 (1H, s), 8.18 (1H, d, *J* = 8.5 Hz), 8.08 (1H, d, *J* = 8.5 Hz), 8.03-7.99 (1H, m), 7.72-7.68 (1H, m), 7.22 (2H, s), 3.96 (3H, s), 3.84 (6H, s).

FAB-Mass: 325 (M+1)

4-(3-Benzyloxybenzoyl)quinazoline (**4m**)

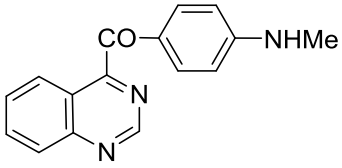


Yield ; 69%

^{1}H-NMR (500 MHz, $CDCl_3$) δ: 9.42 (1H, s), 8.17 (1H, d, *J* = 8.5 Hz), 8.05 (1H, d, *J* = 8.5 Hz), 8.01-7.98 (1H, m), 7.69-7.66 (1H, m), 7.62-7.61 (1H, m), 7.47-7.45 (1H, m), 7.42-7.27 (7H, m), 5.11 (2H).

FAB-Mass: 341 (M+1)

4-(4-Methylaminobenzoyl)quinazoline **(4o)**

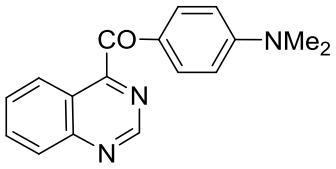


Yield ; 41%

A mixture of **4b** (50 mg, 0.2 mmol), methylamine (40% in water, 1 ml) in 1,4-dioxane (8 ml) was stirred at 115 °C for 17 h in a sealed tube. The product was extracted with ethyl acetate and washed with brine, and dried over Na_2SO_4. The organic layer was concentrated and purified by silica gel column chromatography (*n*-hexane/ethyl acetate) to afford **4o** (42 mg, 80%).

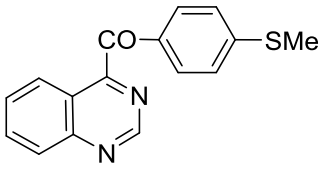
^{1}H-NMR (500 MHz, $CDCl_3$) δ: 9.40 (1H, s), 8.13 (1H, d, *J* = 8.5 Hz), 8.05 (1H, d, *J* = 8.5 Hz), 7.97-7.94 (1H, m), 7.79 (2H, t, *J* = 8.5 Hz), 7.65-7.61 (1H, m), 6.57 (2H, d, *J* = 8.5 Hz), 4.57 (1H, br s), 2.93 (3H, d, *J* = 3.5 Hz).
FAB-Mass: 264 (M+1)

4-(4-Dimethylaminobenzoyl)quinazoline **(4p)**



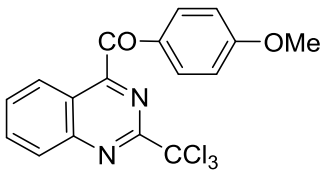
Yield ; 82%
^{1}H-NMR (500 MHz, $CDCl_3$) δ: 9.40 (1H, s), 8.13 (1H, d, *J* = 8.5 Hz), 8.05 (1H, d, *J* = 8.5 Hz), 7.96-7.92 (1H, m), 7.82 (2H, d, *J* = 9.5 Hz), 7.62 (1H, dt, *J* = 8.5, 3.7 Hz), 6.66 (2H, d, *J* = 9.5 Hz), 3.09 (6H, s).
FAB-Mass: 278 (M+1)

4-(4-Methylthiobenzoyl)quinazoline **(4q)**



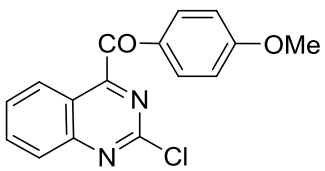
MeSNa (15% in water, 2 ml) was added to a mixture of **4b** (126 mg, 0.5 mg) in 1,4-dioxane (10 ml). The mixture was refluxed overnight, and then cooled. The product was extracted with ethyl acetate, washed with brine, and dried over Na_2SO_4. The organic layer was evaporated and the residue was purified by silica gel column chromatography (hexane/ ethyl acetate) to obtain **4q** (118 mg, 84%) as a yellow solid.
^{1}H-NMR (500 MHz, $CDCl_3$) δ: 9.43 (1H, s), 8.17 (1H, d, *J* = 8.5 Hz), 8.08 (1H, d, *J* = 8.5 Hz), 8.01-7.98 (1H, m), 7.88 (2H, d, *J* = 8.5 Hz), 7.69-7.66 (1H, m), 7.30 (2H, d, *J* = 8.5 Hz), 2.54 (3H, s).
FAB-Mass: 281 (M+1)

4-Anisoyl-2-trichloromethylquinazoline (**12b**)



Yield ; 79%
^{1}H-NMR (500 MHz, $CDCl_3$) δ: 8.09 (1H, d, *J* = 8.5 Hz), 8.03-7.99 (2H, m), 7.94 (2H, d, *J* = 9.0 Hz), 7.65 (1H, td, *J* = 7.5, 1.0 Hz), 6.99 (2H, d, *J* = 9.0 Hz), 3.90 (3H, s).
FAB-Mass: 382 (M+1)

4-Anisoyl-2-chloroquinazoline (**13b**)

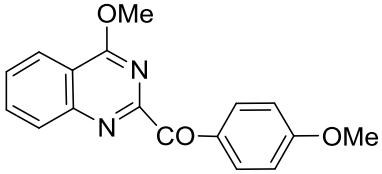


Yield ; 70%

^{1}H-NMR (500 MHz, $CDCl_3$) δ: 8.09 (1H, d, *J* = 8.5 Hz), 8.02-7.98 (2H, m), 7.94 (2H, d, *J* = 9.1 Hz), 7.65 (1H, t, *J* = 7.7 Hz), 6.98 (2H, d, *J* = 9.1 Hz), 3.90 (3H, s).

FAB-Mass: 299 (M+1)

2-Anisoyl-4-methoxylquinazoline (**36**)



To a mixture of the 2-chloro-4-methoxyquinazoline (293 mg, 1.5 mmol), anisaldehyde (245 mg, 1.8 mmol), and 1,3-dimethylimidazolium iodide (17 mg, 0.075 mmol) in THF (15 ml), NaH (60% in oil, 90 mg, 2.25 mmol) was added with stirring under argon atmosphere. The reaction mixture was then refluxed for 1.5 h and poured into ice water. Subsequently, the products were extracted with ethyl acetate and washed with brine; the solvent was then evaporated. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate) to afford **36** (173 mg, 39%) and 4-anisoyl-2-hydroxyquinazoline or 2-anisoyl-4-hydroxyquinazoline (95 mg, 34%).

FAB-Mass: 295 (M+1)

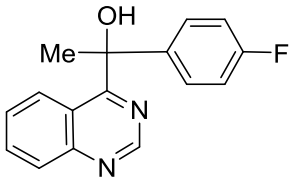
(ii) Synthesis of 1a-q

General Procedure

To a mixture of 4-aroylquinazoline in THF, 1 M methyl magnesium iodide in diethyl ether was added with stirring under argon atmosphere. The reaction mixture was then stirred at room temperature and the mixture was poured into an aqueous solution of ammonium chloride. Subsequently, the products were extracted with ethyl acetate and washed with brine and dried over Na_2SO_4. The solvent was then evaporated. The residue was purified by silica gel chromatography (*n*-hexane/ethyl acetate) to obtain PVHD derivatives.

For the spectrum data and synthesis of **1a**, **1c, 1e**: see ref. S3

1-(4-Fluorophenyl)-1-(quinazolin-4-yl)ethanol **(1b)**



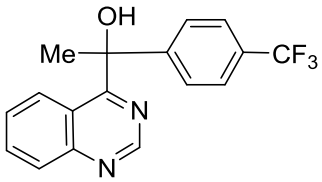
Yield ; 64%

^{1}H-NMR (500 MHz, $CDCl_3$) δ: 9.34 (1H, s), 8.08 (1H, d, *J* = 8.5 Hz), 7.83-7.80 (1H, m), 7.70 (1H, d, *J* = 8.5 Hz), 7.42-7.36 (3H, m), 7.03-6.99 (2H, m), 6.40 (1H, s), 2.12 (3H, s).

^{13}C-NMR (126 MHz, $CDCl_3$) δ: 172.01, 162.17 (d, *J* = 251.9 Hz), 152.29, 151.29, 141.11, 133.59, 129.54, 128.29 (d, *J* = 13.1 Hz), 127.52, 126.34, 121.22, 115.6 (d, *J* = 19.2 Hz), 74.96, 28.77.

FAB-Mass: 269 (M+1). IR (ATR): 3160 cm^{-1}

1-(4-Trifluoromethylphenyl)-1-(quinazolin-4-yl)ethanol **(1d)**



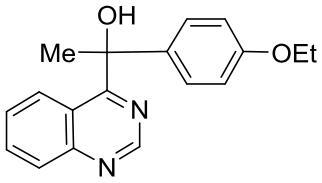
Yield ; 66%

^{1}H-NMR (500 MHz, $CDCl_3$) δ: 9.35 (1H, s), 8.08 (1H, d, *J* = 8.6 Hz), 7.84-7.81 (1H, m), 7.71 (1H, d, *J* = 8.6 Hz), 7.59 (2H, d, *J* = 8.0 Hz), 7.53 (2H, d, *J* = 8.0 Hz), 7.49-7.41 (1H, m), 6.36 (1H, s), 2.15 (3H, s).

^{13}C-NMR (126 MHz, $CDCl_3$) δ: 171.34, 152.30, 151.33, 149.14, 133.73, 130.07 (d, *J* = 31.7 Hz), 129.64, 127.71, 126.77, 126.17, 125.74 (d, *J* = 3.6 Hz), 123.92 (q, *J* = 271.7 Hz), 121.22, 75.36, 28.65.

FAB-Mass: 319 (M+1). IR (ATR): 3177 cm^{-1}

1-(4-Ethoxylphenyl)-1-(quinazolin-4-yl)ethanol **(1f)**



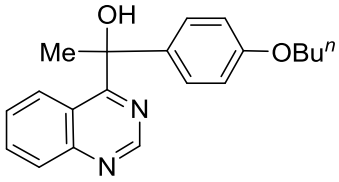
Yield ; 74%

^{1}H-NMR (500 MHz, $CDCl_3$) δ: 9.33 (1H, s), 8.06 (1H, d, *J* = 8.5 Hz), 7.79 (1H, dt, *J* = 8.0, 1.0 Hz), 7.74 (1H, d, *J* = 8.0 Hz), 7.39 (1H, t, *J* = 8.5 Hz), 7.29 (2H, d, *J* = 8.5 Hz), 6.84 (2H, d, *J* = 8.5 Hz), 6.50 (1H, s), 4.00 (2H, q, *J* = 7.0 Hz), 2.10 (3H, s), 1.39 (3H, t, *J* = 7.0 Hz).

^{13}C-NMR (126 MHz, $CDCl_3$) δ: 172.69, 158.44, 152.26, 151.19, 137.31, 133.46, 129.38, 127.68, 127.34, 126.64, 121.38, 114.53, 74.87, 63.54, 28.65, 14.90.

FAB-Mass: 295 (M+1). IR (ATR): 3162 cm^{-1}

1-(4-*n*-Butoxylphenyl)-1-(quinazolin-4-yl)ethanol **(1g)**



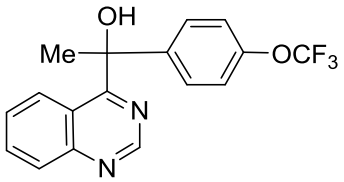
Yield ; 63%

^{1}H-NMR (500 MHz, $CDCl_3$) δ: 9.32 (1H, s), 8.05 (1H, d, *J* = 8.5 Hz), 7.80-7.76 (2H, m), 7.38 (1H, dt, *J* = 11.1, 3.8 Hz), 7.29 (2H, d, *J* = 8.5 Hz), 6.83 (2H, d, *J* = 8.5 Hz), 6.46 (1H, s), 3.92 (2H, t, *J* = 6.5 Hz), 2.09 (3H, s), 1.76-1.70 (2H, m), 1.48-1.44 (2H, m), 0.95 (3H, t, *J* = 7.5 Hz).

^{13}C-NMR (126 MHz, $CDCl_3$) δ: 172.75, 158.59, 152.23, 151.14, 137.25, 133.42, 129.37, 127.65, 127.37, 126.66, 121.37, 114.56, 74.96, 67.68, 31.32, 28.71, 19.26, 13.91.

HRMS (FAB) *m/z* Calcd for $C_{20}H_{22}N_2O_2$ (M^+): 322.1681, Found: 322.1670. IR (ATR): 3133 cm^{-1}

1-(4-Trifluoromethoxylphenyl)-1-(quinazolin-4-yl)ethanol **(1h)**



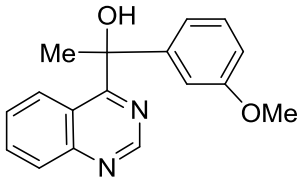
Yield ; 66%

^{1}H-NMR (500 MHz, $CDCl_3$) δ: 9.35 (1H, s), 8.09 (1H, d, *J* = 8.5 Hz), 7.84-7.81 (1H, m), 7.71 (1H, d, *J* = 8.5 Hz), 7.44-7.40 (3H, m), 7.17 (2H, d, *J* = 8.5 Hz), 6.35 (1H, s), 2.13 (3H, s).

^{s13}C-NMR (126 MHz, $CDCl_3$) δ: 171.70, 152.28, 151.30, 148.48 (dd, *J* = 1.4 Hz), 143.87, 133.70, 129.65, 128.03, 127.66, 126.23, 120.37 (q, *J* = 256.94 Hz), 121.21, 121.06, 74.94, 28.76.

HRMS (FAB) *m/z* Calcd for $C_{17}H_{13}F_3N_2O_2$ (M^+): 334.0929, Found: 334.0948. IR (ATR): 3149 cm^{-1}

1-(3-Methoxyphenyl)-1-(quinazolin-4-yl)ethanol **(1i)**



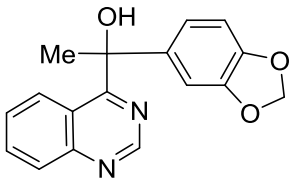
Yield ; 59%

^{1}H-NMR (500 MHz, $CDCl_3$) δ: 9.34 (1H, s), 8.06 (1H, dd, *J* = 9.0, 1.0 Hz), 7.81-7.78 (2H, m), 7.41-7.39 (1H, m), 7.24 (1H, d, *J* = 8.0 Hz), 6.97-6.92 (2H, m), 6.81 (1H, dd, *J* = 9.0, 2.5 Hz), 6.33 (1H, s), 3.74 (3H, s), 2.10 (3H, s).

^{13}C-NMR (126 MHz, $CDCl_3$) δ: 172.30, 159.83, 152.26, 151.14, 146.83, 133.58, 129.75, 129.38, 127.46, 126.55, 121.46, 118.88, 112.81, 112.79, 75.36, 55.30, 28.66.

FAB-Mass: 281 (M+1). IR (ATR): 3186 cm^{-1}

1-(2,3-Methylenedioxyphenyl)-1-(quinazoline-4-yl)-ethanol **(1j)**



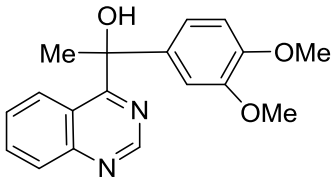
Yield ; 57%

^{1}H-NMR (500 MHz, $CDCl_3$) δ: 9.32 (1H, s), 8.07 (1H, dd, *J* = 9.0, 1.0 Hz), 7.83-7.80 (2H, m), 7.42 (1H, td, *J* = 8.0, 1.5 Hz), 6.95 (1H, dd, *J* = 8.0, 2.0 Hz), 6.78-6.76 (2H, m), 6.41 (1H, s), 5.94 (1H, d, *J* = 1.2 Hz), 5.92 (1H, d, *J* = 1.2 Hz), 2.07 (3H, s).

^{13}C-NMR (126 MHz, $CDCl_3$) δ: 172.32, 152.26, 151.17, 148.01, 147.17, 139.32, 133.58, 129.41, 127.52, 126.49, 121.36, 119.74, 108.18, 107.50, 101.26, 75.09, 28.71.

FAB-Mass: 295 (M+1). IR (ATR): 3138 cm^{-1}

1-(3,4-Dimethoxyphenyl)-1-(quinazoline-4-yl)ethanol **(1k)**



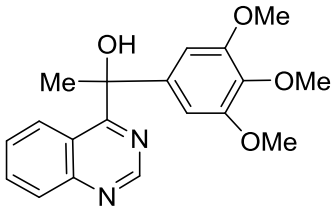
Yield ; 61%

^{1}H-NMR (500 MHz, $CDCl_3$) δ: 9.34 (1H, s), 8.07 (1H, d, *J* = 8.5 Hz), 7.83-7.77 (2H, m), 7.41-7.38 (1H, m), 7.01 (1H, dd, *J* = 8.2, 2.1 Hz), 6.84-6.82 (2H, m), 6.41 (1H, s), 3.86 (3H, s), 3.74 (3H, s), 2.10 (3H, s).

^{13}C-NMR (126 MHz, $CDCl_3$) δ: 172.49, 152.26, 151.13, 149.11, 148.68, 137.85, 133.53, 129.35, 127.46, 126.53, 121.43, 118.74, 110.83, 110.06, 75.20, 55.87, 55.83, 28.86.

FAB-Mass: 311 (M+1). IR (ATR): 3330 cm^{-1}

1-(3,4,5-Trimethylphenyl)1-(quinazoline-4-yl)ethanol **(1l)**



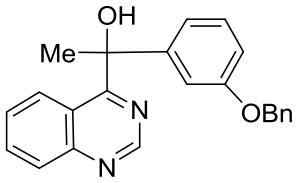
Yield ; 44%

^{1}H-NMR (500 MHz, $CDCl_3$) δ: 9.34 (1H, s), 8.08 (1H, d, *J* = 7.9 Hz), 7.85-7.80 (2H, m), 7.45-7.42 (1H, m), 6.60 (2H, s), 6.29 (1H, s), 3.82 (3H, s), 3.76 (6H, s), 2.09 (3H, s).

^{13}C-NMR (126 MHz, $CDCl_3$) δ: 172.20, 153.35, 152.29, 151.12, 140.76, 137.83, 133.69, 129.38, 127.60, 126.46, 121.44, 104.07, 75.53, 60.89, 56.28, 28.95.

FAB-Mass: 341 (M+1). IR (ATR): 3118 cm^{-1}

1-(3-Benzyloxyphenyl)-1-(quinazolin-4-yl)ethanol (**1m**)



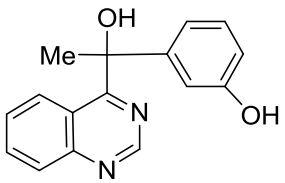
Yield ; 51%

^{1}H-NMR (500 MHz, $CDCl_3$) δ: 9.33 (1H, s), 8.06 (1H, d, *J* = 8.5 Hz), 7.80 (1H, t, *J* = 7.5 Hz), 7.72 (1H, d, *J* = 8.5 Hz), 7.39-7.24 (7H, m), 7.00 (2H, d, *J* = 8.0 Hz), 6.90-6.88 (1H, m), 6.41 (1H, s), 5.02 (1H, d, *J* = 11.5 Hz), 4.97 (1H, d, *J* = 11.5 Hz), 2.09 (3H, s).

^{13}C-NMR (126 MHz, $CDCl_3$) δ: 172.21, 158.91, 152.22, 151.12, 146.82, 136.68, 133.49, 129.77, 129.35, 128.52, 127.97, 127.45, 126.49, 121.39, 119.04, 113.91, 113.78, 75.33, 70.02, 28.59.

HRMS (FAB) *m/z* Calcd for $C_{23}H_{20}N_2O_2$ (M^+): 356.1525, Found: 356.1524. IR (ATR): 3493 cm^{-1}

1-(3-Hydroxyphenyl)-1-(quinazolin-4-yl)ethanol (**1n**)



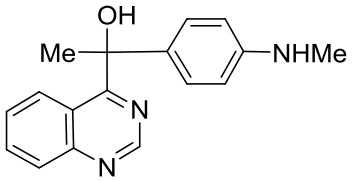
A mixture of **1m** (80 mg, mmol), palladium charcoal (10%, 10 mg) and a few drops of hydrochloric acid in ethyl acetate was equipped with a hydrogen balloon, stirred at room temperature for 15 h, and then filtered. The filtrate was concentrated and purified by silica gel chromatography (*n*-hexane/ethyl acetate) to afford **1n** (20 mg, 35%).

^{1}H-NMR (500 MHz, $CDCl_3$) δ: 9.31 (1H, s), 8.05 (1H, d, *J* = 8.4 Hz), 7.82-7.77 (2H, m), 7.42-7.39 (1H, m), 7.22 (1H, t, *J* = 7.8 Hz), 7.02 (1H, dd, *J* = 6.9, 1.5 Hz), 6.81 (1H, t, *J* = 2.3 Hz), 6.76-6.74 (1H, m), 6.34 (1H, s), 4.98 (1H, s), 2.10 (3H, s).

^{13}C-NMR (126 MHz, DMSO-d_6) δ: 172.82, 157.11, 153.18, 150.66, 149.38, 133.23, 129.22, 128.38, 126.64, 122.25, 115.06, 113.51, 111.45, 77.99, 32.22.

HRMS (FAB) *m/z* Calcd for $C_{16}H_{15}N_2O_2$ (M+1): 267.1134, Found: 267.1124.

1-(4-Methylaminophenyl)-1-(quinazoline-4-yl)ethanol **(1o)**



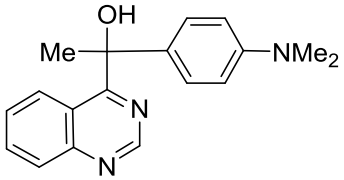
Yield ; 31%

^{1}H-NMR (500 MHz, $CDCl_3$) δ: 9.31 (1H, s), 8.05 (1H, d, *J* = 8.0 Hz), 7.82-7.77 (2H, m), 7.38 (1H, ddd, *J* = 8.5, 8.0, 1.0 Hz), 7.18 (2H, d, *J* = 8.5 Hz), 6.54 (2H, d, *J* = 8.5 Hz), 6.46 (1H, s), 2.81 (3H, s), 2.07 (3H, s).

^{13}C-NMR (126 MHz, $CDCl_3$) δ: 173.12, 152.24, 151.11, 148.52, 134.21, 133.43, 129.32, 127.49, 127.32, 126.84, 121.54, 112.63, 74.91, 30.89, 28.63.

HRMS (FAB) *m/z* Calcd for $C_{17}H_{18}N_3O$ (M+1): 280.1450, Found: 280.1425. IR (ATR): 3352 cm^{-1}

1-(4Dimethylaminophenyl)-1-(quinazoline-4-yl)ethanol **(1p)**



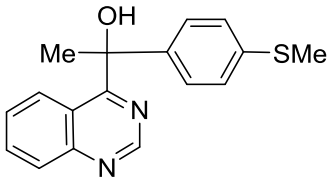
Yield ; 66%

^{1}H-NMR (500 MHz, $CDCl_3$) δ: 9.32 (1H, s), 8.05 (1H, d, *J* = 8.0 Hz), 7.82-7.76 (2H, m), 7.40-7.37 (1H, ddd, *J* = 8.5, 8.0, 1.0 Hz), 7.22 (2H, d, *J* = 8.5 Hz), 6.66 (2H, d, *J* = 8.5 Hz), 6.39 (1H, s), 2.92 (6H, s), 2.08 (3H, s).

^{13}C-NMR (126 MHz, $CDCl_3$) δ: 173.21, 152.24, 151.08, 149.95, 133.36, 132.98, 129.28, 127.32, 127.27, 126.87, 121.57, 112.51, 74.95, 40.49, 28.70.

HRMS (FAB) *m/z* Calcd for $C_{18}H_{20}N_3O$ (M+1): 294.1606, Found: 294.1581. IR (ATR): 3353 cm^{-1}

1-(4-Methylthiophenyl)-1-(quinazoline-4-yl)ethanol **(1q)**



Yield ; 68%

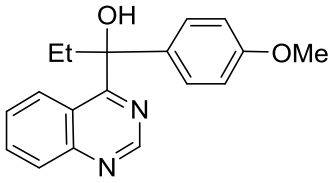
^{1}H-NMR (500 MHz, $CDCl_3$) δ: 9.34 (1H, s), 8.09 (1H, d, *J* = 8.5 Hz), 7.82-7.79 (1H, m), 7.74 (1H, d, *J* = 8.5 Hz), 7.40 (1H, ddd, *J* = 8.5, 7.0, 1.0 Hz), 7.30 (2H, d, *J* = 8.5 Hz), 7.20 (2H, d, *J* = 8.5 Hz), 6.40 (1H, s), 2.45 (3H, s), 2.10 (3H, s).

^{13}C-NMR (126 MHz, $CDCl_3$) δ: 172.24, 152.25, 151.17, 142.02, 138.25, 133.53, 129.43, 127.51, 126.94, 126.58, 126.52, 121.33, 75.15, 28.58, 15.68.

HRMS (FAB) *m/z* Calcd for $C_{17}H_{17}N_2OS$ (M+1): 297.1062, Found: 297.1090. IR (ATR): 3350 cm^{-1}

(iii) Synthesis of 5-8

1-(4-Methoxyphenyl)-1-(quinazoline-4-yl)propan-4-ol **(5)**



Yield ; 57%

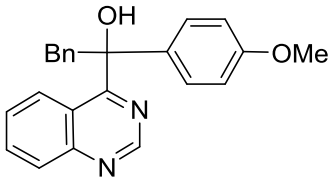
Grignard reaction with EtMgI

^{1}H-NMR (500 MHz, $CDCl_3$) δ: 9.33 (1H, s), 8.06 (1H, d, *J* = 7.5 Hz), 7.82-7.78 (2H, m), 7.40 (1H, td, *J* = 7.5, 1.0 Hz), 7.31 (2H, d, *J* = 8.5 Hz), 6.84 (2H, d, *J* = 8.5 Hz), 6.45 (1H, s), 3.77 (3H, s), 2.70 (1H, dt, *J* = 14.5, 7.5 Hz), 2.62 (1H, dt, *J* = 14.5, 7.5 Hz), 0.64 (3H, t, *J* = 7.5 Hz).

^{13}C-NMR (76 MHz, $CDCl_3$) δ: 171.38, 158.96, 152.00, 150.94, 137.76, 133.48, 129.47, 127.99, 127.37, 126.38, 121.71, 113.89, 77.29, 55.27, 32.52, 7.88.

HRMS (FAB) *m/z* Calcd for $C_{18}H_{19}N_2O_2$ (M+1): 295.1447, Found: 295.1475. IR (ATR): 3117 cm^{-1}

1-(4-Methoxyphenyl)-2-phenyl-1-(quinazoline-4-yl)ethanol **(6)**



Yield ; 91%

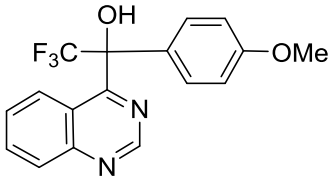
Grignard reaction with BnMgI

^{1}H-NMR (500 MHz, $CDCl_3$) δ: 9.06 (1H, s), 8.07 (1H, d, *J* = 8.0 Hz), 7.99 (1H, d, *J* = 8.5 Hz), 7.87-7.83 (1H, m), 7.49 (1H, t, *J* = 8.0 Hz), 7.39 (2H, d, *J* = 9.0 Hz), 7.08 (1H, t, *J* = 8.0 Hz), 7.00 (2H, t, *J* = 8.0 Hz), 6.90 (2H, d, *J* = 9.0 Hz), 6.65 (2H, d, *J* = 8.0 Hz), 5.95 (1H, s), 3.97 (1H, d, *J* = 13.0 Hz), 3.93 (1H, d, *J* = 13.0 Hz), 3.82 (3H, s).

^{13}C-NMR (76 MHz, $CDCl_3$) δ: 170.58, 159.08, 151.81, 150.88, 137.26, 135.52, 133.42, 130.24, 129.55, 127.90, 127.72, 127.48, 126.57, 122.16, 114.04, 77.66, 55.31, 45.94.

HRMS (FAB) *m/z* Calcd for $C_{23}H_{21}N_2O_2$ (M+1): 357.1603, Found: 357.1625. IR (ATR): 3117 cm^{-1}

2,2,2-Trifluoro-1-(4-methoxyphenyl)-1-(quinazoline-4-yl)ethanol **(7)**



Under an atmosphere of argon, trimethyltrimethylsilane (177 μM, 1.2 mmol) and 1M tetrabutylammonium fluoride in THF (20 μL, 0.02 mmol) were added to a solution of 4-anisoylquinazoline (132 mg, 0.5 mmol) in THF (4 mL) at 0 °C. The mixture was stirred at room temperature overnight and then poured into ice water. Subsequently, the product was extracted with ethyl acetate, washed with brine, and dried over Na_2SO_4. The organic layer was evaporated, and the residue was purified by silica gel column chromatography to obtain **7**

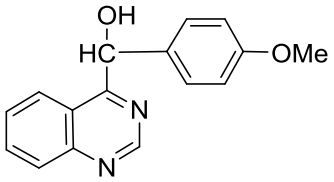
(95 mg, 0.28 mmol, 57%) as a colorless solid.

^{1}H-NMR (500 MHz, $CDCl_3$) δ: 9.41 (1H, s), 8.10 (1H, d, *J* = 8.5 Hz), 7.83 (1H, m), 7.69 (1H, d, *J* = 9.1 Hz), 7.41-7.34 (3H, m), 7.13 (1H, s), 6.88 (2H, d, *J* = 9.1 Hz), 3.80 (3H, s).

^{13}C-NMR (76 MHz, $CDCl_3$) δ: 164.00, 159.95, 151.87, 151.63, 134.14, 129.97, 129.29, 128.92 (d, *J* = 2.2 Hz), 124.7 (q, *J* =287.2), 122.34, 114.29, 78.91 (d, *J* = 28.9), 77.26, 55.41.

HRMS (FAB) *m/z* Calcd for $C_{17}H_{14}F_3N_2O_2$ (M+1): 335.1007, Found: 335.0987. IR (ATR): 3435 cm^{-1}

(4-Methoxyphenyl)(quinazoline-4-yl)methanol **(8)**



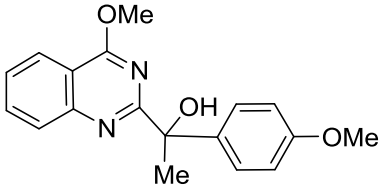
$NaBH_4$ (1 mmol) was added to a mixture of **4a** (132 mg, 0.5 mmo) in dry ethanol (20 ml). The mixture was stirred at room temperature for 1 h. After the mixture was concentrated to half, water was added to it. The resulting colorless precipitates were filtered and dried to give crude **8** (30 mg, 22%), which was purified by crystallization from aceton/ hexane.

^{1}H-NMR (500 MHz, $CDCl_3$) δ: 9.44 (1H, s), 8.18 (1H, d, *J* = 8.5 Hz), 8.06 (2H, d, *J* = 8.0 Hz), 8.01-7.95 (3H, m), 7.68 (1H, t, *J* = 8.0 Hz), 6.99 (2H, d, *J* = 9.0 Hz), 6.97 (1H, d, *J* = 7.5 Hz), 3.91 (3H, s), 3.90 (1H, d, *J* = 7.5 Hz).

^{13}C-NMR (76 MHz, $CDCl_3$) δ: 164.75, 153.90, 151.07, 134.65, 133.17, 132.27, 128.98, 128.68, 128.22, 127.76, 122.14, 114.16, 55.71, 55.53.

HRMS (FAB) *m/z* Calcd for $C_{16}H_{14}N_2O_2$ (M^+): 266.1055, Found: 266.1047. IR (ATR): 3135 cm^{-1}

1-(4-Methoxyphenyl)-1-(4-methoxyquinazoline-2-yl)ethanol (**9**)



Yield ; 92%

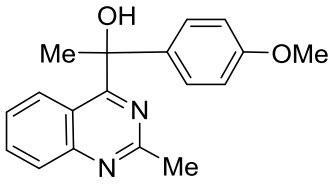
^{1}H-NMR (500 MHz, $CDCl_3$) δ: 8.10 (1H, dd, *J* = 8.0, 1.4 Hz), 7.91 (1H, d, *J* = 8.5 Hz), 7.82-7.78 (1H, m), 7.71 (2H, d, *J* = 8.5 Hz), 7.55-7.49 (1H, m), 6.84 (2H, d, *J* = 8.5 Hz), 5.93 (1H, s), 4.18 (3H, s), 3.77 (3H, s), 2.04 (3H, s).

^{13}C-NMR (76 MHz, $CDCl_3$) δ: 169.86, 169.08, 159.89, 151.45, 140.32, 135.19, 128.82, 128.58, 128.27, 124.94, 116.38, 114.64, 77.06, 56.68, 55.90, 30.44.

HRMS (FAB) *m/z* Calcd for $C_{18}H_{19}N_2O_3$ (M+1): 311.1396, Found: 311.1398. IR (ATR): 3047 cm^{-1}

(iv) Synthesis of 2-Substituted Derivatives 14-34

1-(4-Methoxyphenyl)-1-(2-methylquinazoline-4-yl)ethanol **(14)**



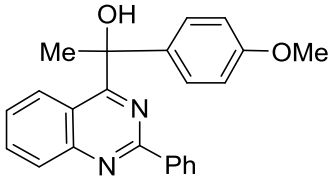
Yield ; 68%

^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.97 (1H, d, *J* = 8.5 Hz), 7.77-7.73 (1H, m), 7.64 (1H, d, *J* = 8.5 Hz), 7.33-7.29 (3H, m), 6.86 (2H, d, *J* = 8.5 Hz), 6.85 (1H, s), 3.79 (3H, s), 2.98 (3H, s), 2.09 (3H, s).

^{13}C-NMR (76 MHz, $CDCl_3$) δ: 172.40, 161.37, 158.98, 151.63, 137.43, 133.38, 128.61, 127.80, 126.44, 119.05, 113.95, 74.38, 55.31, 28.39, 26.16.

HRMS (FAB) *m/z* Calcd for $C_{18}H_{19}N_2O_2$ (M+1): 295.1447, Found: 295.1460. IR (ATR): 3298 cm^{-1}

1-(4-Methoxyphenyl)-1-(2-phenylquinazoline-4-yl)ethanol (**15**)

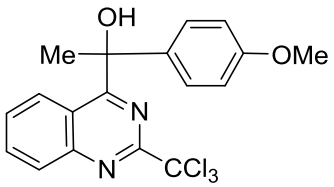


^{1}H-NMR (500 MHz, $CDCl_3$) δ: 8.68 (2H, dd, *J* = 7.9, 1.8 Hz), 8.10 (2H, d, *J* = 7.9 Hz), 7.78-7.72 (2H, m), 7.60-7.53 (3H, m), 7.38-7.31 (3H, m), 6.85 (2H, d, *J* = 8.5 Hz), 6.69 (1H, s), 3.78 (3H, s), 2.15 (3H, s).

^{13}C-NMR (76 MHz, $CDCl_3$) δ: 172.64, 159.04, 157.82, 152.16, 137.54, 137.31, 133.54, 130.97, 129.68, 128.77, 128.56, 127.85, 126.80, 126.59, 119.85, 114.02, 75.06, 55.27, 28.60.

HRMS (FAB) *m/z* Calcd for $C_{23}H_{21}N_2O_2$ (M+1): 357.1603, Found: 357.1581. IR (ATR): 3115 cm^{-1}

1-(4-Methoxyphenyl(-1-(2-trichloromethylquinazoline-4-yl)ethanol **(16)**

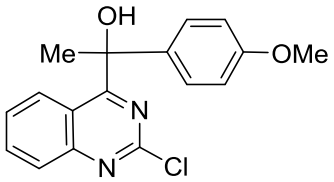


Yield ; 32%

^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.98 (1H, d, *J* = 9.0 Hz), 7.82-7.79 (2H, m), 7.40-7.37 (1H, m), 7.32 (2H, d, *J* = 8.5 Hz), 6.86 (2H, d, *J* = 8.5 Hz), 5.53 (1H, s), 3.78 (3H, s), 2.10 (3H, s).

FAB-Mass: 397 (M+1). IR (ATR): 3114 cm^{-1}

1-(4-Methoxyphenyl)-1-(2-chloroquinazoline-4-yl)ethanol **(17)**



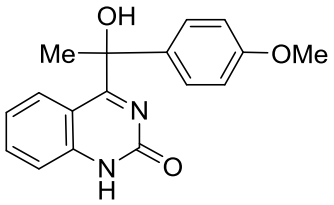
Yield ; 64%

^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.96 (1H, d, *J* = 8.5 Hz), 7.83-7.78 (2H, m), 7.41-7.36 (1H, m), 7.31 (2H, d, *J* = 8.5 Hz), 6.85 (2H, d, *J* = 8.5 Hz), 5.58 (1H, s), 3.77 (3H, s), 2.09 (3H, s).

^{13}C-NMR (126 MHz, $CDCl_3$) δ: 176.48, 159.10, 154.95, 153.09, 136.85, 134.49, 128.42, 127.50, 127.44, 127.05, 119.94, 114.04, 75.87, 55.25, 29.23.

HRMS (FAB) *m/z* Calcd for $C_{17}H_{16}ClN_2O_2$ (M+1): 315.0900, Found: 315.0901. IR (ATR): 3140 cm^{-1}.

4-[1-Hydroxy-1-(4-methoxyphenyl)ethyl]quinazoline-2*(1H)*-one **(18)**



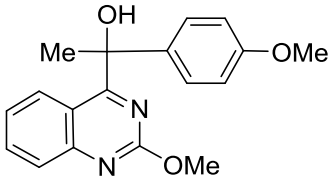
A mixture of **17** (124 mg, 0.4 mg) and 10% NaOH (5 ml) in THF (10 ml) was refluxed for 6 h, and then poured to ice-water. After neutralization with dil. HCl, the product was extracted with dichloromethane, washed with brine, and dried over Na_2SO_4. The organic layer was evaporated and the residue was purified by silica gel column chromatography (dichloromethane) to obtain **18** (19 mg, 16%) as a colorless solid.

^{1}H-NMR (500 MHz, $CDCl_3$) δ: 12.28 (1H, s), 7.61 (1H, t, *J* = 8.5 Hz), 7.56 (1H, d, *J* = 8.5 Hz), 7.49 (1H, d, *J* = 8.5 Hz), 7.38 (2H, d, *J* = 8.5 Hz), 7.03 (1H, t, *J* = 8.5 Hz), 6.88 (2H, d, *J* = 8.5 Hz), 6.02 (1H, s), 3.79 (3H, s), 2.09 (3H, s).

^{13}C-NMR (76 MHz, $CDCl_3$) δ: 181.18, 159.28, 156.36, 143.21, 136.35, 135.23, 128.43, 127.62, 123.12, 116.80, 114.24, 113.10, 75.53, 55.34, 28.43.

HRMS (FAB) *m/z* Calcd for $C_{17}H_{17}N_2O_3$ (M+1): 297.1239, Found: 297.1255. IR (ATR): 3114 cm^{-1}

1-(4-Methoxyphenyl)-1-(2-methoxyquinazoline-4-yl)ethanol **(19)**



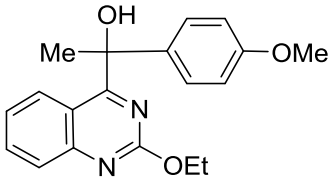
MeONa (1M in methanol, 33 μl, 0.33 mmol) was added to a mixture of **17** (62 mg, 0.2 mmol) in dry methanol (3 ml). The mixture was stirred at room temperature for 1 h, and then concentrated. The product was extracted with ethyl acetate, washed with brine, and dried over Na_2SO_4. The organic layer was evaporated and the residue was purified by silica gel column chromatography (hexane/ ethyl acetate) to obtain **19** (57 mg, 97%) as a colorless amorphous.

^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.83 (1H, d, *J* = 8.5 Hz), 7.70-7.65 (2H, m), 7.33 (2H, d, *J* = 8.5 Hz), 7.19-7.15 (1H, m), 6.85 (2H, d, *J* = 8.5 Hz), 5.96 (1H, s), 4.21 (3H, s), 3.79 (3H, s), 2.10 (3H, s).

^{13}C-NMR (76 MHz, $CDCl_3$) δ: 176.46, 160.38, 158.97, 153.30, 137.22, 133.71, 127.55, 127.52, 127.02, 124.38, 118.03, 113.93, 75.21, 55.22, 55.00, 28.79.

HRMS (FAB) *m/z* Calcd for $C_{18}H_{19}N_2O_3$ (M+1): 311.1396, Found: 311.1418. IR (ATR): 3273 cm^{-1}:,

1-(2-Ethoxyquinazoline-4-yl)-1-(4-methoxyphenyl)ethanol **(20)**



The same procedure with the synthesis of **23**.

Yield ; 82%

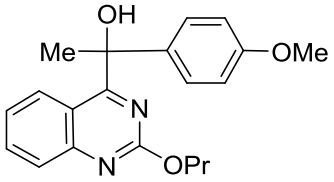
^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.80 (1H, d, *J* = 8.5 Hz), 7.68-7.62 (2H, m), 7.32 (2H, d, *J* = 9.0 Hz), 7.17-7.13 (1H, m), 6.84 (2H, d, *J* = 9.0 Hz), 6.02 (1H, s), 4.64 (2H, q, *J* = 7.0 Hz), 3.78 (3H, s), 2.08 (3H, s), 1.56 (3H, t, *J* = 7.0 Hz).

^{13}C-NMR (76 MHz, $CDCl_3$) δ: 176.40, 159.08, 153.43, 137.29, 133.78, 127.68, 127.53, 127.05, 124.41, 118.02,

113.98, 75.15, 63.69, 55.31, 28.75, 14.62.

HRMS (FAB) *m/z* Calcd for $C_{19}H_{21}N_2O_3$ (M+1): 325.1552, Found: 325.1545. IR (ATR): 3062 cm^{-1}

1-(4-Methoxyphenyl)-1-(2-propoxyquinazoline-4-yl)ethanol **(21)**



The same procedure with the synthesis of **23**.

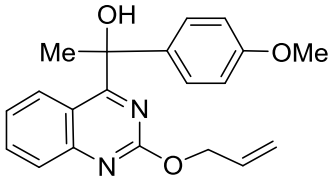
Yield ; 67%

^{1}H -NMR (500 MHz, $CDCl_3$) δ: 7.80 (1H, d, *J* = 8.0 Hz), 7.68-7.64 (1H, m), 7.62 (1H, d, *J* = 8.0 Hz), 7.32 (2H, d, *J* = 9.0 Hz), 7.16-7.13 (1H, m), 6.84 (2H, d, *J* = 9.0 Hz), 6.09 (1H, s), 4.55-4.51 (2H, m), 3.78 (3H, s), 2.08 (3H, s), 1.97 (2H, sextet, *J* = 7.5 Hz), 1.13 (3H, t, *J* = 7.4 Hz).

^{13}C-NMR (76 MHz, $CDCl_3$) δ: 176.40, 160.12, 159.03, 153.40, 137.28, 133.80, 127.72, 127.56, 126.95, 124.32, 117.99, 113.98, 75.08, 69.52, 55.30, 28.63, 22.35, 10.67.

HRMS (FAB) *m/z* Calcd for $C_{20}H_{23}N_2O_3$ (M+1): 339.1709, Found: 339.1706. IR (ATR): 3148 cm^{-1}

1-(2-Allyloxyquinazoline-4-yl)-1-(4-methoxyphenyl)ethanol **(22)**



The same procedure with the synthesis of **23**.

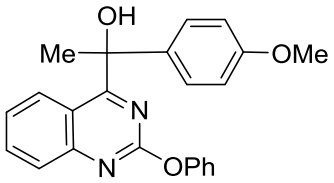
Yield ; 78%

^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.81 (1H, d, *J* = 8.5 Hz), 7.68-7.63 (2H, m), 7.32 (2H, d, *J* = 9.0 Hz), 7.18-7.15 (1H, m), 6.84 (2H, d, *J* = 9.0 Hz), 6.27-6.19 (1H, m), 6.01 (1H, s), 5.54 (1H, dq, *J* = 17.1, 1.5 Hz), 5.37 (1H, dd, *J* = 10.5, 1.5 Hz), 5.10 (2H, dt, *J* = 5.5, 1.0 Hz), 3.78 (3H, s), 2.08 (3H, s).

^{13}C-NMR (76 MHz, $CDCl_3$) δ: 176.59, 159.69, 159.01, 153.35, 137.28, 133.80, 132.70, 127.68, 127.63, 126.93, 124.51, 118.74, 118.11, 113.99, 75.24, 68.51, 55.38, 28.78.

HRMS (FAB) *m/z* Calcd for $C_{20}H_{21}N_2O_3$ (M+1): 337.1552, Found: 337.1578. IR (ATR): 3033 cm^{-1}

1-(4-Methoxyphenyl)-1-(2-phenoxyquinazoline-4-yl)ethanol **(23)**



To a mixture of phenol (36.4 mg, 0.4 mmol) and **17** (100.5 mg, 0.3 mmol) in THF (2 ml), NaH (50% in oil, 36.4 mg, 0.4 mmol) was added with stirring under argon atmosphere at 0 °C. The mixture was refluxed for 24 h. Then the reaction mixture was quenched with water, neutralized with hydrochloric acid, and extracted with dichloromethane. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and then evaporated. The residue was purified by silica gel column chromatography (hexane : ethyl acetate = 3 : 1) to give compound **23**.(91.5 mg, 77%).

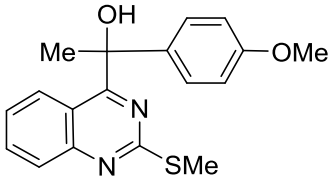
^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.79 (1H, d, *J* = 8.5 Hz), 7.70-7.66 (2H, m), 7.48 (2H, t, *J* = 7.5 Hz), 7.36-7.28 (5H,

m), 7.23-7.19 (1H, m), 6.86 (2H, d, *J* = 9.0 Hz), 5.77 (1H, s), 3.79 (3H, s), 2.08 (3H, s).

^{13}C-NMR (76 MHz, $CDCl_3$) δ: 176.89, 159.73, 158.98, 153.37, 152.97, 137.09, 134.03, 129.49, 127.85, 127.46, 126.94, 125.35, 125.03, 121.61, 118.54, 113.89, 75.60, 55.19, 28.88

HRMS (FAB) *m/z* Calcd for $C_{23}H_{21}N_2O_3$ (M+1): 373.1552, Found: 373.1562. IR (ATR): 3324 cm^{-1}

1-(4-Methoxyphenyl)-1-(2-methylthioquinazoline-4-yl)ethanol **(24)**



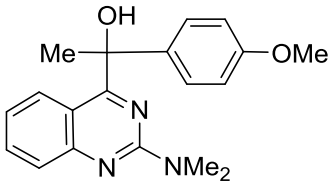
MeSNa (15% in water, 2 ml) was added to a mixture of **17** (62 mg, 0.2 mg) in 1,4-dioxane (10 ml). The mixture was refluxed for 2 h, and then cooled. The product was extracted with ethyl acetate, washed with brine, and dried over Na_2SO_4. The organic layer was evaporated and the residue was purified by silica gel column chromatography (hexane/ ethyl acetate) to obtain **24** quantitatively.

^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.86 (1H, d, *J* = 8.0 Hz), 7.71-7.67 (1H, m), 7.61 (1H, d, *J* = 8.5 Hz), 7.31 (2H, d, *J* = 8.5 Hz), 7.23-7.20 (1H, m), 6.85 (2H, d, *J* = 8.5 Hz), 6.21 (1H, s), 3.78 (3H, s), 2.74 (3H, s), 2.08 (3H, s).

^{13}C-NMR (76 MHz, $CDCl_3$) δ: 172.32, 165.73, 159.00, 152.18, 137.20, 133.66, 127.84, 127.68, 126.85, 125.58, 118.50, 113.95, 74.96, 55.23, 28.57, 14.27.

HRMS (FAB) *m/z* Calcd for $C_{18}H_{19}N_2O_2S$ (M+1): 327.1167, Found: 327.1168. IR (ATR): 3133 cm^{-1}

1-(2-Dimethylaminoquinazoline-4-yl)-1-(4-methoxyphenyl)ethanol **(25)**



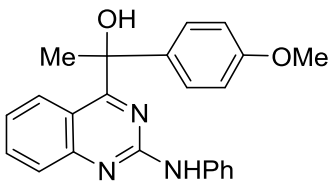
Dimethylamine (50% in water, 1 ml) was added to a mixture of **17** (31 mg, 0.1 mg) in 1,4-dioxane (8 ml). The mixture was refluxed for 17 h, and then cooled. The product was extracted with ethyl acetate, washed with brine, and dried over Na_2SO_4. The organic layer was evaporated and the residue was purified by silica gel column chromatography (hexane/ ethyl acetate) to obtain **25** quantitatively.

^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.59 (1H, d, *J* = 8.5 Hz), 7.52-7.48 (1H, m), 7.39 (1H, d, *J* = 8.5 Hz), 7.32 (2H, d, *J* = 9.0 Hz), 6.91-6.87 (1H, m), 6.84 (2H, d, *J* = 9.0 Hz), 6.60 (1H, s), 3.78 (3H, s), 3.38 (6H, s), 2.05 (3H, s).

^{13}C-NMR (76 MHz, $CDCl_3$) δ: 164.14, 158.77, 156.43, 147.51, 137.51, 133.33, 129.20, 127.71, 126.81, 124.70, 119.57, 113.89, 74.57, 55.23, 42.24, 28.25.

HRMS (FAB) *m/z* Calcd for $C_{19}H_{21}N_3O_2$ (M+1): 324.1712, Found: 324.1715. IR (ATR): 3125 cm^{-1}

1-(4-Methoxyphenyl)-1-(2-phenylaminoquinazoline-4-yl)ethanol (**26**)



Yield ; 76%

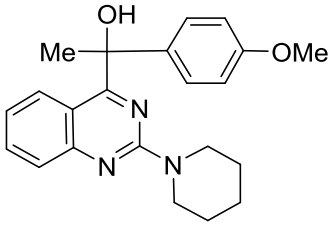
^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.82 (2H, d, *J* = 8.0 Hz), 7.76 (1H, d, *J* = 8.0 Hz), 7.62-7.55 (2H, m), 7.51 (1H, d, *J* =

8.5 Hz), 7.41-7.34 (4H, m), 7.11-7.03 (2H, m), 6.86 (2H, d, *J* = 9.0 Hz), 6.25 (1H, s), 3.78 (3H, s), 2.10 (3H, s).

^{13}C-NMR (76 MHz, $CDCl_3$) δ: 174.11, 159.11, 154.05, 153.21, 139.33, 137.19, 133.67, 129.12, 127.82, 127.37, 127.01, 123.32, 122.86, 119.20, 116.88, 114.06, 74.86, 55.33, 28.50.

HRMS (FAB) *m/z* Calcd for $C_{22}H_{21}N_3O_2$ (M+1): 372.1712, Found: 372.1708. IR (ATR): 3166 cm^{-1}

1-(4-Methoxyphenyl)-1-[2-(piperidine-1-yl)quinazoline-4-yl]ethanol (**27**)



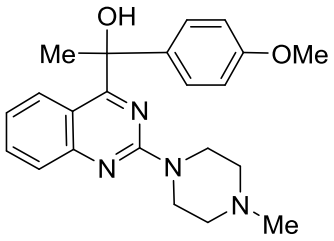
Yield: 74%

^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.56 (1H, d, *J* = 7.9 Hz), 7.51-7.48 (1H, m), 7.38 (1H, d, *J* = 8.5 Hz), 7.33 (2H, d, *J* = 9.2 Hz), 6.89 (1H, ddd, *J* = 8.5, 6.9, 1.7 Hz), 6.85 (2H, d, *J* = 9.2 Hz), 6.52 (1H, s), 4.00-3.98 (4H, m), 3.79 (3H, s), 2.06 (3H, s), 1.77-1.70 (6H, m).

^{13}C-NMR (76 MHz, $CDCl_3$) δ: 173.11, 158.84, 156.36, 154.16, 137.48, 133.24, 127.67, 126.74, 126.50, 121.55, 115.08, 113.82, 74.61, 55.19, 45.15, 28.23, 25.84, 24.82.

HRMS (FAB) *m/z* Calcd for $C_{22}H_{26}N_3O_2$ (M+1): 364.2025, Found: 364.2040. IR (ATR): 3122 cm^{-1}

1-(4-Methoxyphenyl)-1-[2-(4-methylpiperadine-1-yl)quinazoline-4-yl]ethanol (**28**)



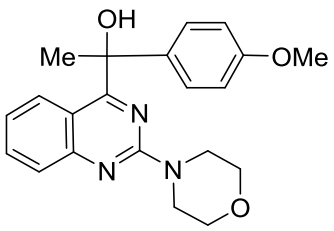
Yield ; quant.

^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.58 (1H, d, *J* = 7.5 Hz), 7.52 (1H, t, *J* = 7.5 Hz), 7.42 (1H, d, *J* = 7.5 Hz), 7.32 (2H, d, *J* = 8.5 Hz), 6.93 (1H, t, *J* = 7.5 Hz), 6.85 (2H, d, *J* = 8.5 Hz), 6.37 (1H, s), 4.06 (4H, t, *J* = 5.0 Hz), 3.79 (3H, s), 2.58 (4H, t, *J* = 5.0 Hz), 2.40 (3H, s), 2.07 (3H, s).

^{13}C-NMR (76 MHz, $CDCl_3$) δ: 173.43, 158.97, 156.36, 154.00, 137.39, 133.48, 127.66, 126.88, 126.69, 122.10, 115.53, 113.92, 74.83, 55.27, 55.04, 46.30, 44.17, 28.43.

HRMS (FAB) *m/z* Calcd for $C_{22}H_{27}N_4O_2$ (M+1): 379.2134, Found: 379.2128. IR (ATR): 3367 cm^{-1}

1-(4-Methoxyphenyl)-1-(2-morpholinoquinazoline-4-yl)ethanol (**29**)



Yield ; 82%

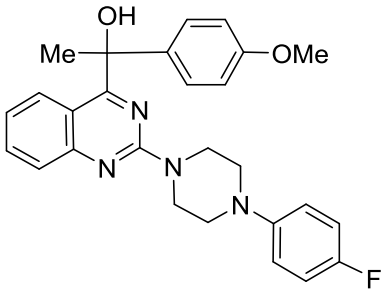
^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.61 (1H, d, *J* = 8.5 Hz), 7.57-7.53 (1H, m), 7.45 (1H, d, *J* = 8.0 Hz), 7.33 (2H, d, *J* =

8.5 Hz), 6.98-6.95 (1H, m), 6.86 (2H, d, *J* = 8.5 Hz), 6.28 (1H, s), 4.02 (4H, t, *J* = 5.0 Hz), 3.88 (4H, t, *J* = 5.0 Hz), 3.80 (3H, s), 2.07 (3H, s).

^{13}C-NMR (76 MHz, $CDCl_3$) δ: 173.61, 158.97, 156.42, 153.83, 137.36, 133.55, 127.66, 126.88, 126.72, 122.34, 115.73, 113.92, 74.92, 66.88, 55.25, 44.61, 23.44.

HRMS (FAB) *m/z* Calcd for $C_{21}H_{24}N_3O_2$ (M+1): 366.1818, Found: 366.1823. IR (ATR): 3418 cm^{-1}

1-(4-Methoxyphenyl)-1-{2-[4-(4-fluorophenyl)piperadine-1-yl]quinazoline-4-yl}ethanol (**30**)



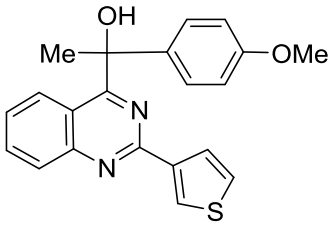
Yield ; 67%

^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.61 (1H, d, *J* = 8.5 Hz), 7.54 (1H, t, *J* = 7.5 Hz), 7.44 (1H, d, *J* = 8.5 Hz), 7.33 (2H, d, *J* = 9.0 Hz), 7.04-6.94 (5H, m), 6.85 (2H, d, *J* = 9.0 Hz), 6.33 (1H, s), 4.19 (4H, t, *J* = 5.0 Hz), 3.79 (3H, s), 3.27 (3H, t, *J* = 5.0 Hz), 2.08 (3H, s).

^{13}C-NMR (76 MHz, $CDCl_3$) δ: 173.62, 159.03, 157.47 (d, *J* = 226.5 Hz), 156.34, 153.94, 148.06, 137.38, 133.59, 127.69, 126.94, 126.74, 122.35, 118.47 (d, *J* = 7.6), 115.870 (d, *J* = 21.8), 115.68, 113.93, 74.93, 55.28, 50.55, 44.26, 28.33.

HRMS (FAB) *m/z* Calcd for $C_{27}H_{28}N_4O_2F$ (M+1): 459.2196, Found: 459.2185. IR (ATR): 3372 cm^{-1}

1-(4-Methoxyphenyl)-1-(3-thienylquinazoline-4-yl)ethanol **(31)**



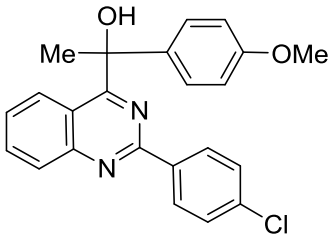
Under an atmosphere of argon, the mixture of **17** (62mg, 0.2 mmol), 3-thienylboroic acid (38 mg, 0.3 mmol), potassium carbonate (55 mg, 0.2 mmol), palladium acetate (23 mg, 0.01 mmol), and 1,1'-bis(di-*tert*-butylphosphino)ferrocene (4.8 mg, 0.01 mmol) in 1,4-dioxane (10 mL) was refluxed for 8 h. The reaction mixture was evaporated. The residue was purified with column chromatography to obtain **31** (50.4 mg, 0.14 mmol, 70%).

^{1}H-NMR (500 MHz, $CDCl_3$) δ: 8.50 (1H, dd, *J* = 3.5, 1.0 Hz), 8.11 (1H, dd, *J* = 5.0, 1.0 Hz), 8.04 (1H, d, *J* = 8.0 Hz), 7.77-7.73 (1H, m), 7.68 (1H, d, *J* = 8.5 Hz), 7.47 (1H, dd, *J* = 5.0, 3.5 Hz), 7.35 (2H, d, *J* = 8.5 Hz), 7.32-7.28 (1H, m), 6.85 (2H, d, *J* = 8.5 Hz), 6.67 (1H, s), 3.78 (4H, s), 2.14 (3H, s).

^{13}C-NMR (76 MHz, $CDCl_3$) δ: 172.62, 158.99, 155.00, 152.05, 141.28, 137.43, 133.47, 129.33, 128.48, 127.76, 127.59, 126.59, 126.50, 126.31, 119.59, 113.97, 74.85, 55.24, 28.56.

HRMS (FAB) *m/z* Calcd for $C_{21}H_{19}N_2O_2S$ (M+1): 363.1168, Found: 363.1169. IR (ATR): 3257 cm^{-1}

1-[2-(4-Chlorophenyl)quinazoline-4-yl]-1-(4-methoxyphenyl)ethanol **(32)**



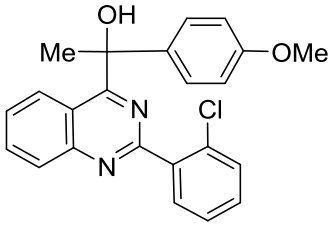
Yield ; 70%

^{1}H-NMR (500 MHz, $CDCl_3$) δ: 8.63 (2H, d, *J* = 8.5 Hz), 8.08 (1H, d, *J* = 8.0 Hz), 7.80-7.76 (1H, m), 7.73 (1H, d, *J* = 8.0 Hz), 7.55 (2H, d, *J* = 8.5 Hz), 7.37-7.27 (3H, m), 6.86 (2H, d, *J* = 9.0 Hz), 6.53 (1H, s), 3.78 (3H, s), 2.15 (3H, s).

^{13}C-NMR (76 MHz, $CDCl_3$) δ: 172.84, 159.07, 156.90, 152.06, 137.43, 137.21, 135.83, 133.65, 129.86, 129.61, 128.98, 127.78, 127.00, 126.68, 119.90, 114.05, 75.19, 55.31, 28.80.

HRMS (FAB) *m/z* Calcd for $C_{23}H_{20}ClN_2O_2$ (M+1): 391.1HRMS (FAB) *m/z* Calcd for $C_{23}H_{20}ClN_2O_2$ (M+1): 391.1214, Found: 391.1194. IR (ATR): 3149 cm^{-1}

1-[2-(2-Chlorophenyl)quinazoline-4-yl]-1-(4-methoxyphenyl)ethanol **(33)**



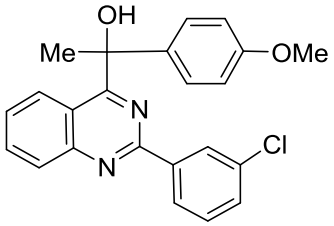
Yield : 90%

^{1}H-NMR (500 MHz, $CDCl_3$) δ: 8.13 (1H, d, *J* = 8.5 Hz), 8.04-8.02 (1H, m), 7.73-7.76 (2H, m), 7.60-7.58 (1H, m), 7.48-7.44 (2H, m), 7.42-7.37 (3H, m), 6.87 (2H, d, *J* = 9.1 Hz), 6.73 (1H, s), 3.78 (3H, s), 2.17 (2/5 x 3H, s), 2.15 (3/5 x 3H, s).

^{13}C-NMR (76 MHz, $CDCl_3$) δ: 172.39, 159.07, 158.73, 151.85, 137.52, 137.23, 133.62, 133.39, 132.08, 130.89, 130.75, 129.60, 127.86, 127.51, 127.04, 126.49, 119.60, 114.05, 74.98, 55.32, 28.62.

FAB-Mass: 391 (M+1). IR (ATR): 3380 cm^{-1}

1-[2-(3-Chlorophenyl)quinazoline-4-yl]-1-(4-methoxyphenyl)ethanol **(34)**



Yield ; 84%

^{1}H-NMR (500 MHz, $CDCl_3$) δ: 8.67 (1H, t, *J* = 2.0 Hz), 8.58-8.55 (1H, m), 8.10 (1H, d, *J* = 8.0 Hz), 7.80-7.74 (2H, m), 7.54-7.51 (2H, m), 7.37-7.34 (3H, m), 6.86 (2H, d, *J* = 9.0 Hz), 6.53 (1H, s), 3.78 (3H, s), 2.16 (3H, s).

^{13}C-NMR (76 MHz, $CDCl_3$) δ: 172.95, 159.09, 156.57, 152.02, 139.21, 137.44, 134.92, 133.71, 130.88, 130.00, 129.69, 128.58, 127.78, 127.18, 126.69, 126.64, 120.08, 114.05, 75.32, 55.27, 28.80.

FAB-Mass: 391 (M+1). IR (ATR): 3352 cm^{-1}

(v) Optical Resolution of 1a

A solution of the racemic **1a** (3 mg/ mL) in 10% isopropanol/ *n*-hexane was subjected to a chiral column chromatography (DICEL CHIRALCEL OD, 10 X 250 mm) by HPLC using 2% isopropanol/ *n*-hexane as an eluent (4 mL/ min). The separation using HPLC was performed several times and the collected fractions are identified as the crude (+)-**1a** (retention time: 31-37.5 min) and (–)-**1a** (retention time: 50-62 min).

Crude (+)-**1a**: HPLC analysis, 98.6% ee; $[a]_D^{25}$ +46.1 (c 0.50, $CHCl_3$)

Crude (–)-**1a**: HPLC analysis, 71.8% ee; $[a]_D^{26}$ –38.5 (c 0.50, $CHCl_3$)

(vi) Purification of the Crude Enantiomers, (+)-1a and (–)-1a

The separated crude enantiomers were recrystallized from dicloromethane/ *n*-hexane to afford (+)-**1a** and (–)-**1a** both as colorless needles.

(+)-**1a**: HPLC analysis

100%ee, DICEL CHIRALCEL OD-H, 4.6 X 150 mm, isopropanol/ *n*-hexane = 2 : 98, 1 mL/min, 26.2 min

(–)-**1a**: HPLC analysis

98%ee, DICEL CHIRALCEL OD-H, 4.6 X 150 mm, isopropanol/ *n*-hexane = 2 : 98, 1 mL/min, 18.6 min

◆Biology

Cell culture

A549 cells (ATCC) were maintained in RPMI1640 medium supplemented with 10% (v/v) heat-inactivated fetal bovine serum, 1 mM sodium pyrvate, 0.1 mM non essencial amino acid and 20 units/mL penicillin and 20 μg/mL streptomycin at 37ºC in an atmosphere of 5% CO_2.

Cell proliferation assay

The cells (5 x 10^3 cells/well) were seeded and treated with different concentrations of compounds for 72 hr. Cell proliferation was measured using a CellTiter 96 Aqueous One Solution Cell Proliferation Assay according to the manufacturer's protocol (Promega Corporation).

Flow cytometric analysis

The cells (5 x 10^5 cells/well) were treated with compounds at varied concentrations for 24 hours. After incubation with test compounds, the cells were harvested and suspended by 0.25% trypsin/EDTA (Gibco). After centrifugation at 800 x g for 5 minutes, the cells were washed in PBS and fixed in 70% ethanol overnight at 4ºC. Fixed cells were permeabilized 0.25% Triton X-100 in PBS, incubated with 1% BSA in PBS for 60 min and stained with propidium iodide and analyzed by a Cytomics FC500 flow cytometer (Beckman Coulter).

Immunofluorescent microscopy analysis

The cells (8 x 10^4 cells/well) were grown on plastic chamber slides in 400 μL RPMI medium and then treated with compounds (0.4% DMSO as a final concentration in the assay). After incubation with test compounds, the cells were fixed with 4% paraformaldehyde (200 μL) for 5 min at room temperature and ice-cold methanol (200 μL) overnight at -20ºC. Fixed cells were permeabilized with 0.5% Triton X-100/PBS (200 μL), blocked with 5% NGS in TBS-T (50 μL) for 1 hr and stained with 50 μL of mouse anti-alpha-tubulin antibody solution in TBS-T (1:50,000) overnight at 4ºC, followed by a 1 hr incubation with 50 μL of goat anti-mouse IgG Alexa Fluor 488 secondary antibody solution (1:800). The cells then were mounted using VECTASHIELD with DAPI and analyzed by fluorescence microscopy IX-71 (Olympus). Images were obtained with a CCD camera DP30BW (Olympus).

In vitro tubulin polymerization assay

Tubulin polymerization assay were performed using the fluorescence-based tubulin polymerization kit according to the manufacturer's protocol (Cytoskeleton, Inc.) .

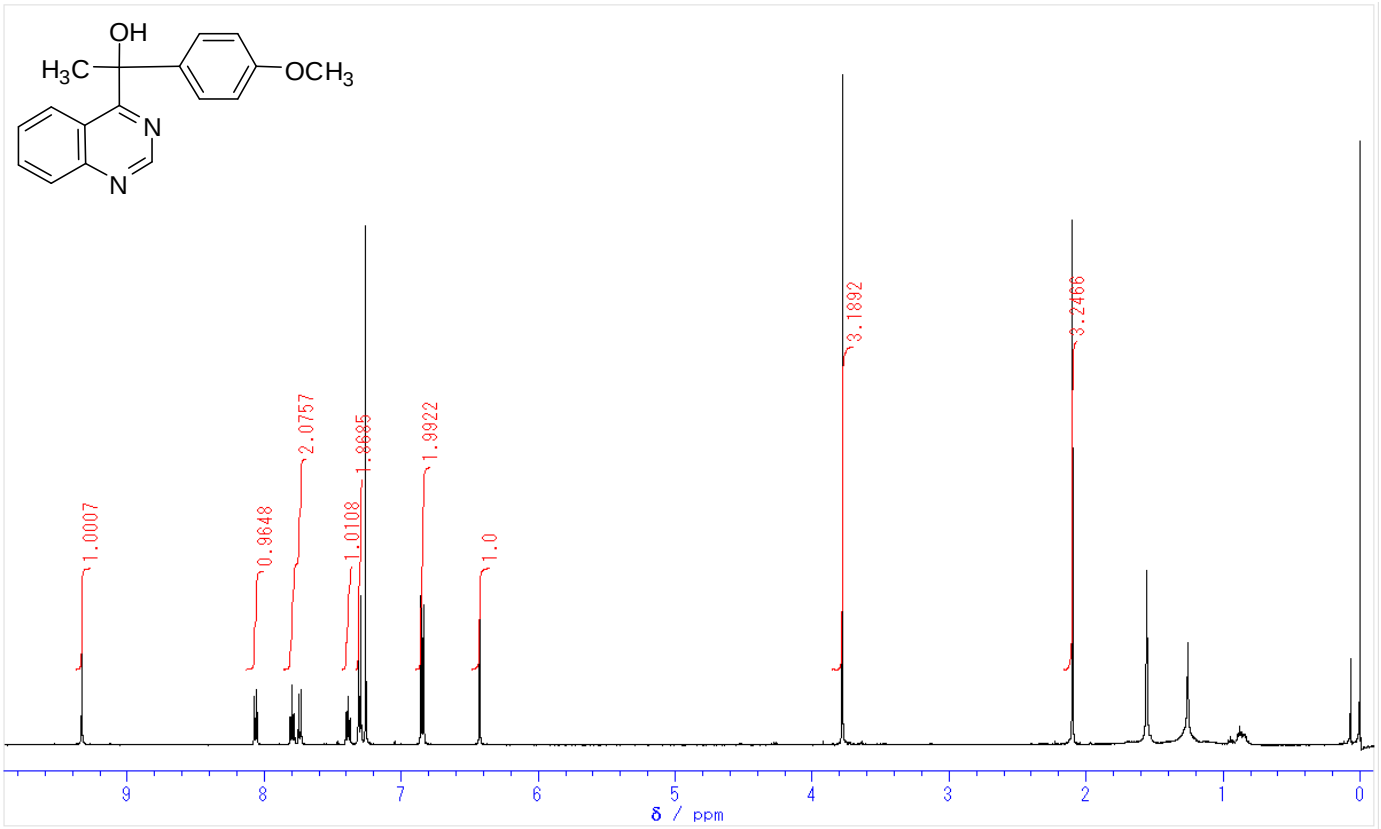
Competitive displacement biding assay

Each reaction was performed in binding buffer (0.25 mM PIPES, pH 6.9, 0.05 mM GTP, 0.25 mM MgCl2), test compounds and >99% purified tubulin stock (1 mg/ml). The reaction mixture (100 μL) was preincubated for 30 min at 37ºC. After preincubation, colchicine (5 μM) was added to the reaction mixture and the mixture was further incubated for 30 min at 37ºC. The reaction mixtures were loaded onto a Sephadex G-25 column previously equilibrated with the binding buffer. The columns were placed into 1.5 ml tubes and spun at 800 x g for 1 min at room temperature. Each fraction was transferred into a 96 well plate. The plate was then read on a fluorescence 96-well spectrophotometer at excitation and emission wavelengths of 360 nm and 450 nm, respectively.

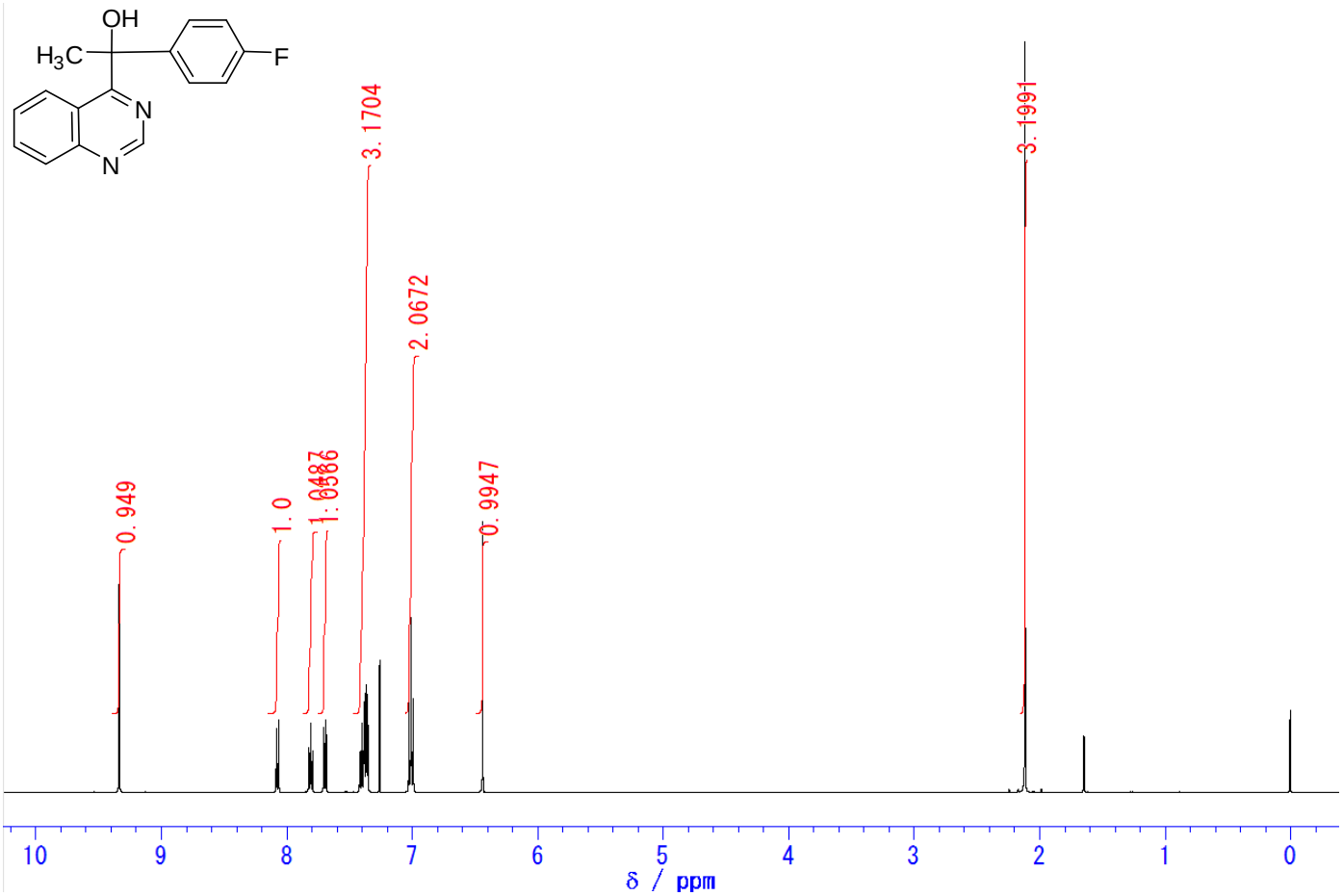
6. NMR Charts

The ^{1}H-NMR (500 MHz[a], 300 MHz[b]) spectra was recorded on JEOL ECA-500 NMR Spectrometer or on JEOL ECA-300 NMR Spectrometer using TMS and $CDCl_3$ as internal standards.

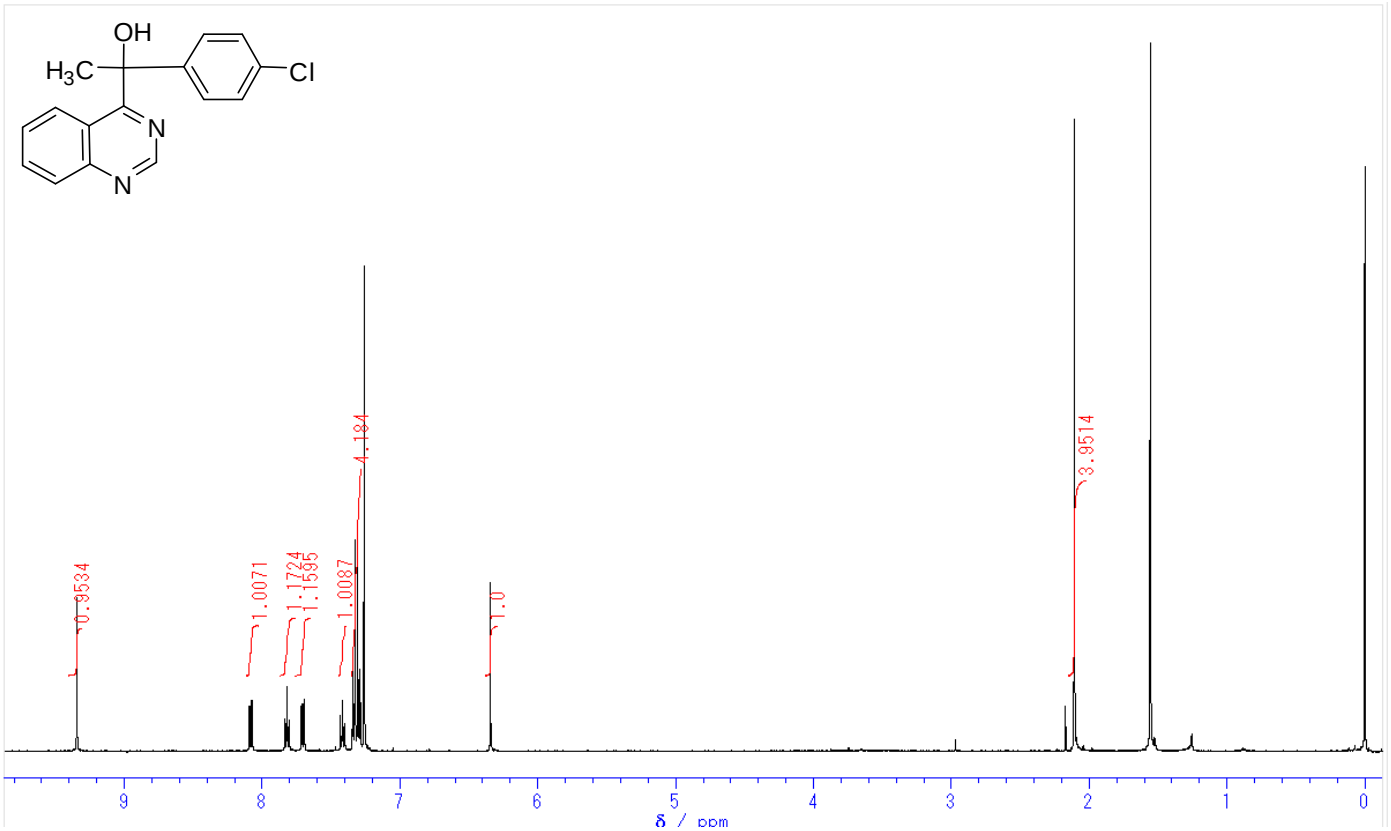
1-(4-Methoxylphenyl)-1-(quinazolin-4-yl)ethanol (**1a**)[a]



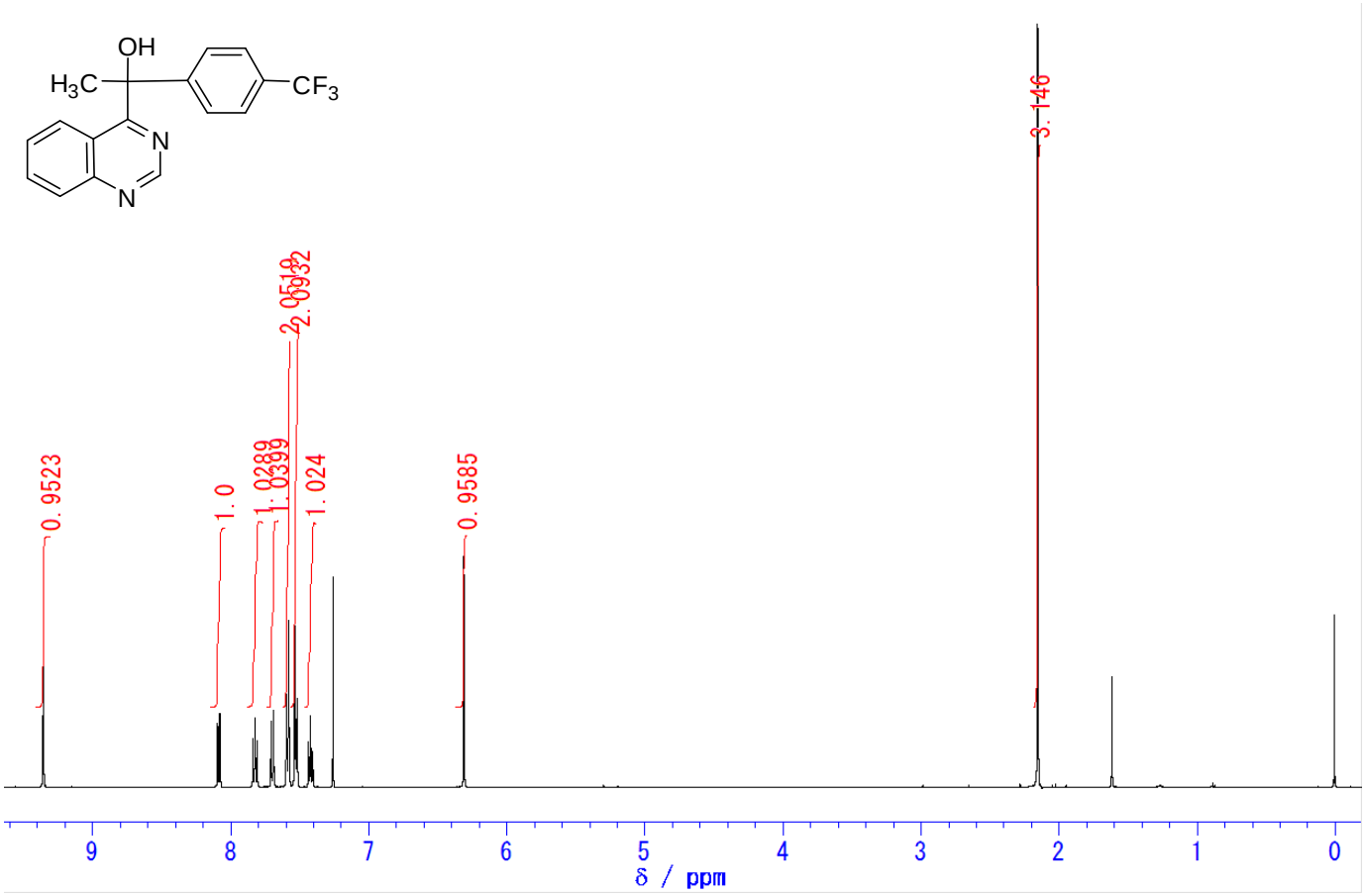
1-(4-Fluorophenyl)-1-(quinazolin-4-yl)ethanol **(1b)**[a]



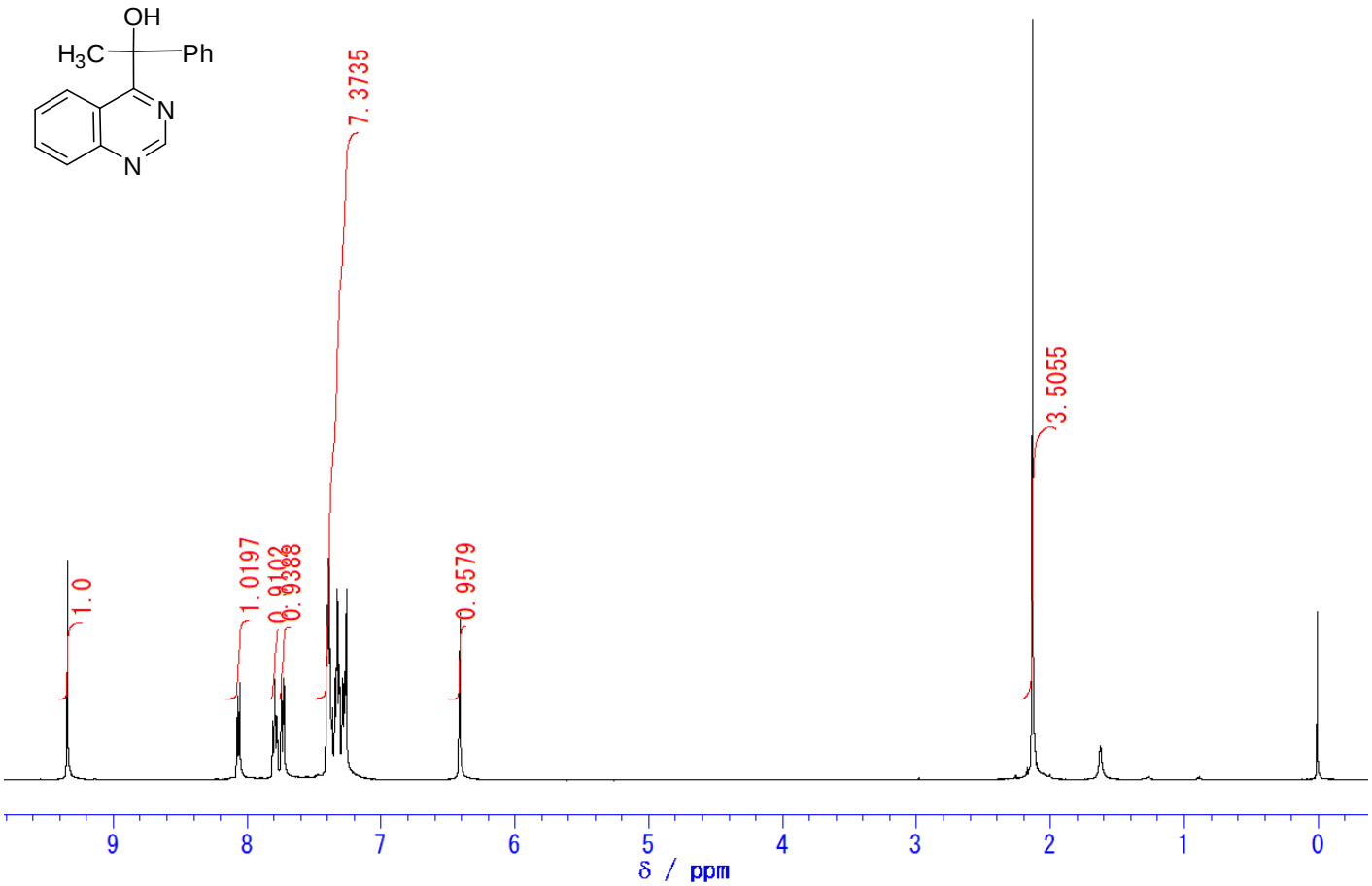
1-(4-Chlorophenyl)-1-(quinazolin-4-yl)ethanol **(1c)**[a]



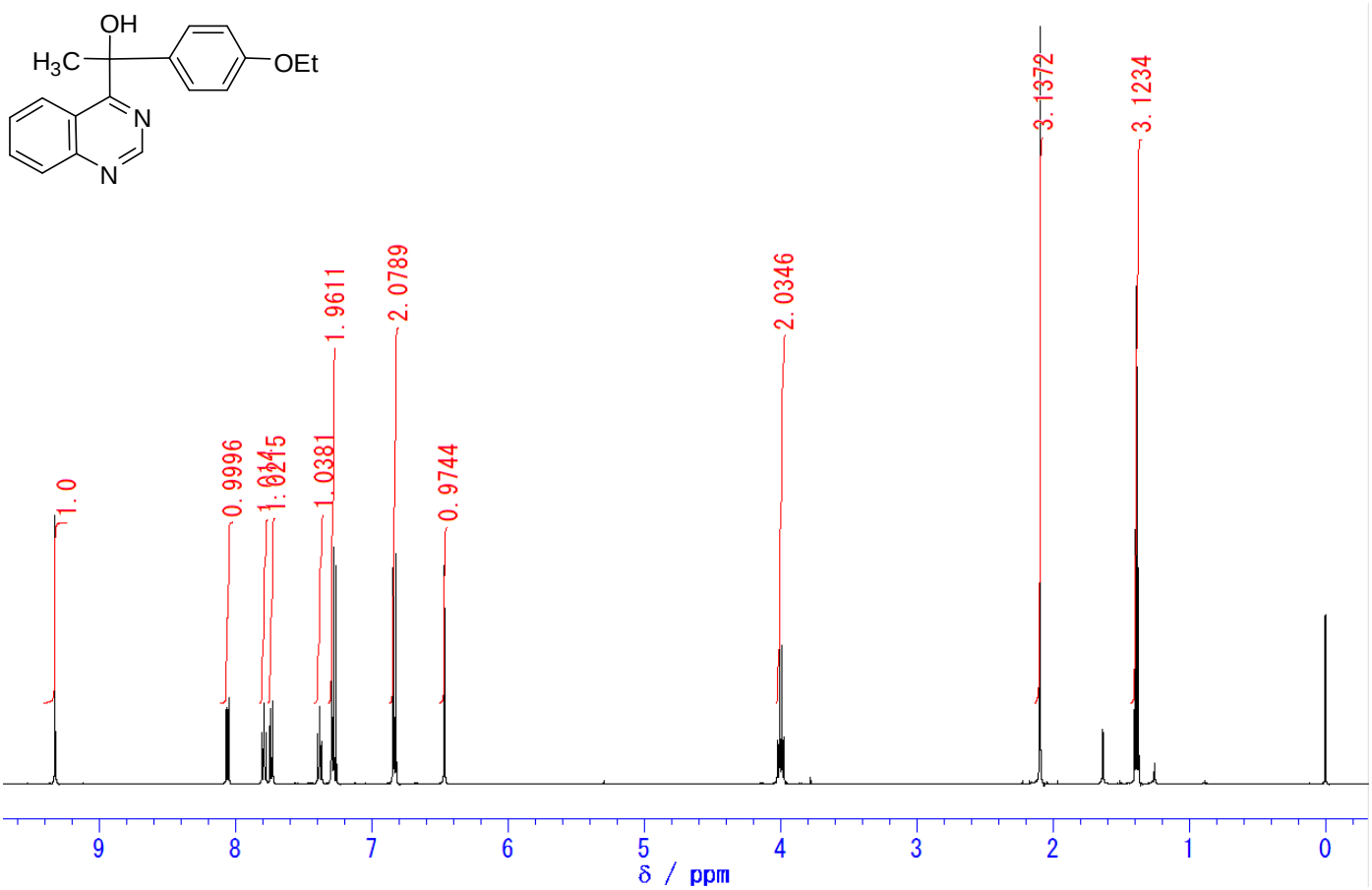
1-(4-Trifluoromethylphenyl)-1-(quinazolin-4-yl)ethanol **(1d)**[a]



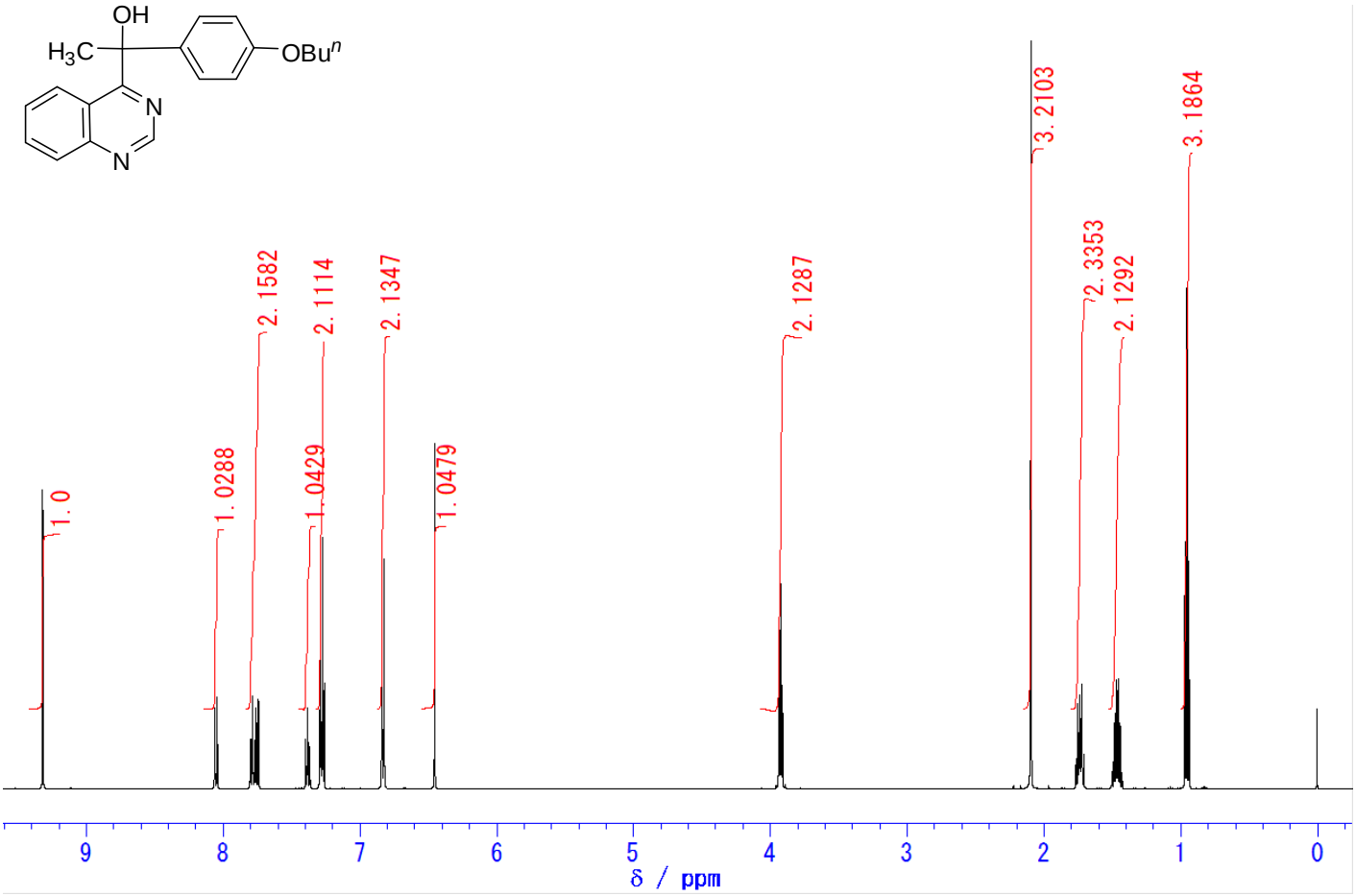
1-Phenyl-1-(quinazolin-4-yl)ethanol **(1e)**[a]



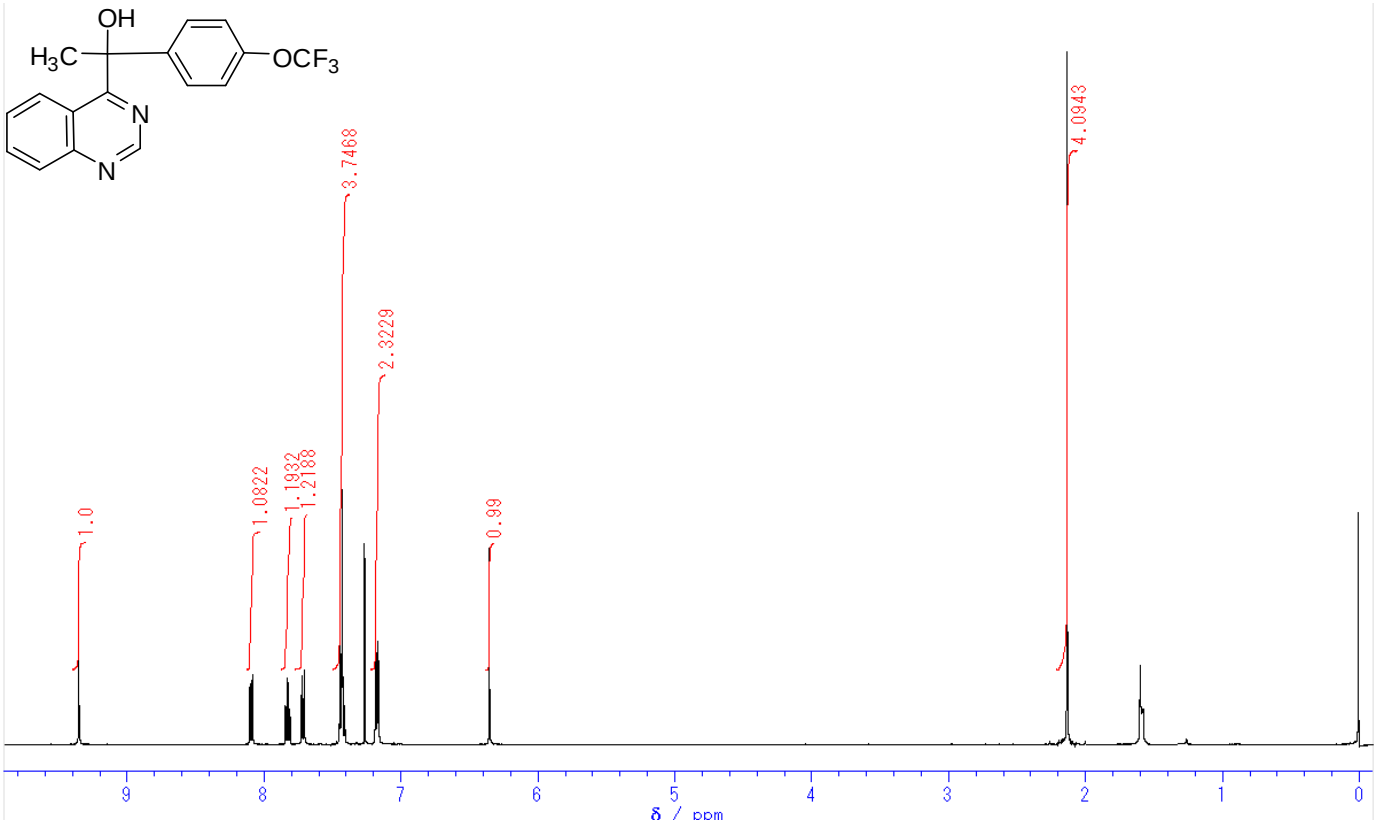
1-(4-Ethoxylphenyl)-1-(quinazolin-4-yl)ethanol **(1f)**[a]



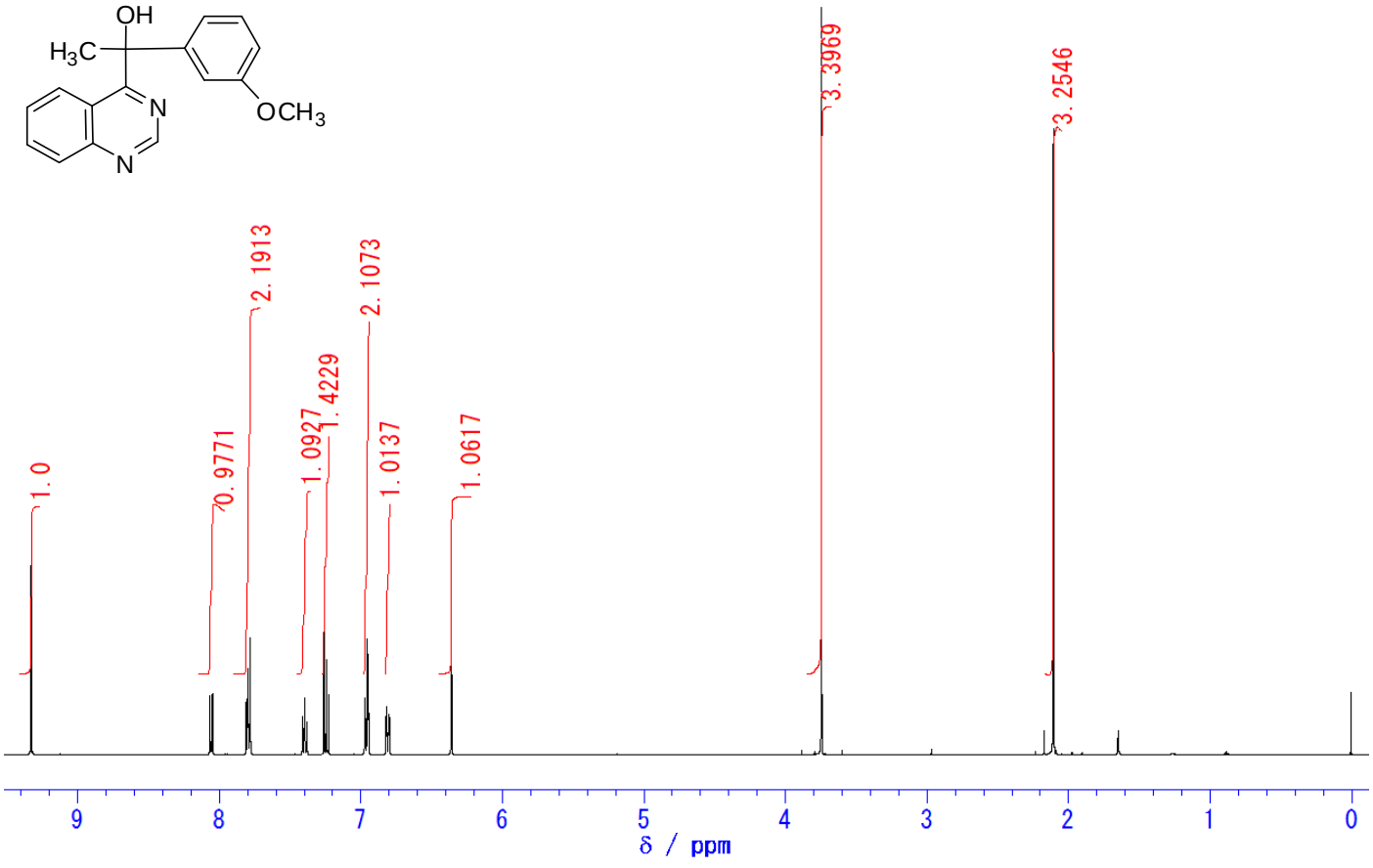
1-(4-*n*-Butoxylphenyl)-1-(quinazolin-4-yl)ethanol **(1g)**[a]



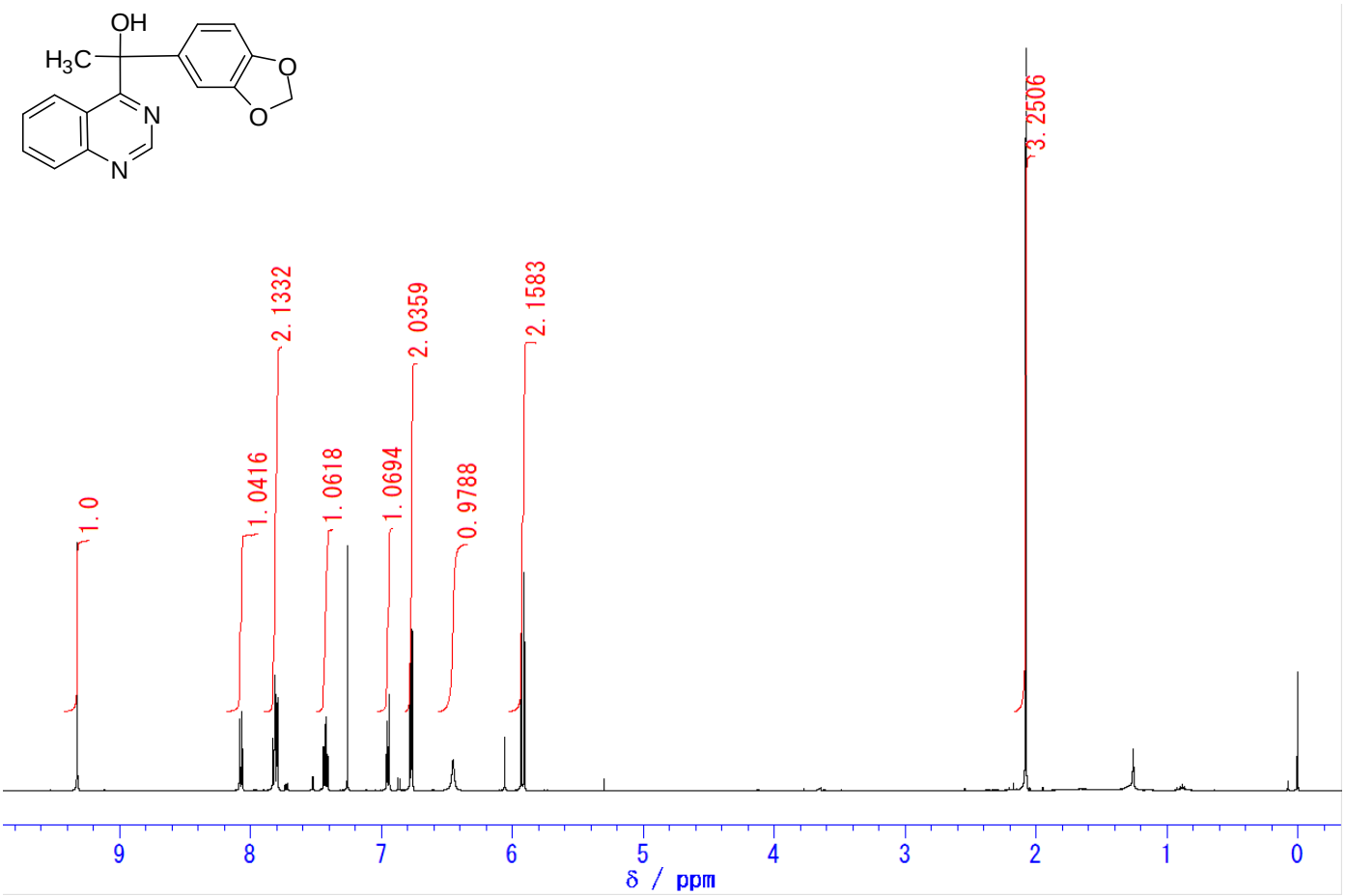
1-(4-Trifluoromethoxylphenyl)-1-(quinazolin-4-yl)ethanol **(1h)**[a]



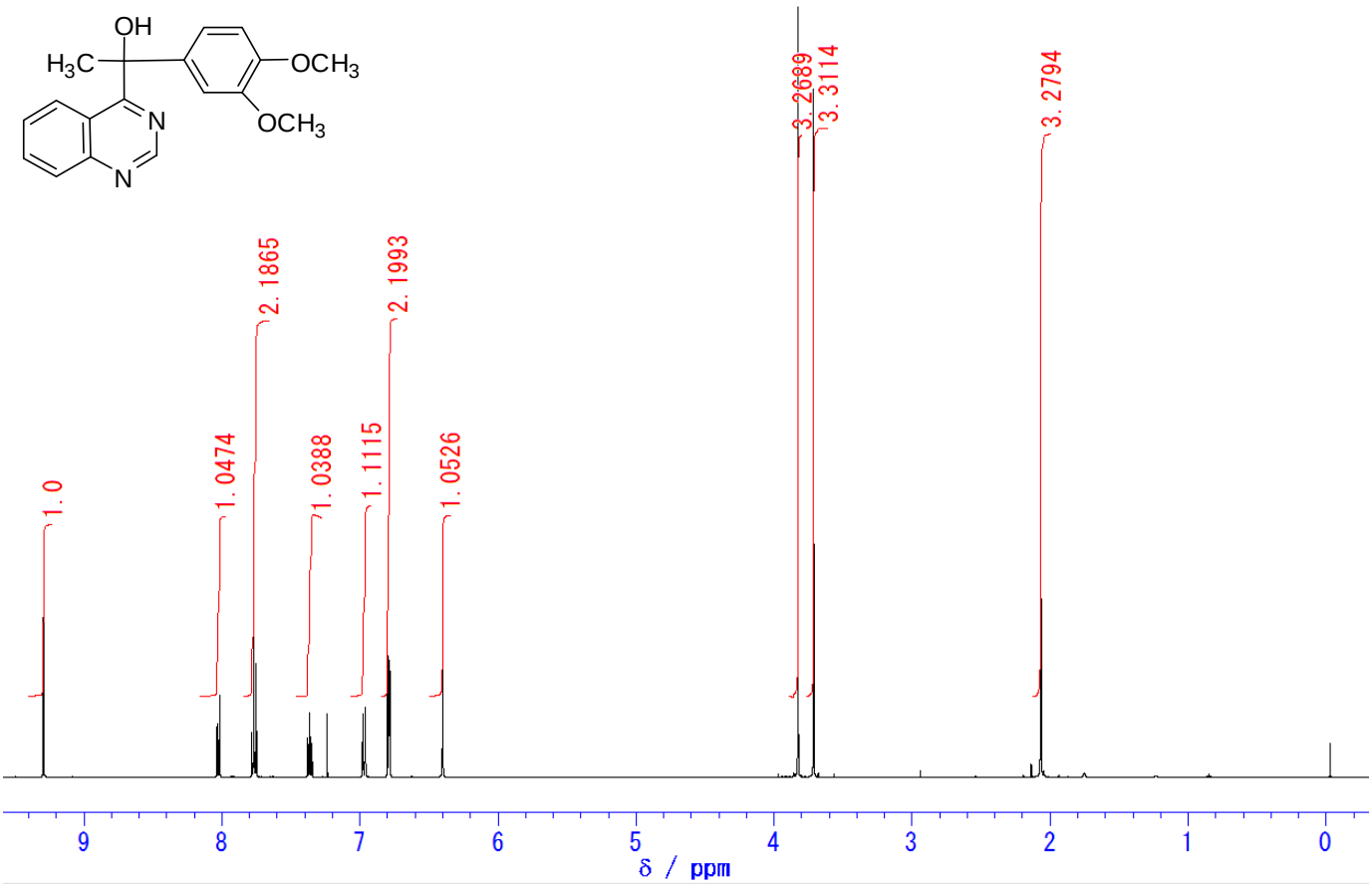
1-(3-Methoxyphenyl)-1-(quinazolin-4-yl)ethanol **(1i)**[a]



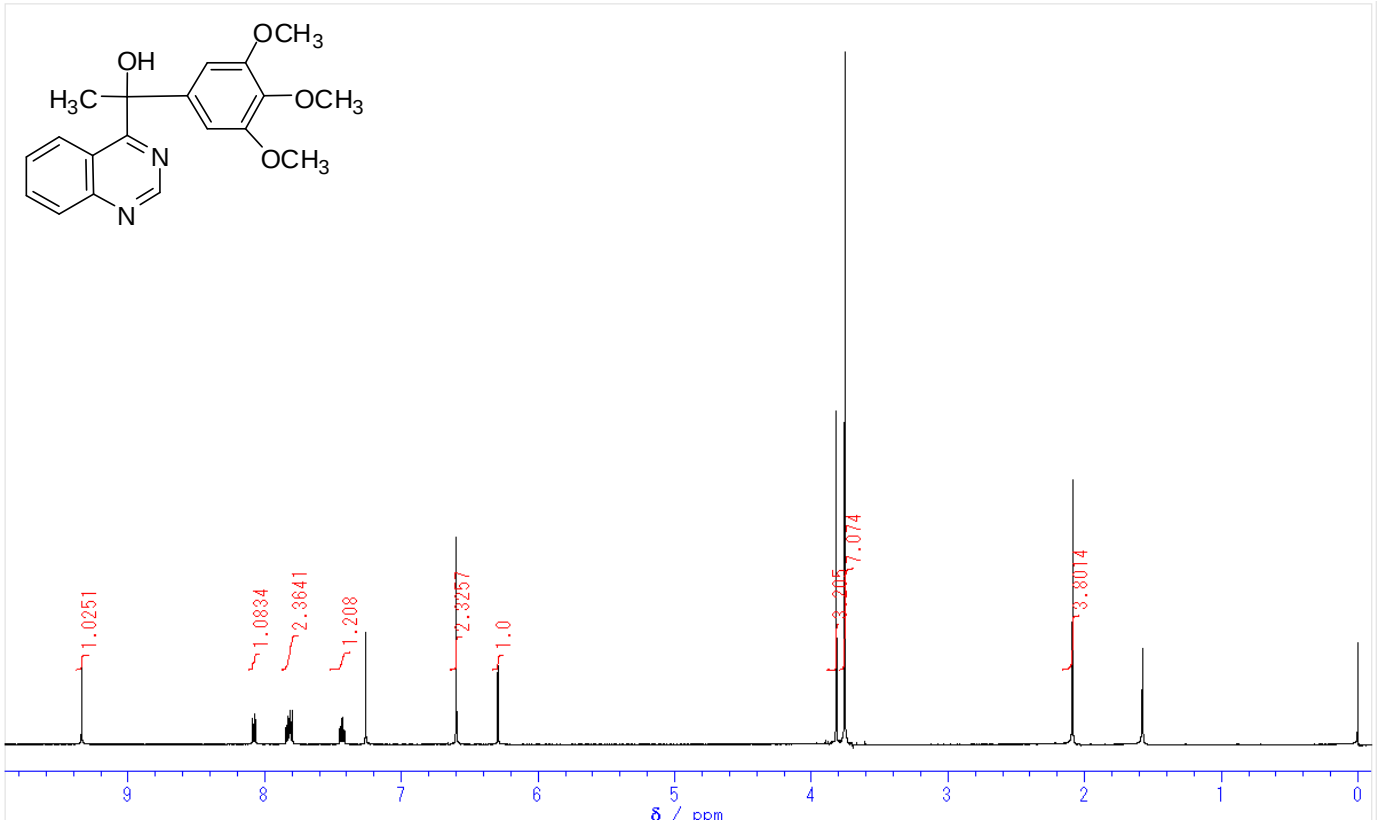
1-(2,3-Methylenedioxyphenyl)-1-(quinazoline-4-yl)-ethanol **(1j)**[a]



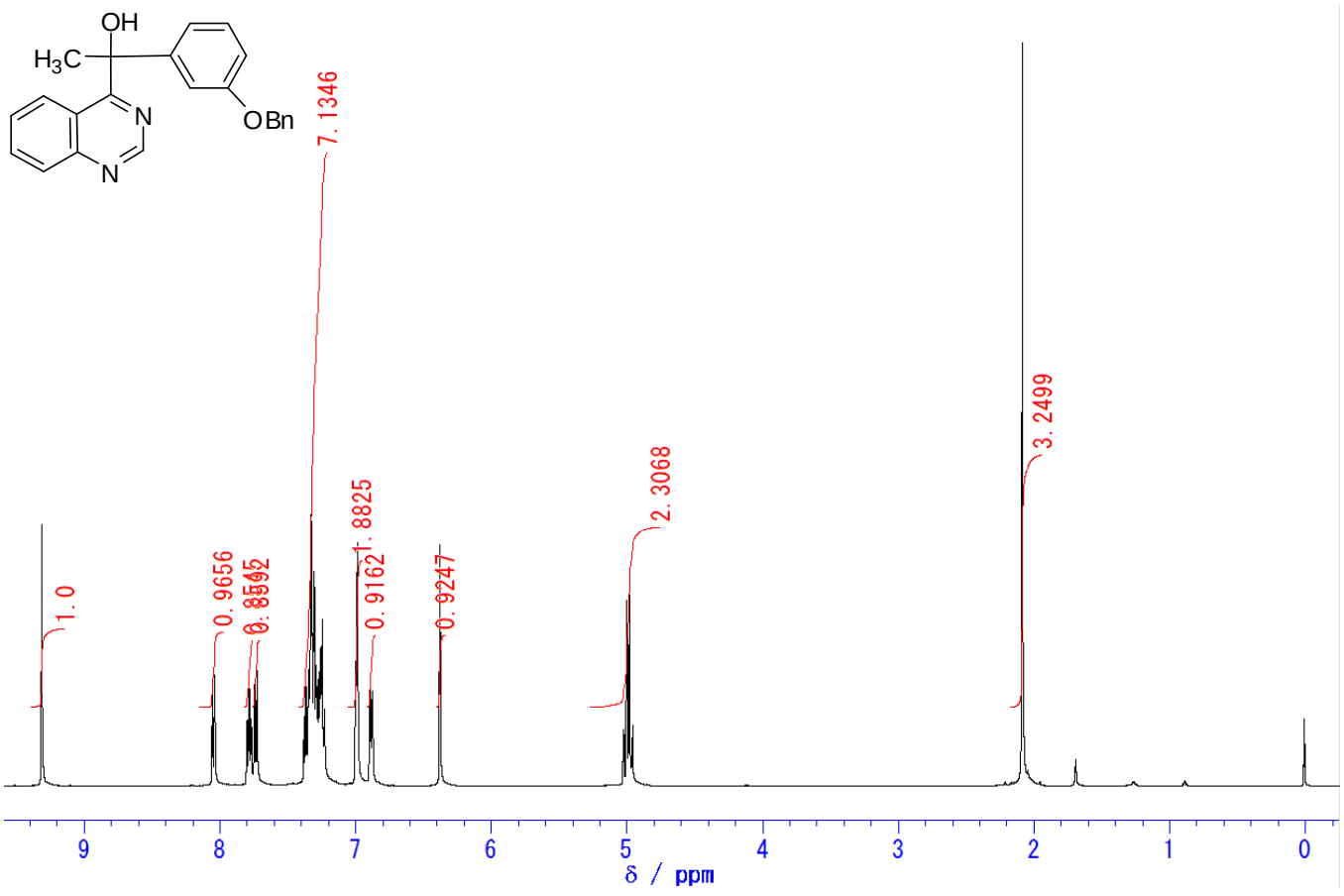
1-(3,4-Dimethoxyphenyl)-1-(quinazoline-4-yl)ethanol **(1k)**[a]



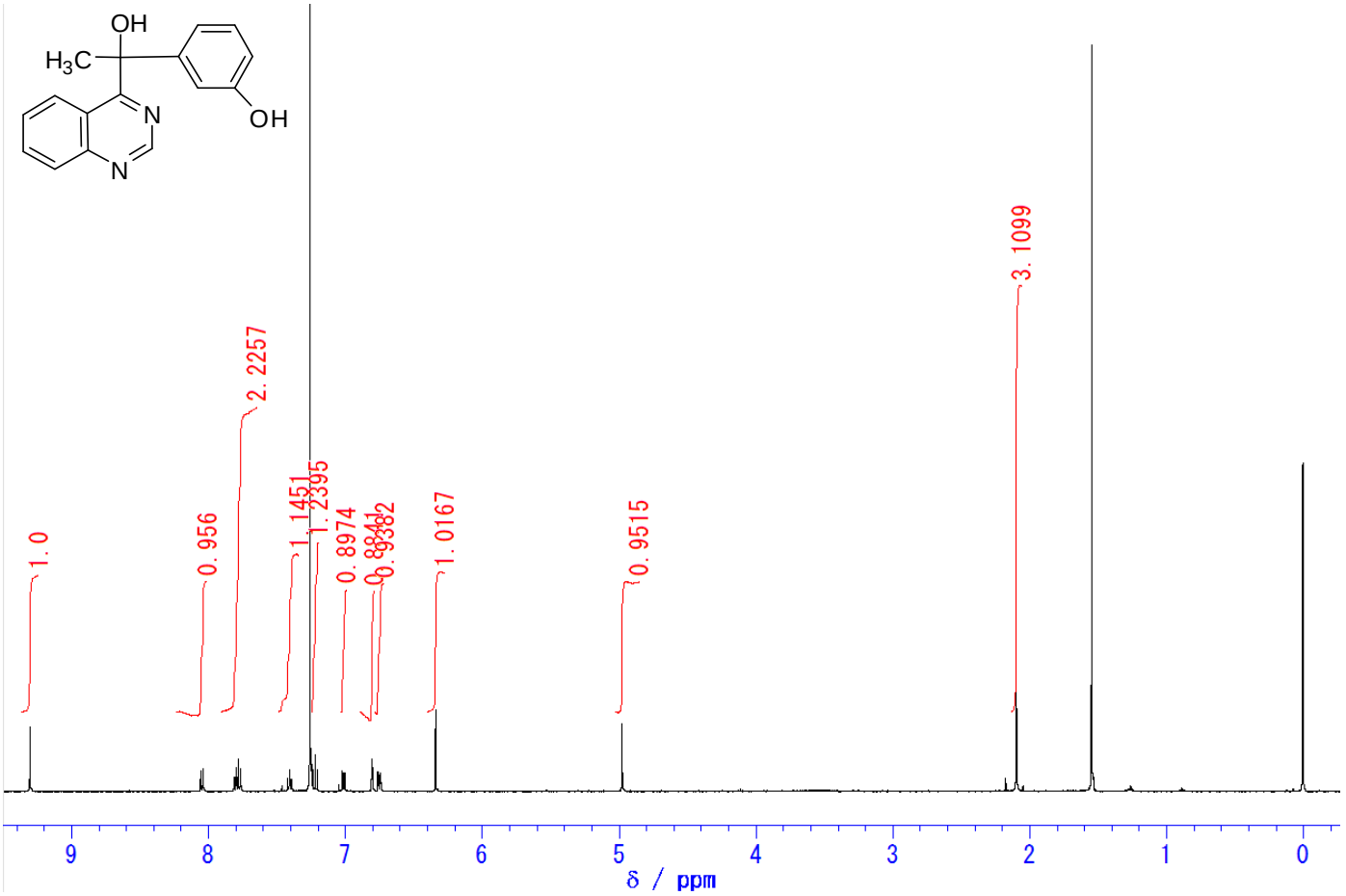
1-(3,4,5-Trimethylphenyl)1-(quinazoline-4-yl)ethanol **(1l)**[a]



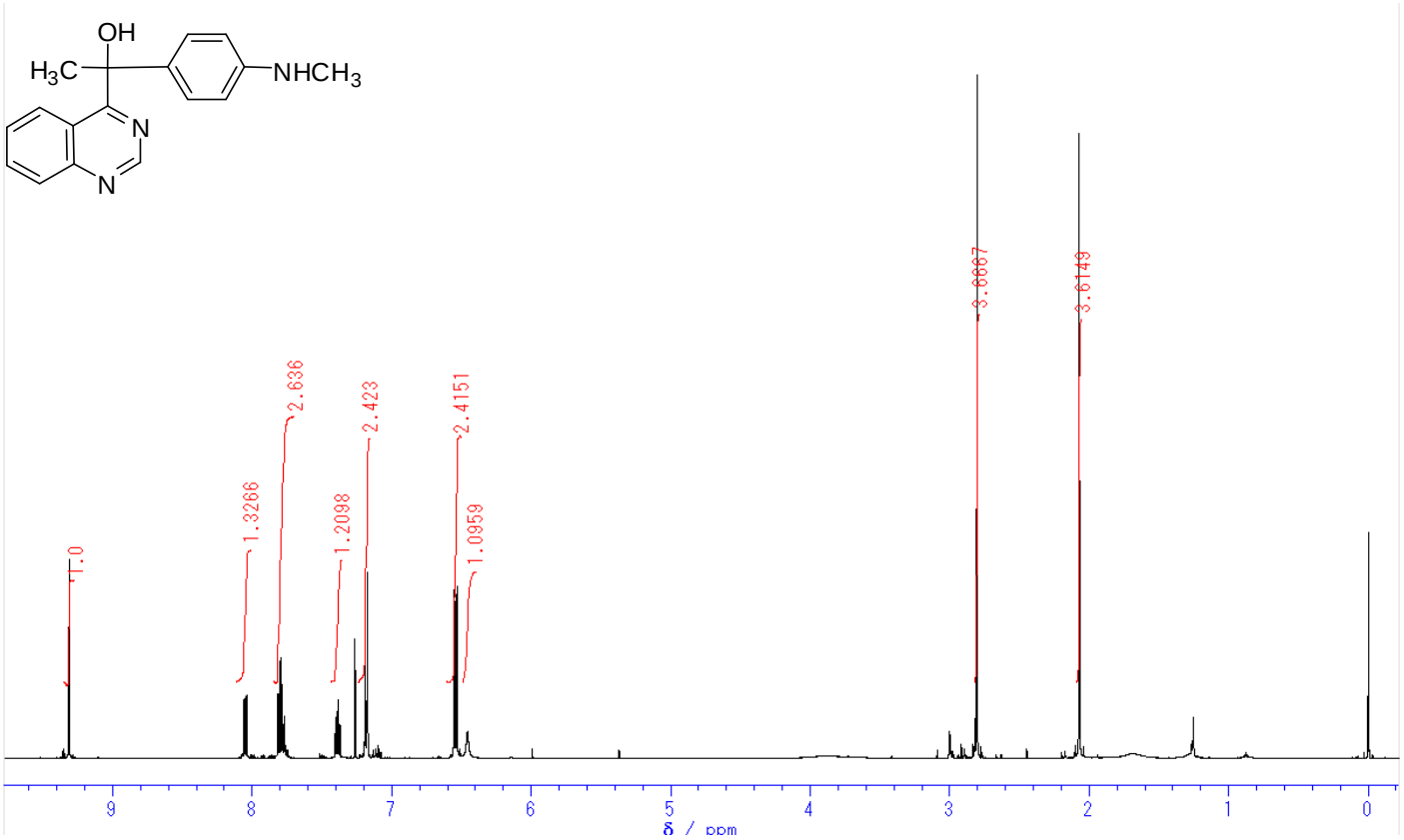
1-(3-Benzyloxyphenyl)-1-(quinazolin-4-yl)ethanol (**1m**)[a]



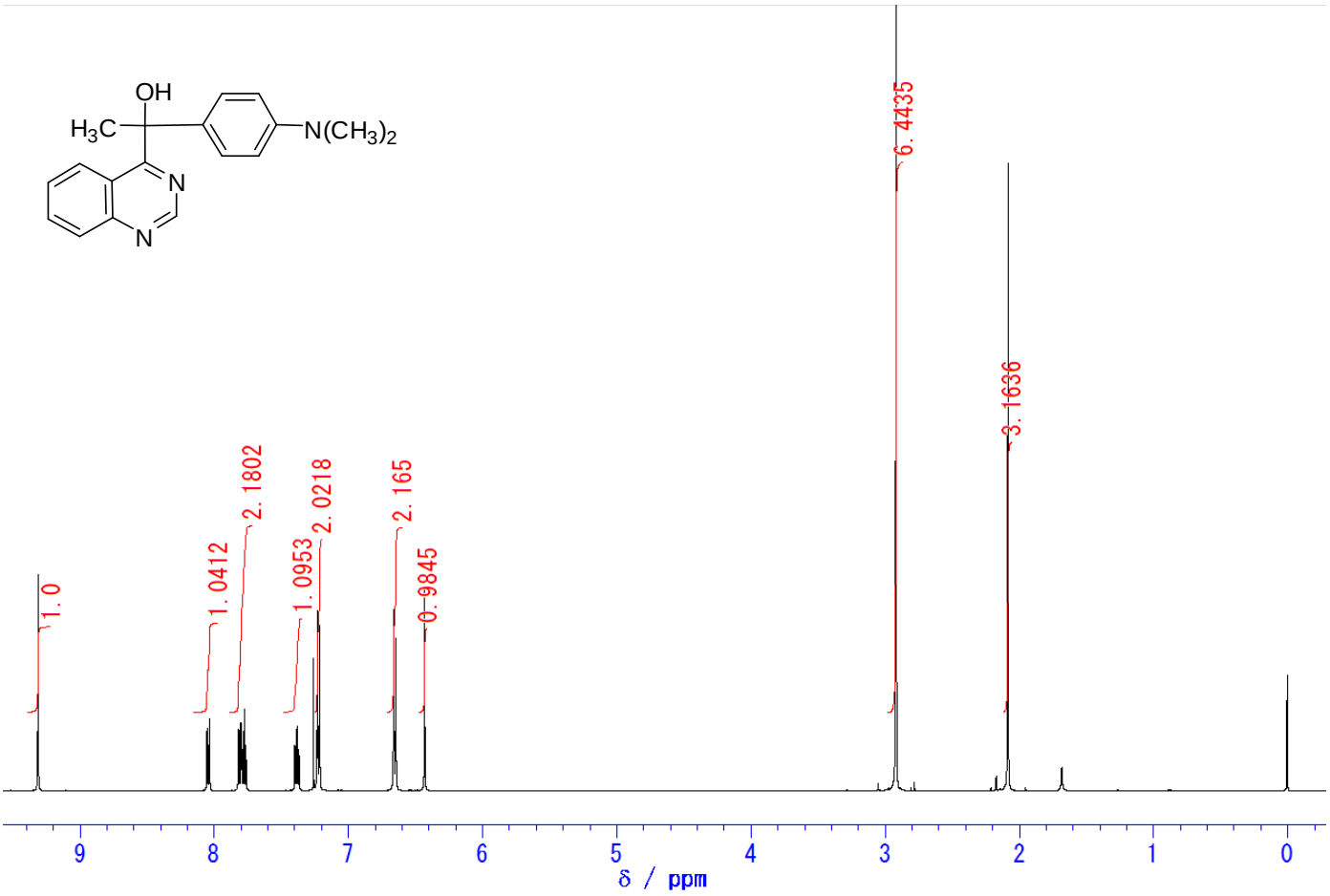
1-(3-Hydroxyphenyl)-1-(quinazolin-4-yl)ethanol (**1n**)[a]



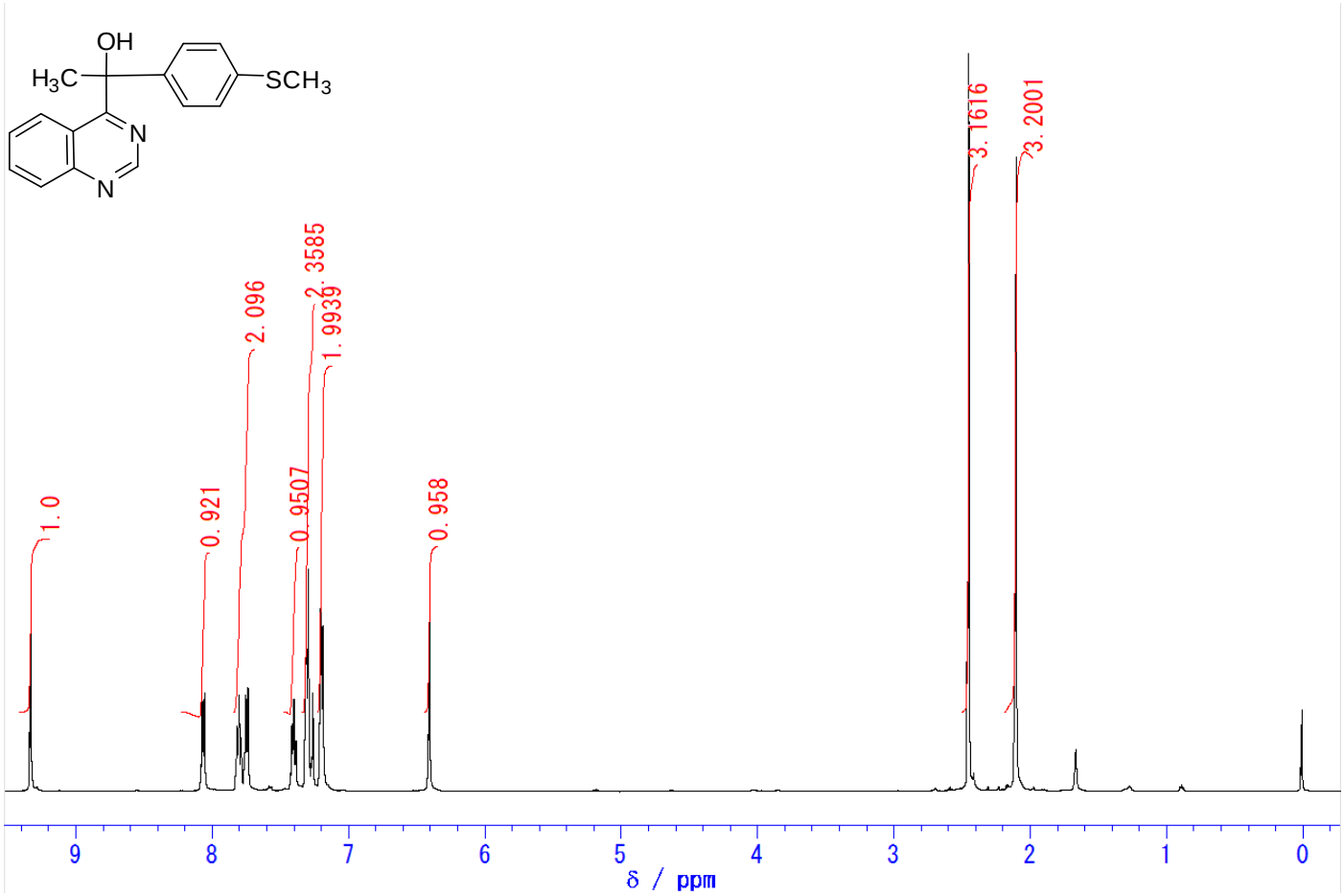
1-(4-ethylaminophenyl)-1-(quinazoline-4-yl)ethanol **(1o)**[a]



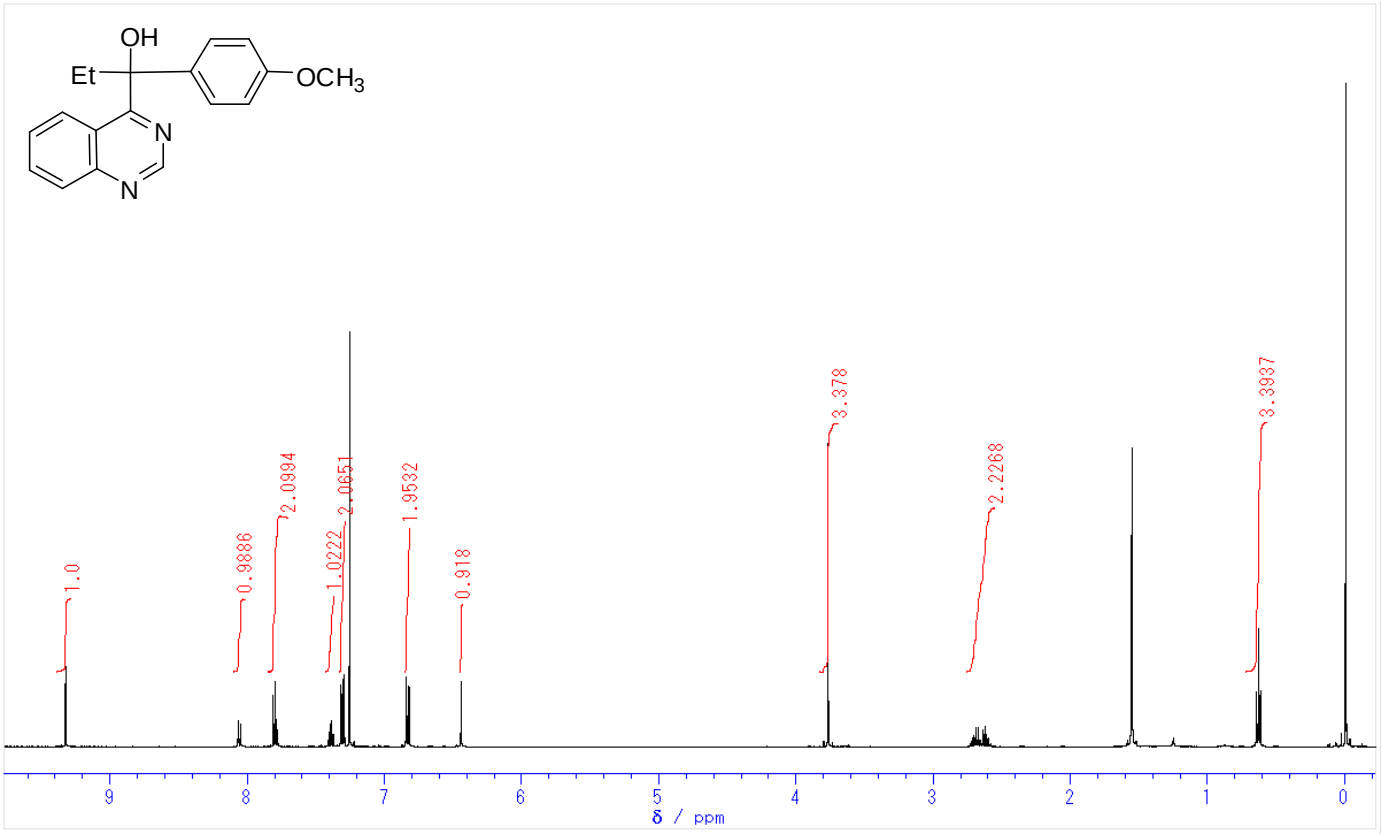
1-(4-Dimethylaminophenyl)-1-(quinazoline-4-yl)ethanol **(1p)**[a]



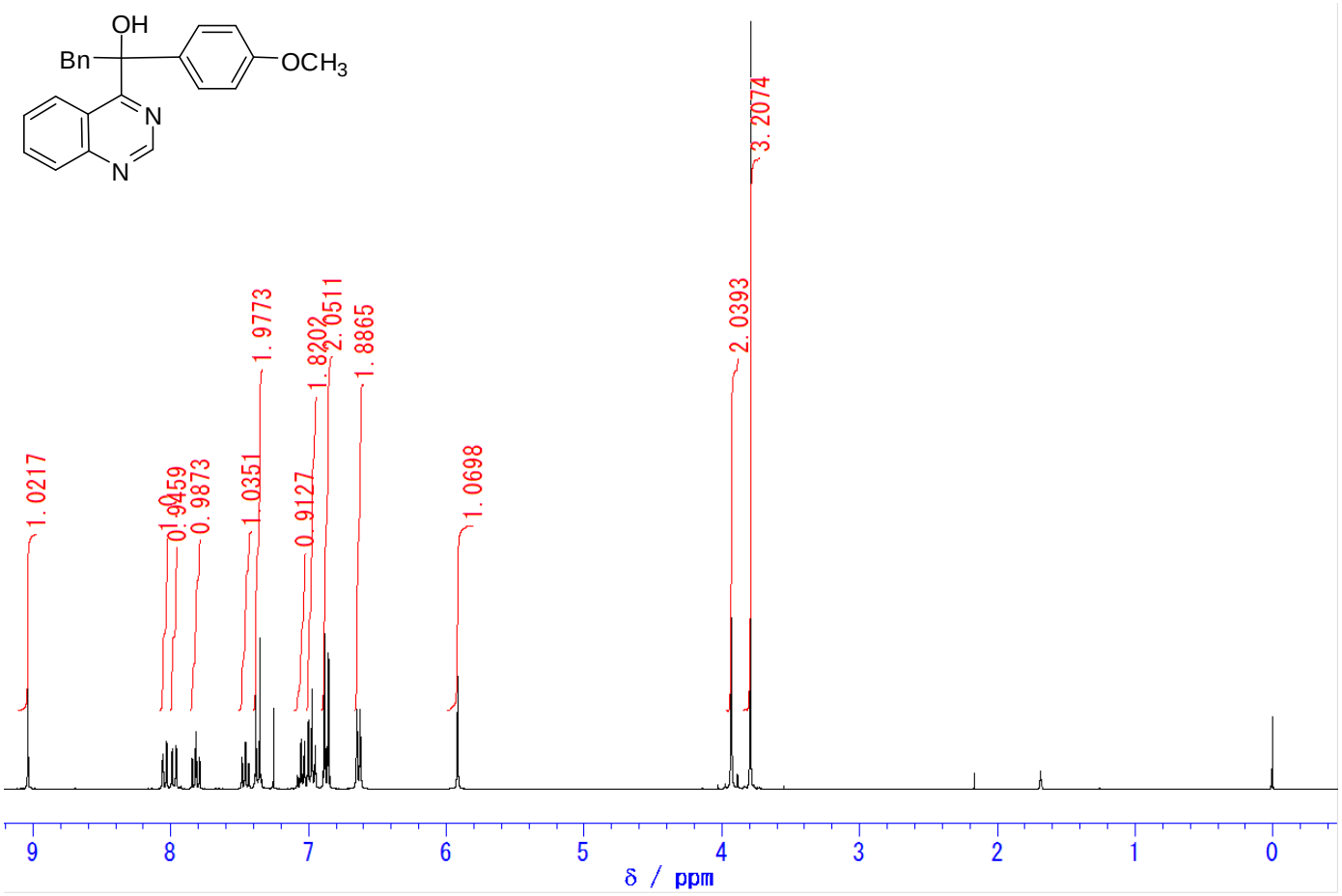
1-(4-Methylthiophenyl)-1-(quinazoline-4-yl)ethanol **(1q)**[a]



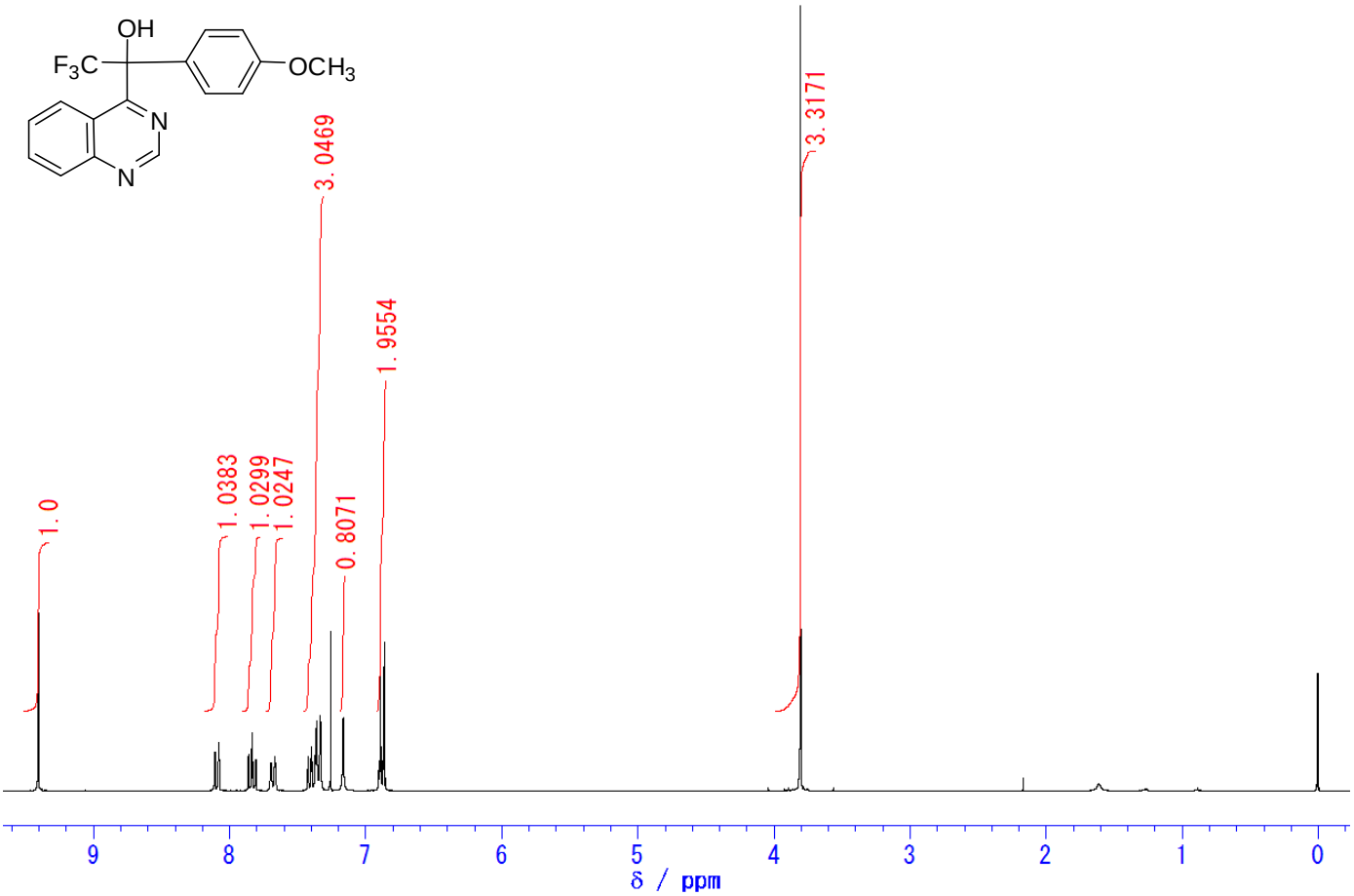
1-(4-Methoxyphenyl)-1-(quinazoline-4-yl)propan-4-ol **(5)**[a]



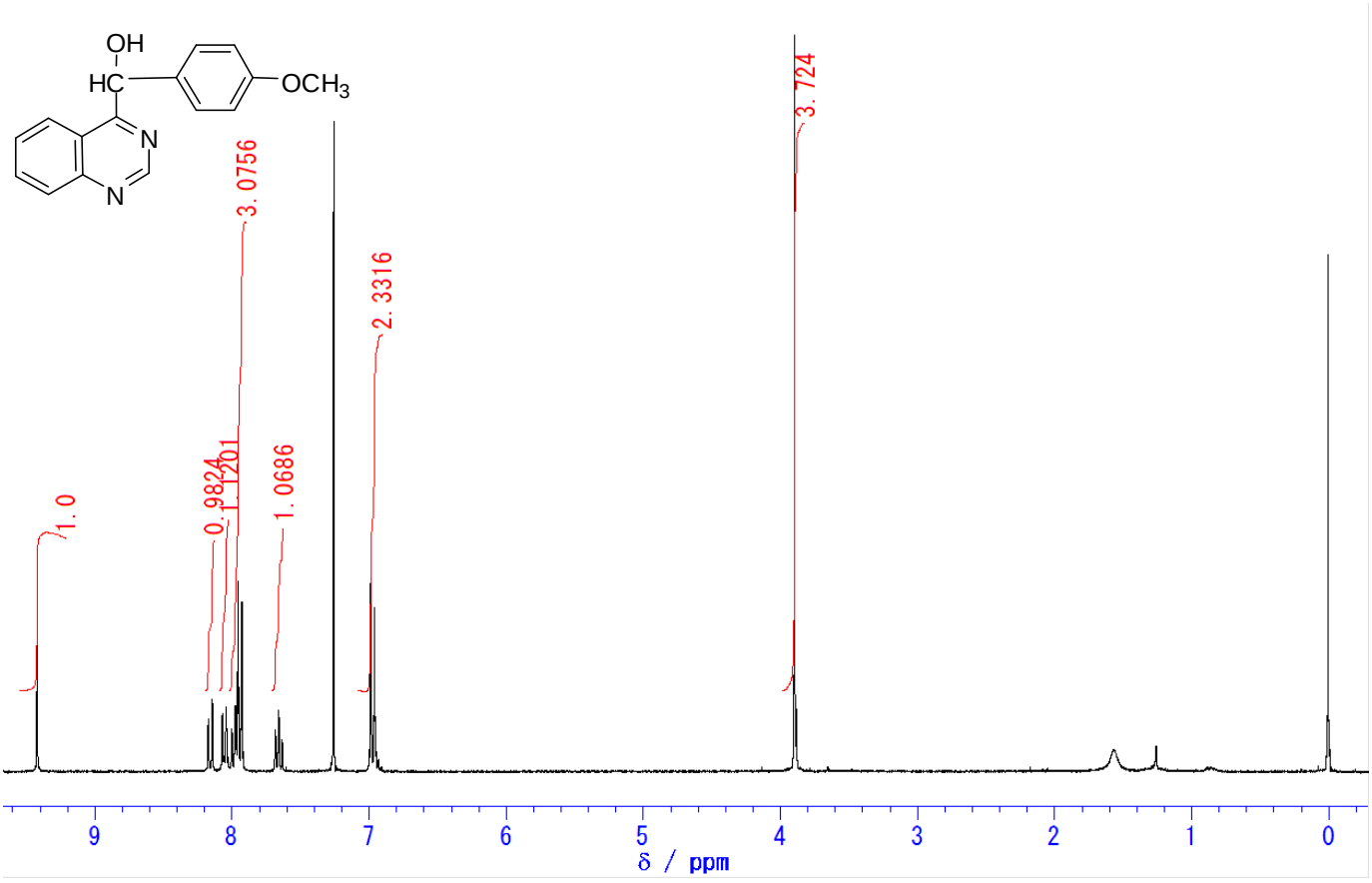
1-(4-Methoxyphenyl)-2-phenyl-1-(quinazoline-4-yl)ethanol **(6)**[b]



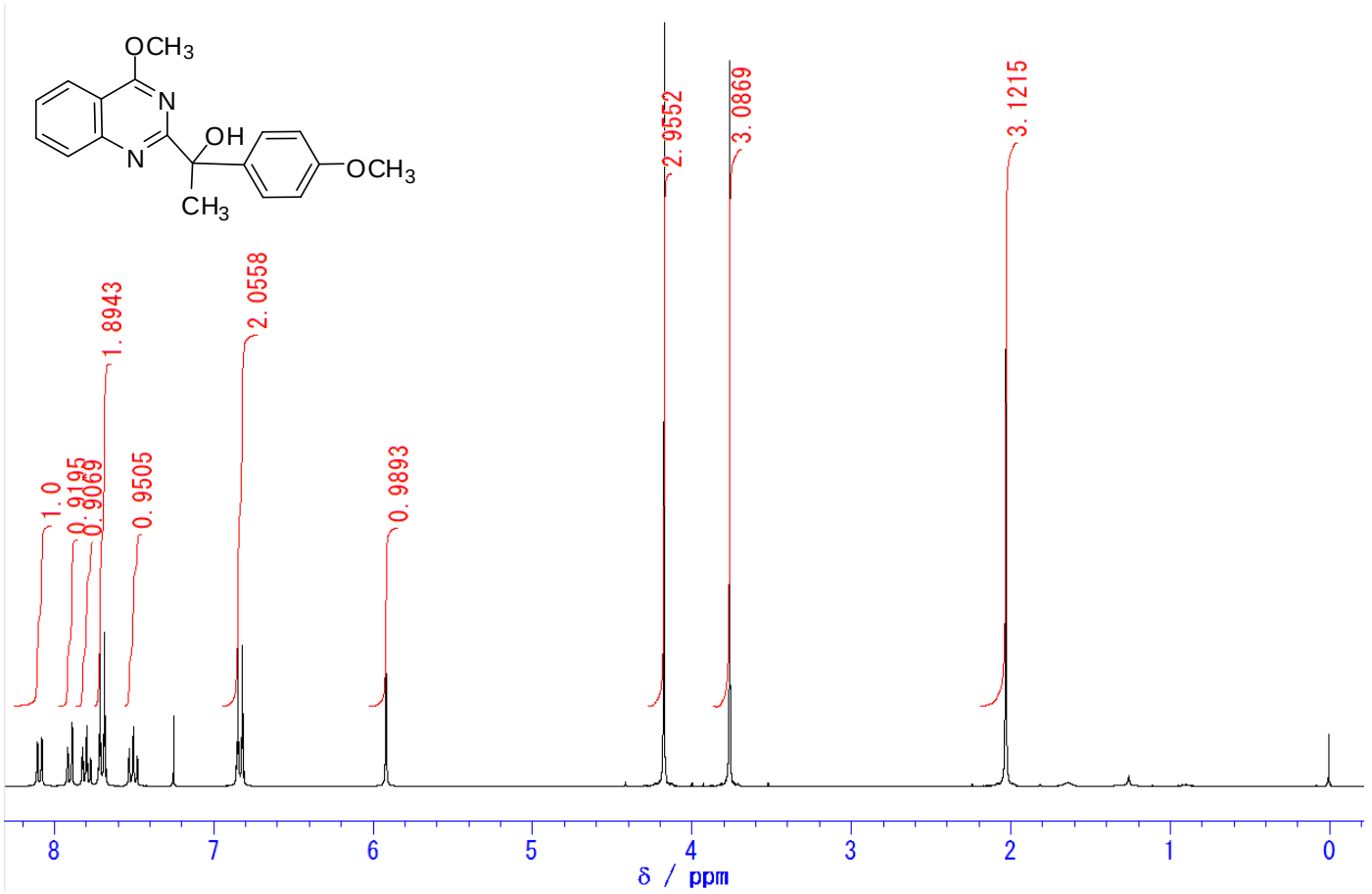
2,2,2-Trifluoro-1-(4-methoxyphenyl)-1-(quinazoline-4-yl)ethanol **(7)**[b]



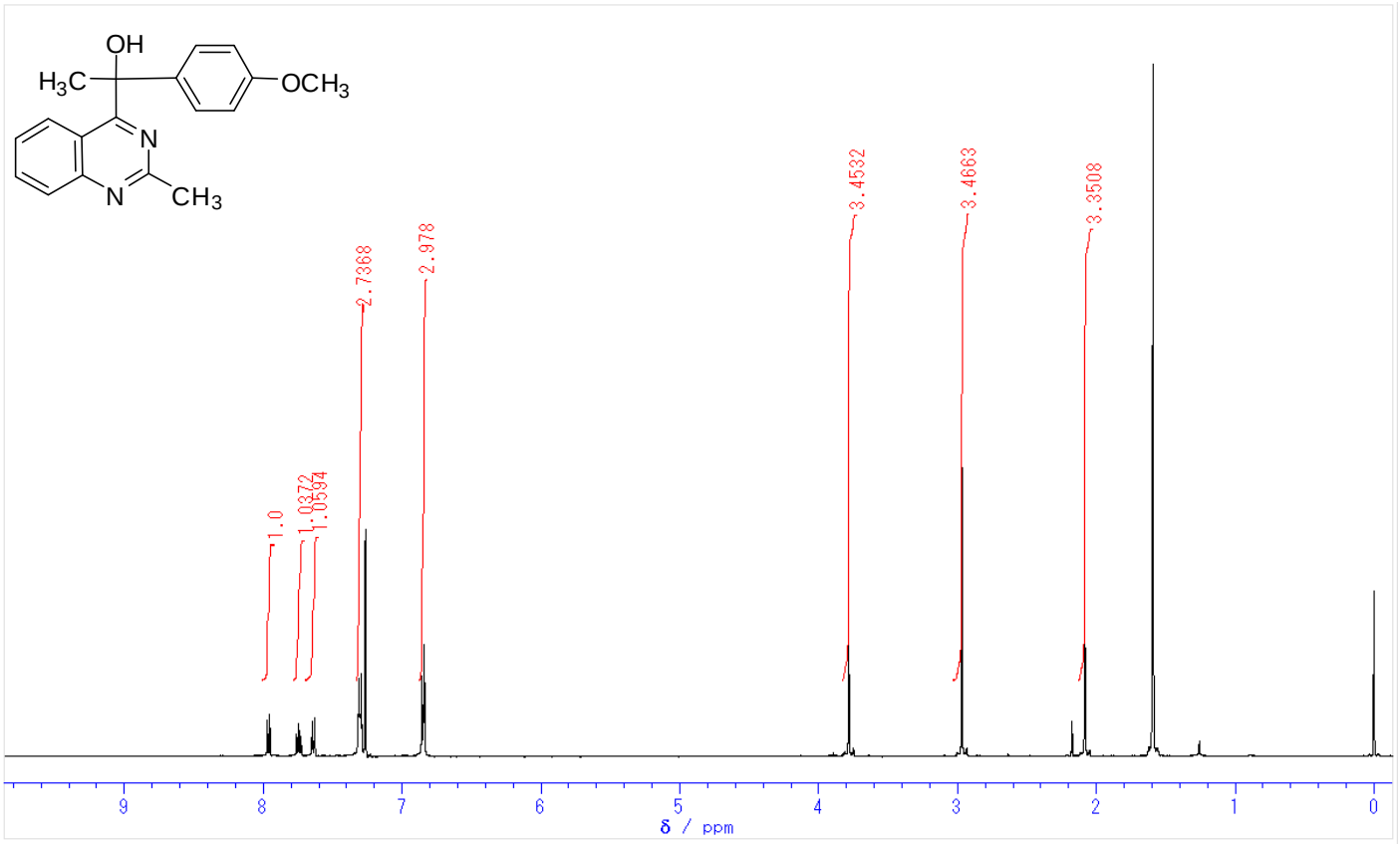
(4-Methoxyphenyl)(quinazoline-4-yl)methanol **(8)**[b]



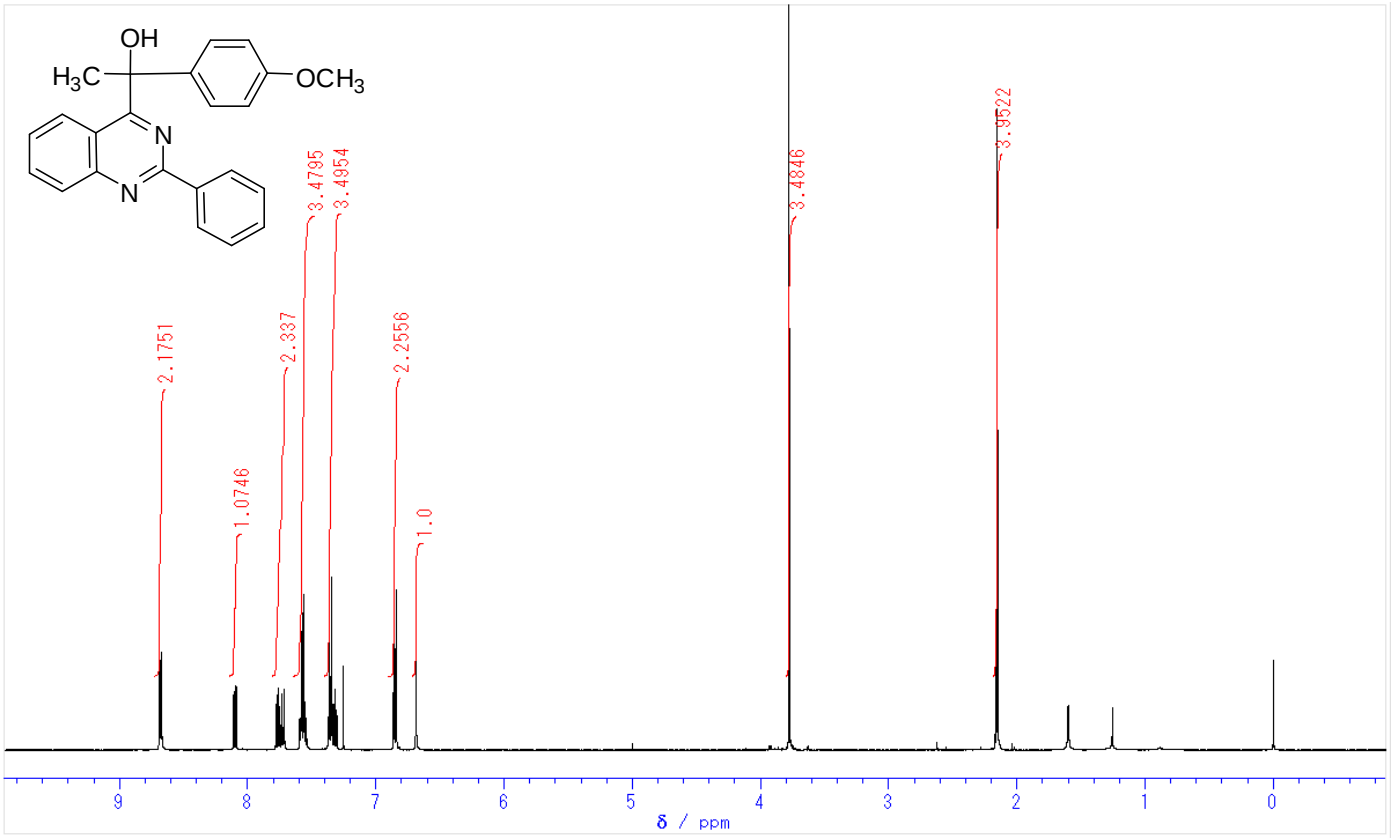
1-(4-Methoxyphenyl)-1-(4-methoxyquinazoline-2-yl)ethanol(**9**)[b]



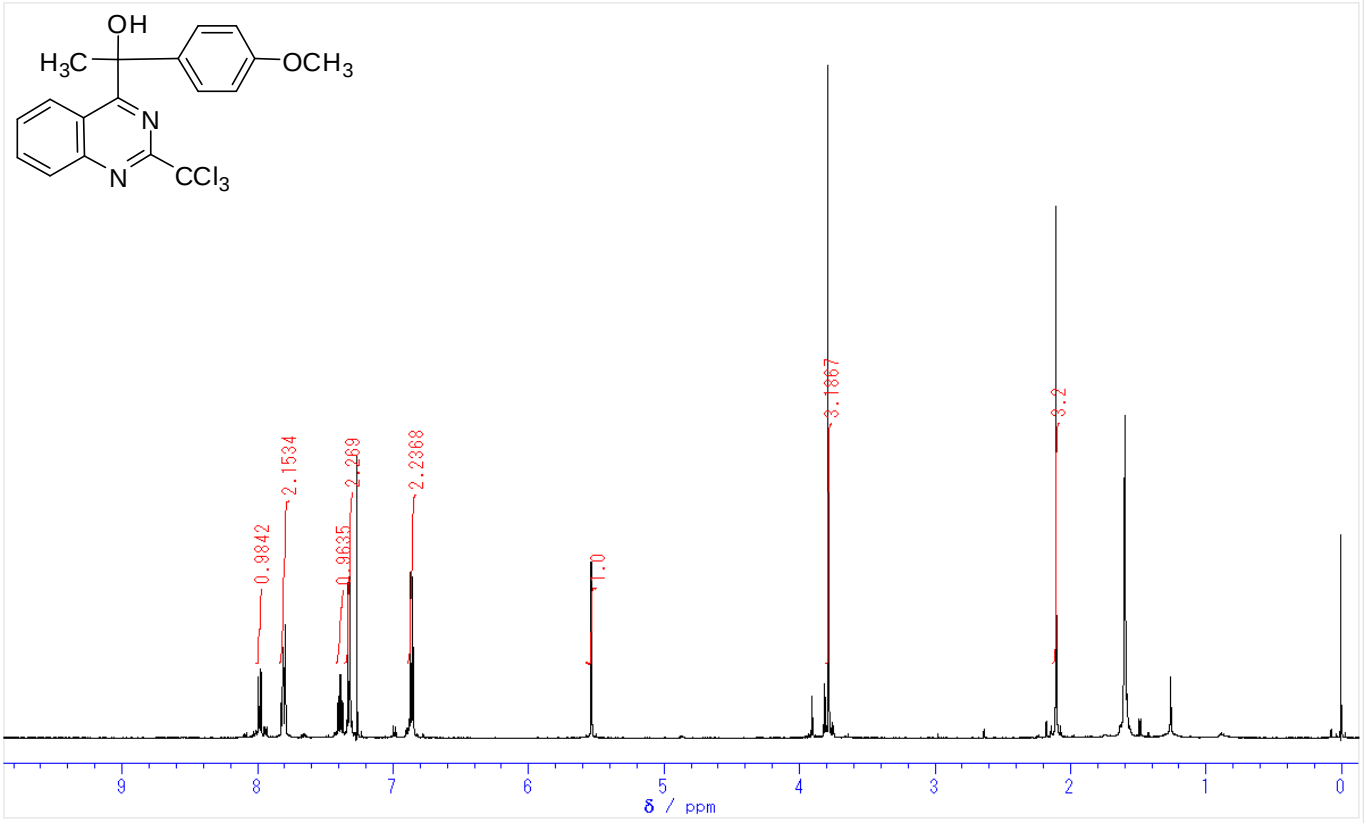
1-(4-Methoxyphenyl)-1-(2-methylquinazoline-4-yl)ethanol **(14)**[a]



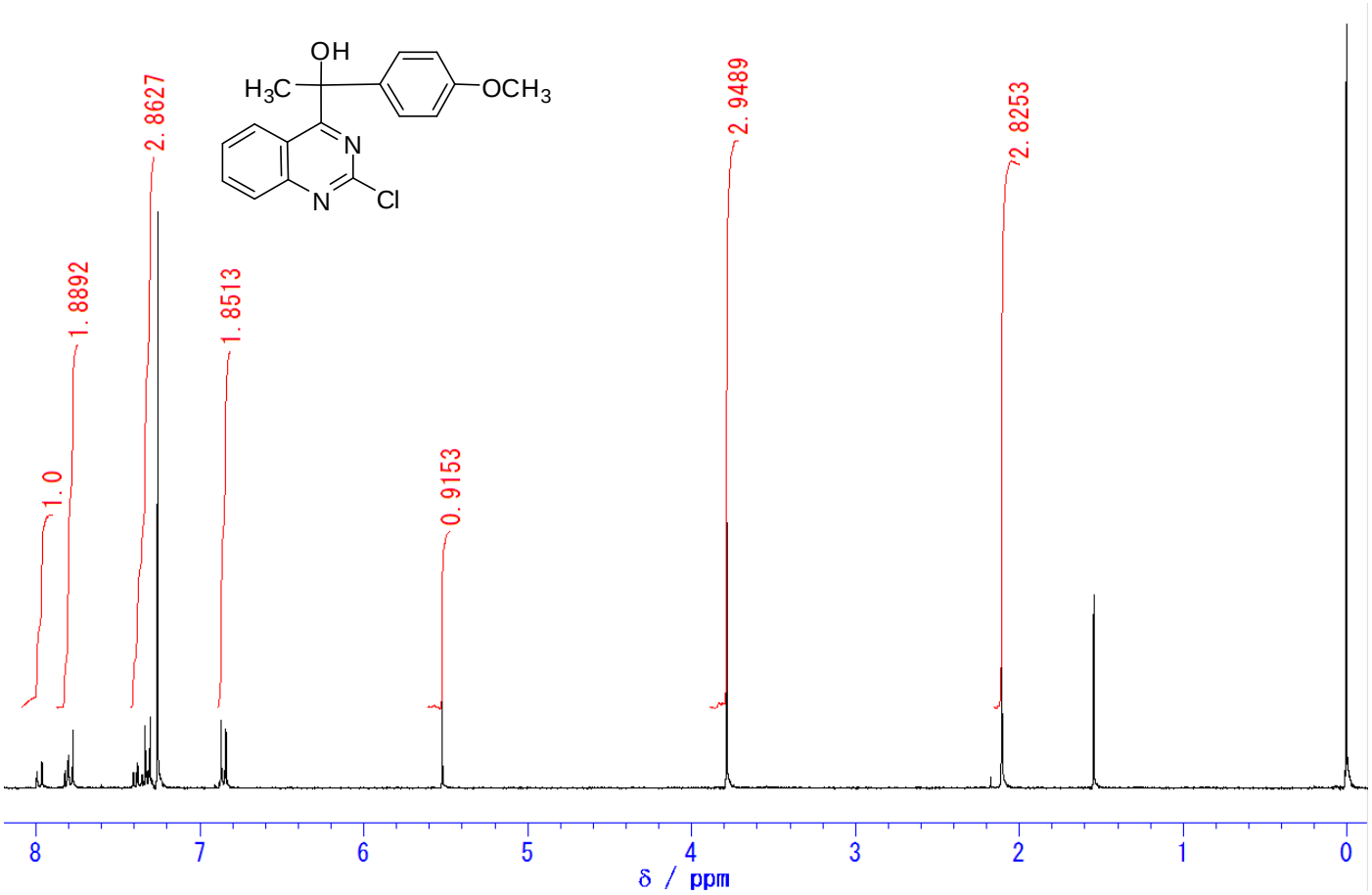
1-(4-Methoxyphenyl)-1-(2-phenylquinazoline-4-yl)ethanol **(15)**[a]



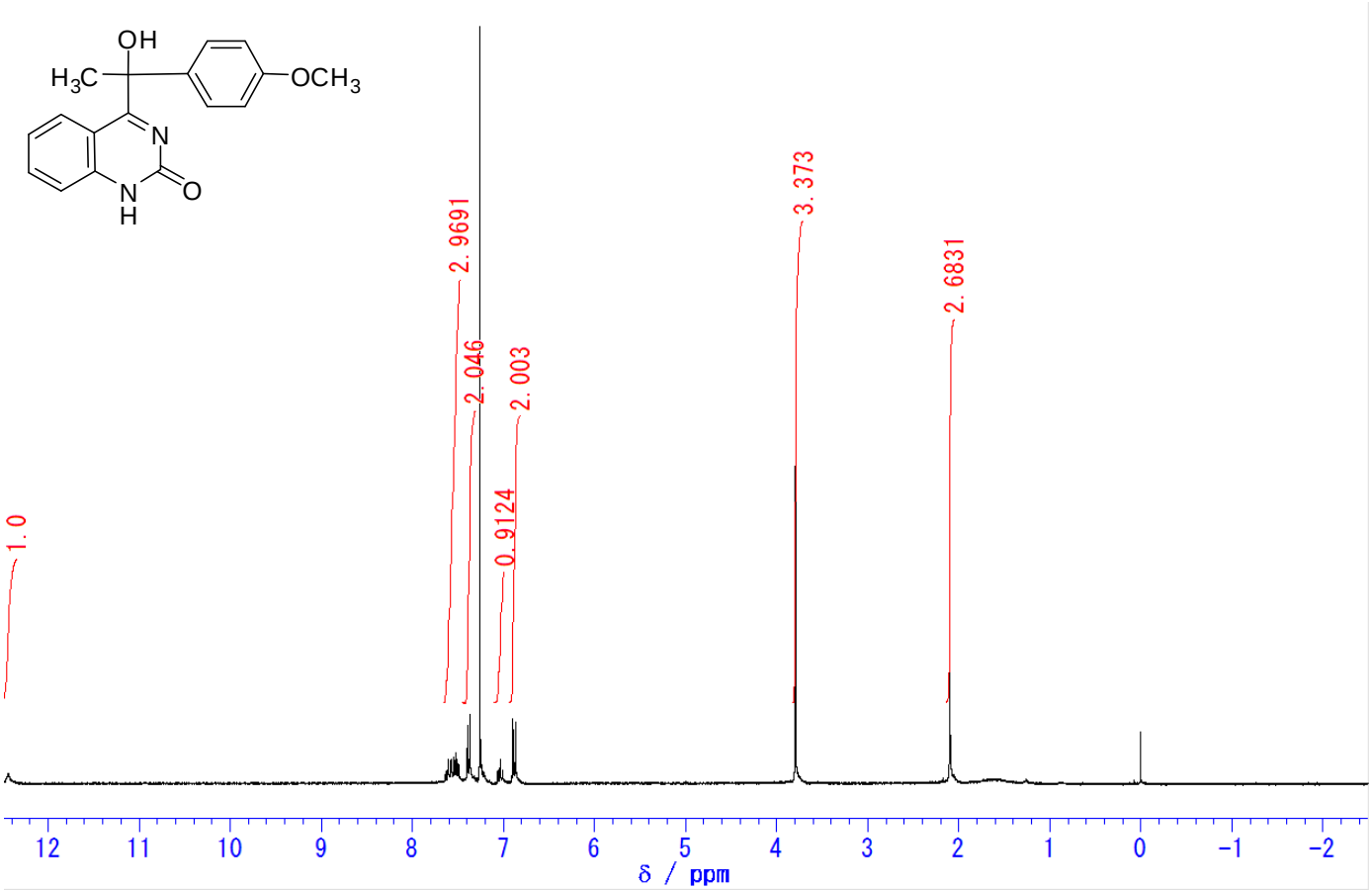
1-(4-Methoxyphenyl(-1-(2-trichloromethylquinazoline-4-yl)ethanol **(16)**[a]



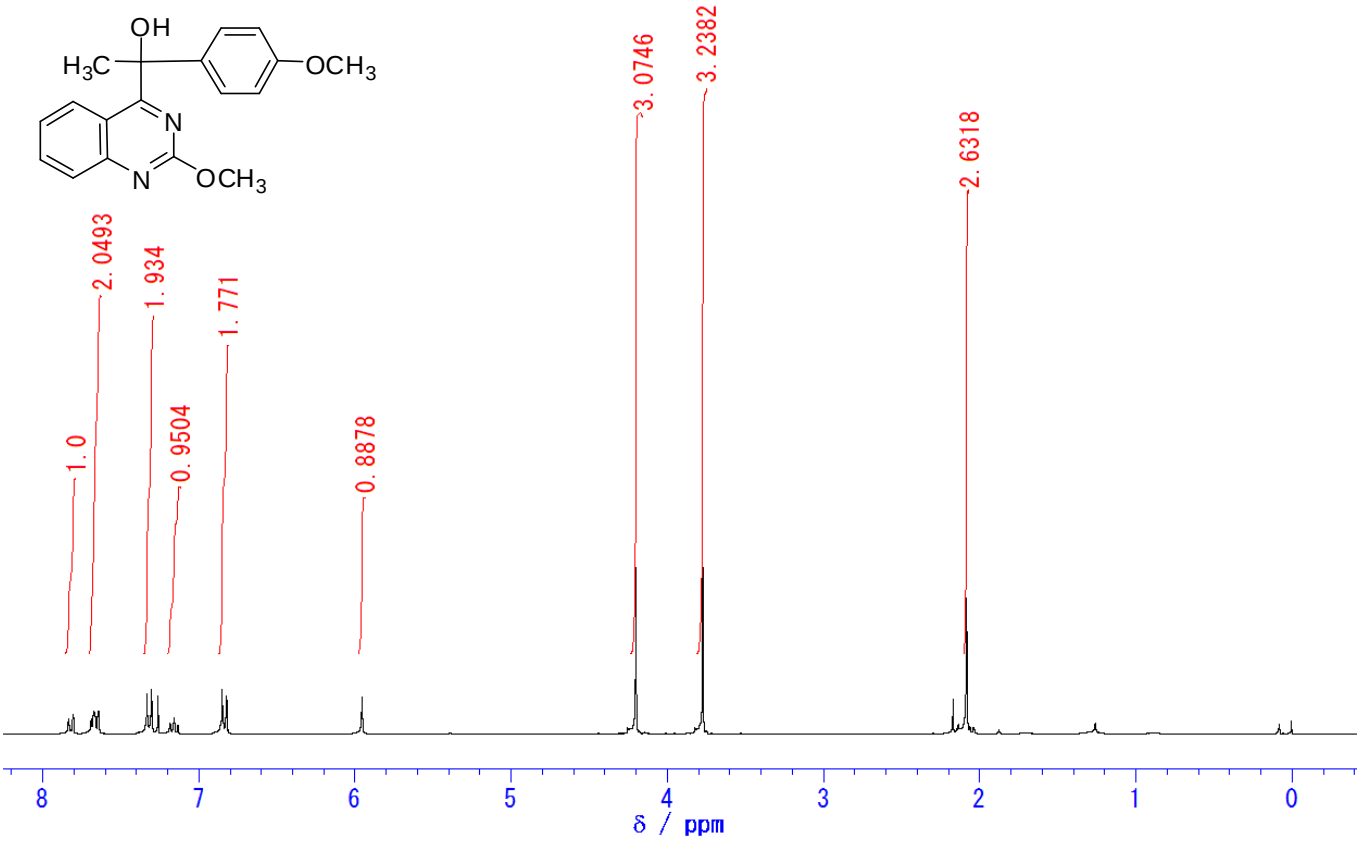
1-(4-Methoxyphenyl)-1-(2-chloroquinazoline-4-yl)ethanol **(17)**[a]



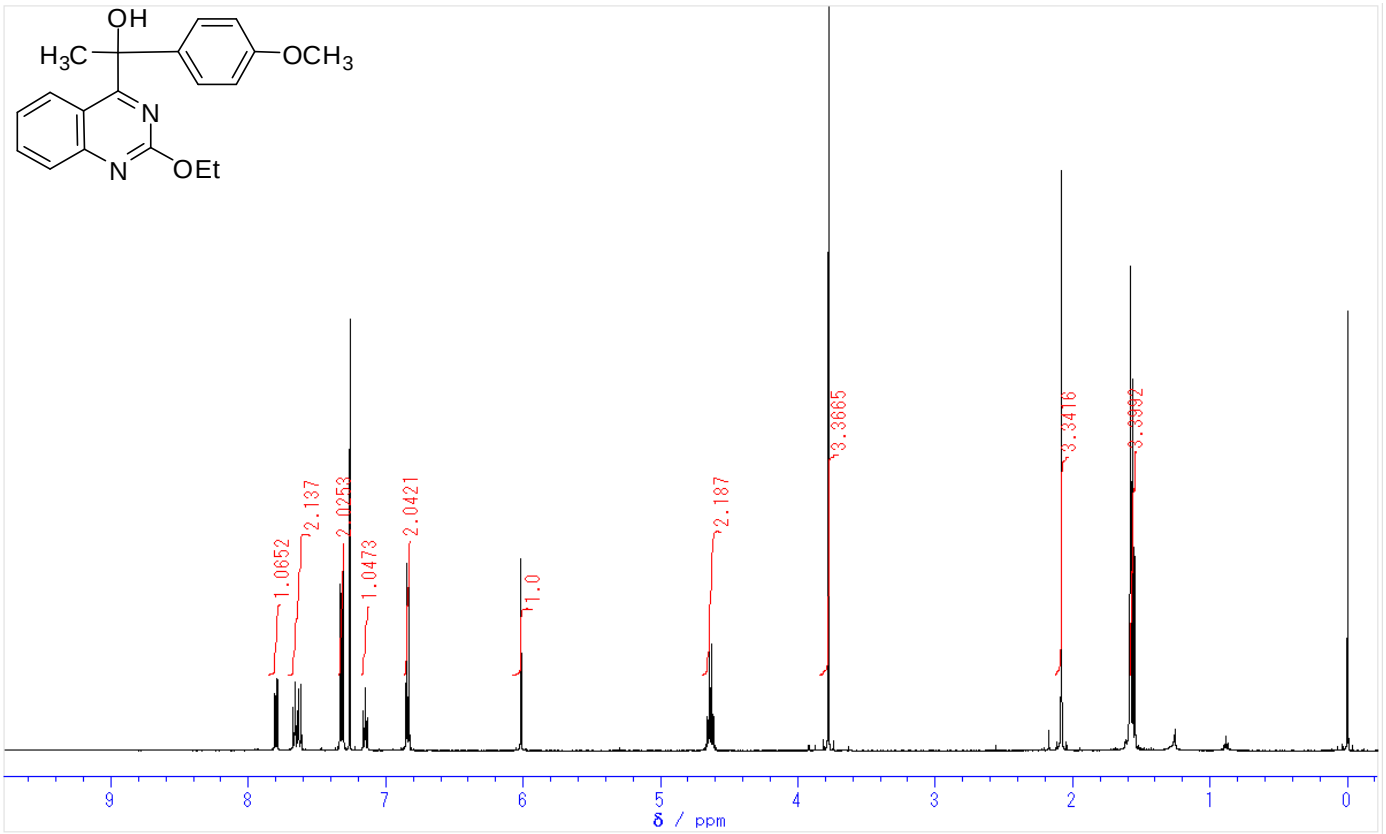
4-[1-Hydroxy-1-(4-methoxyphenyl)ethyl]quinazoline-2*(1H)*-one **(18)**[b]



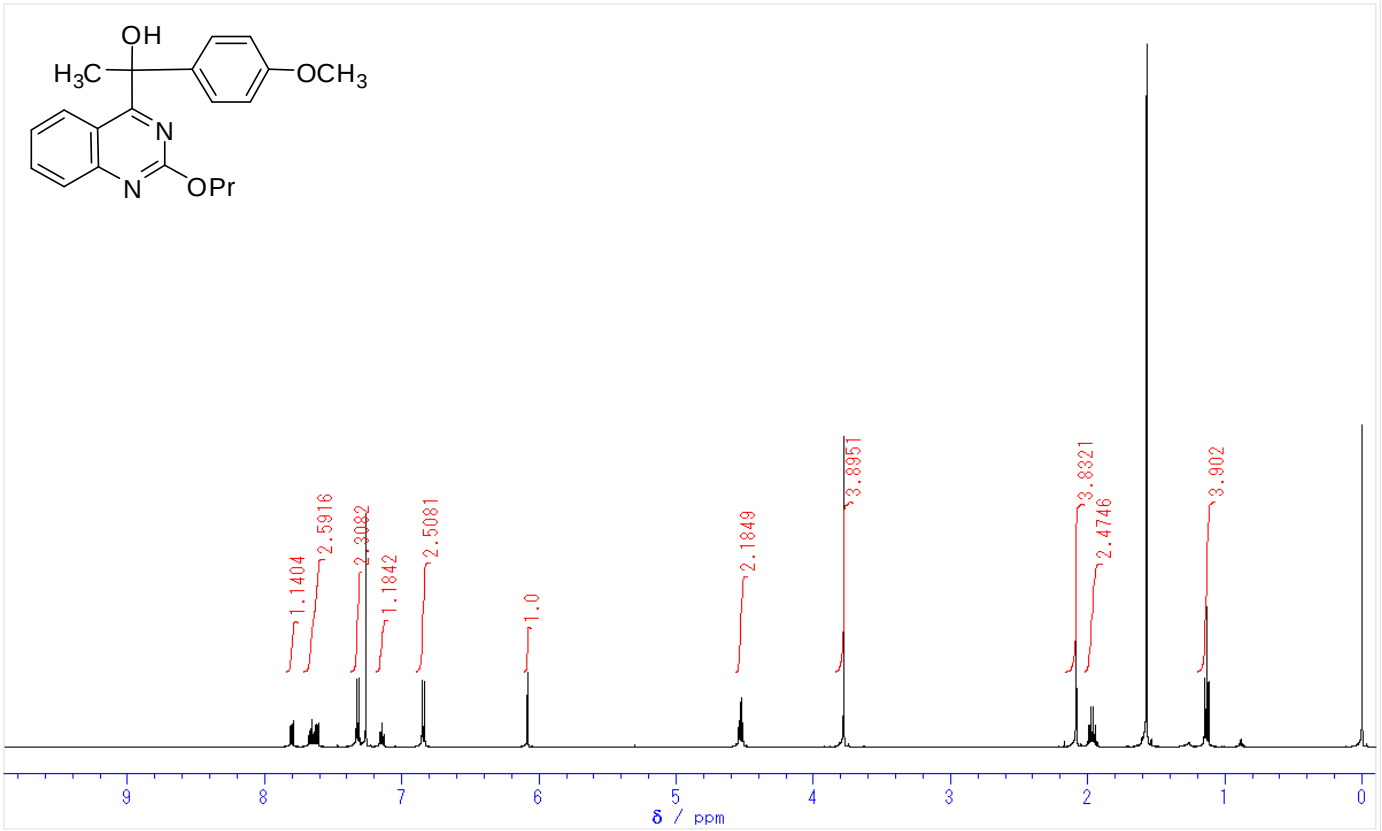
1-(4-Methoxyphenyl)-1-(2-methoxyquinazoline-4-yl)ethanol **(19)**[b]



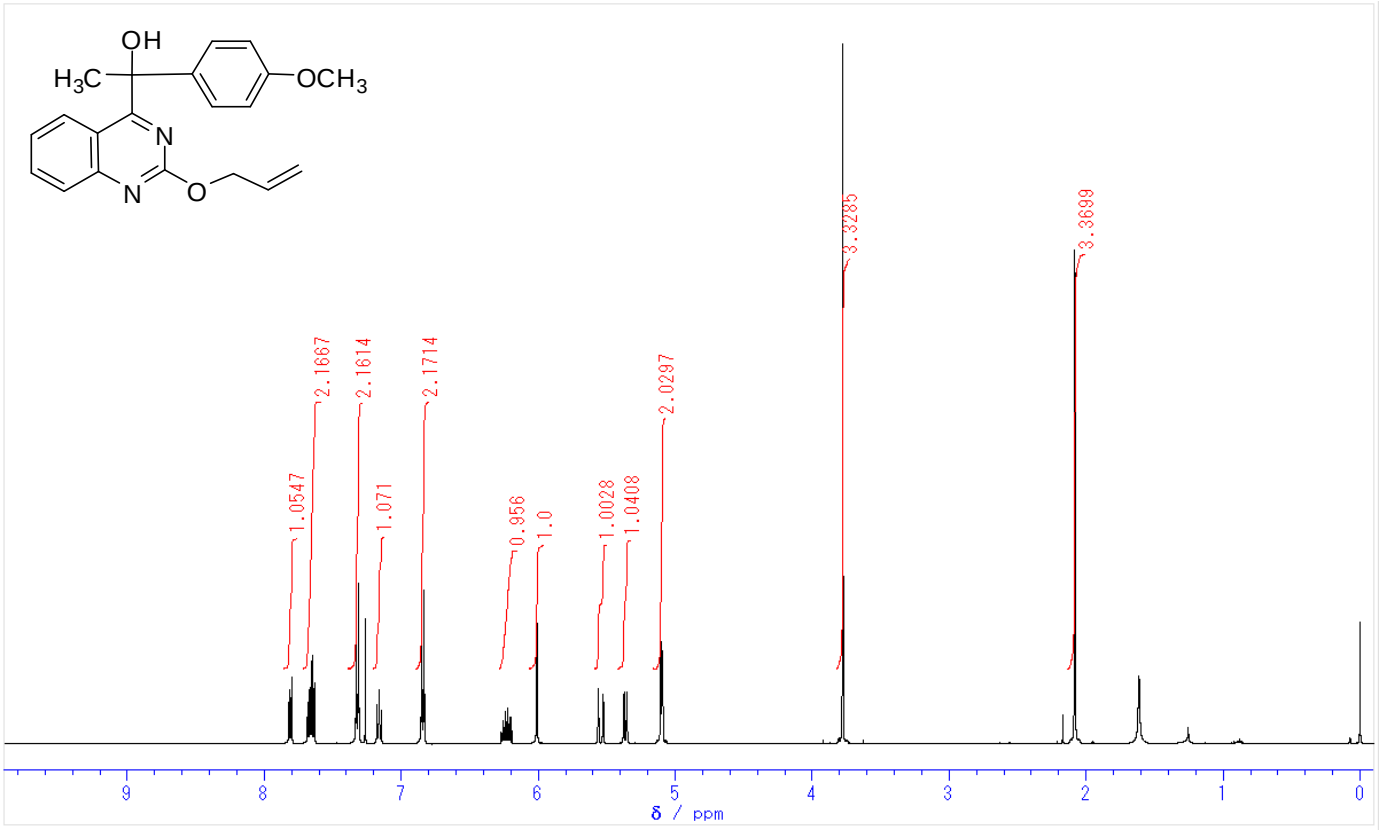
1-(2-Ethoxyquinazoline-4-yl)-1-(4-methoxyphenyl)ethanol **(20)**[a]



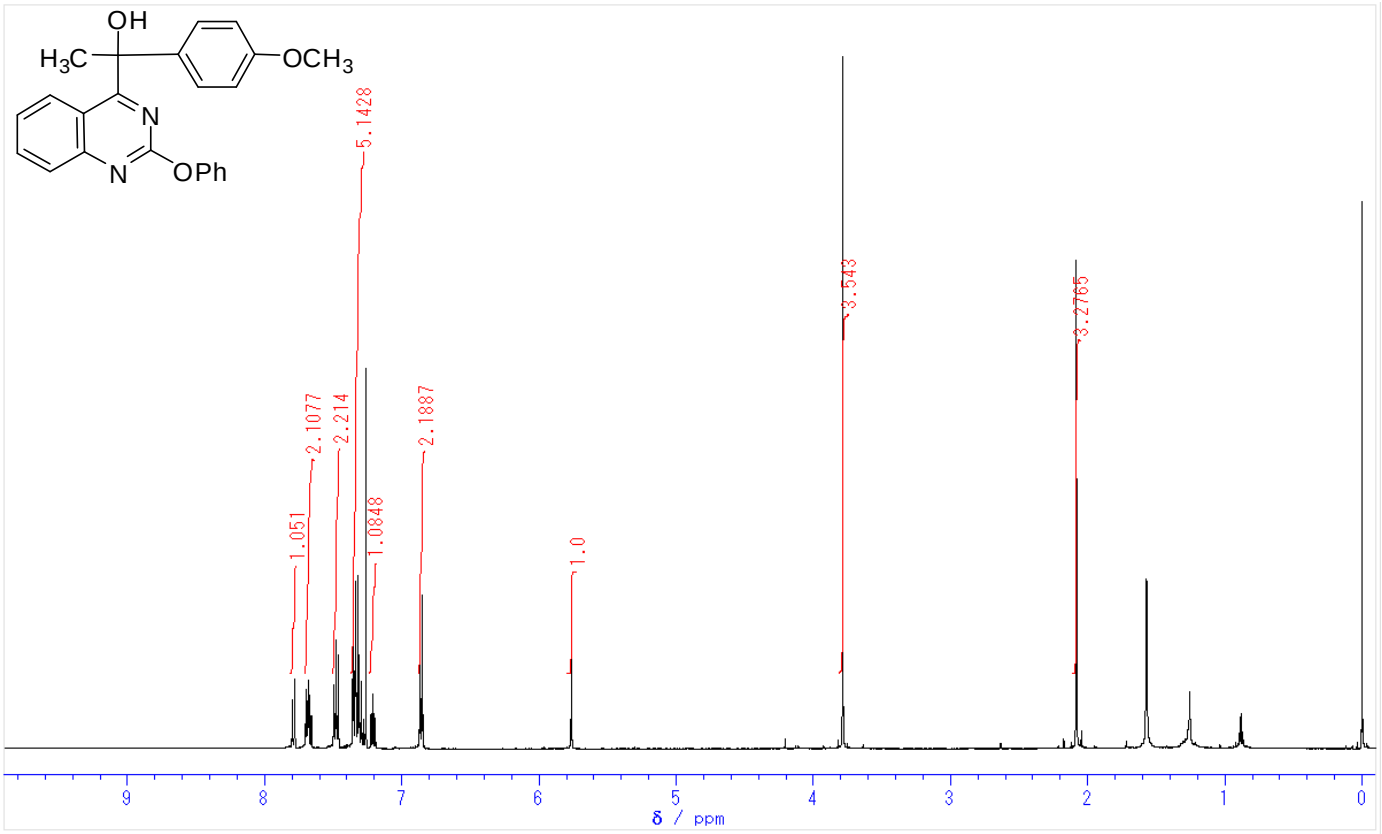
1-(4-Methoxyphenyl)-1-(2-propoxyquinazoline-4-yl)ethanol **(21)**[a]



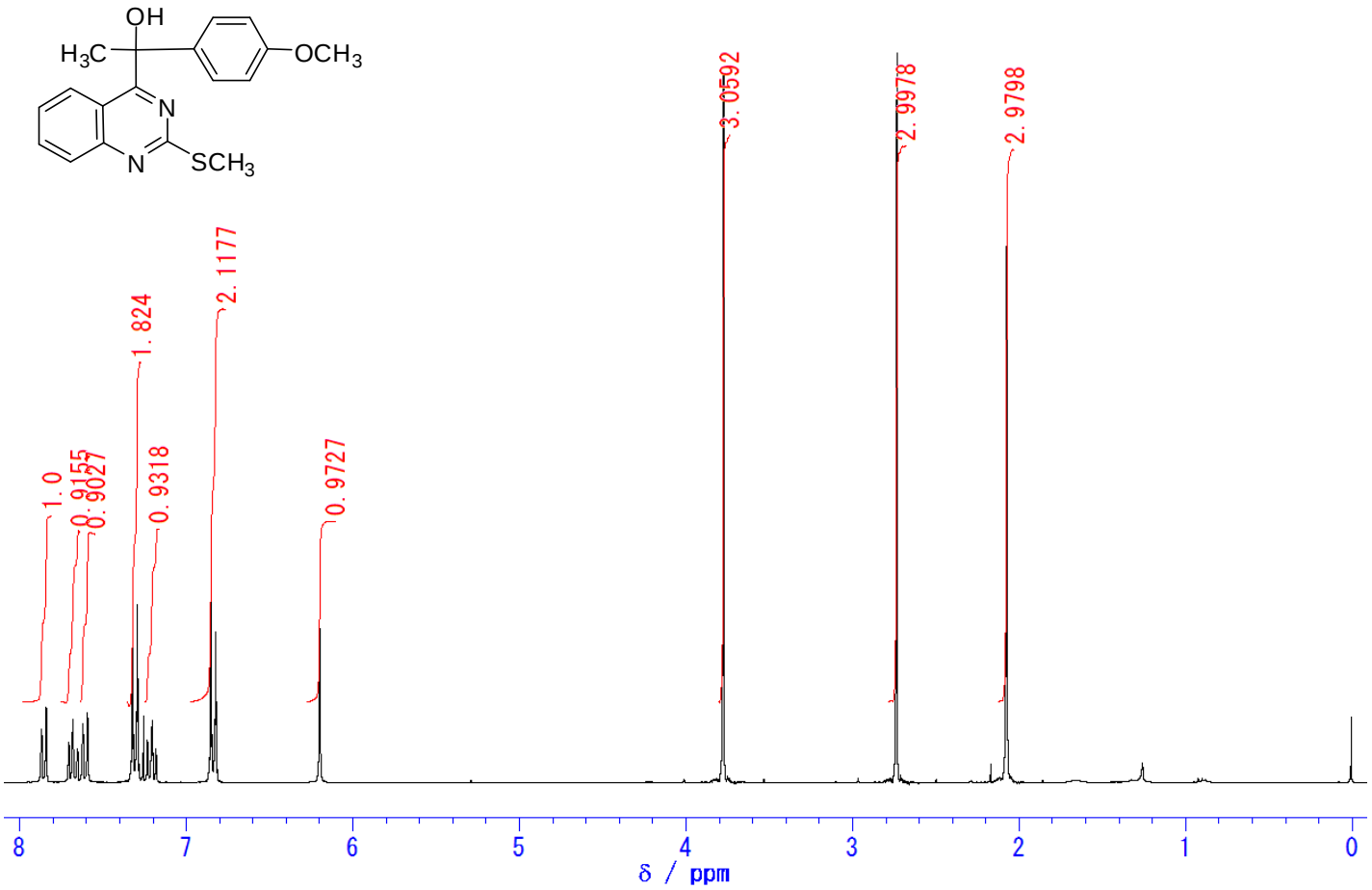
1-(2-Allyloxyquinazoline-4-yl)-1-(4-methoxyphenyl)ethanol **(22)**[a]



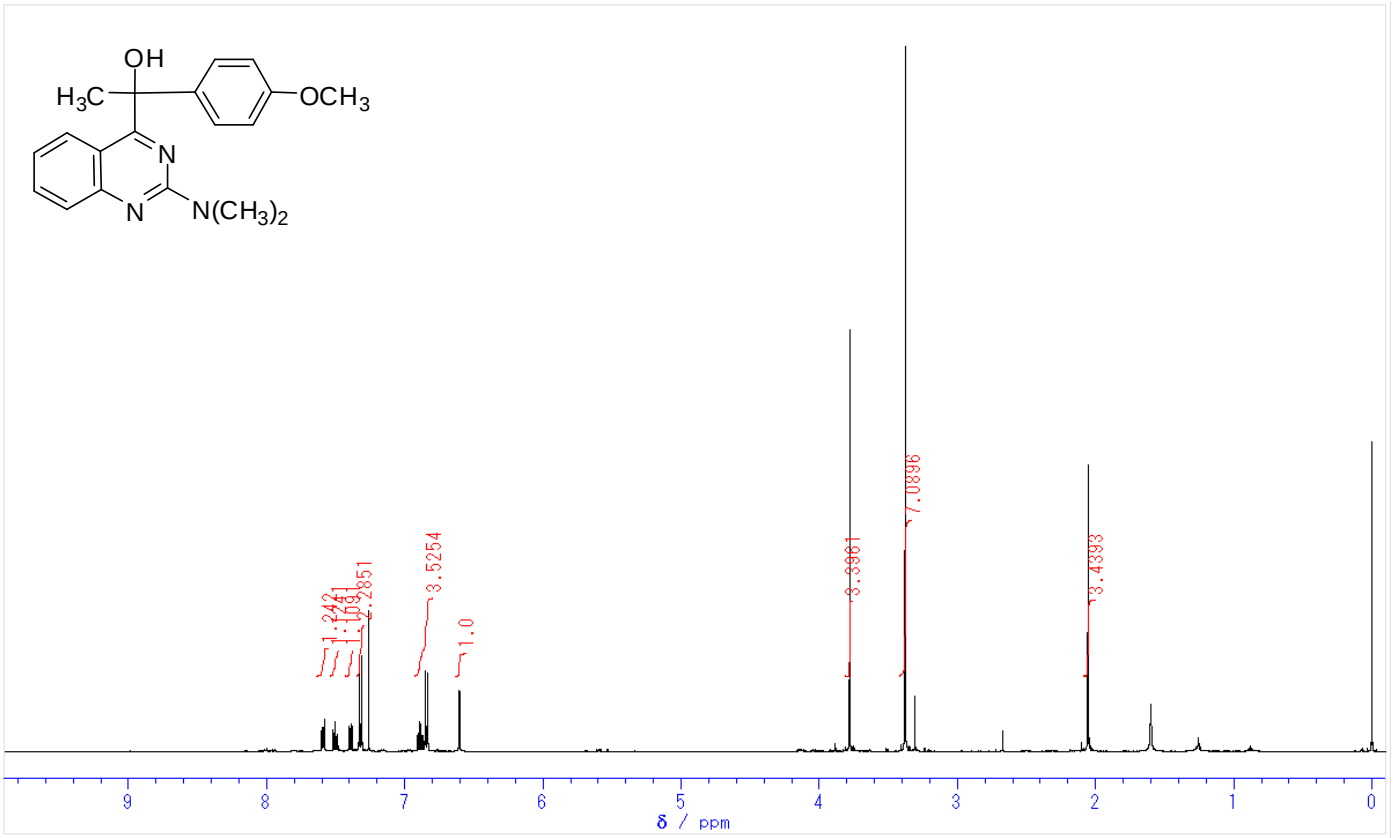
1-(4-Methoxyphenyl)-1-(2-phenoxyquinazoline-4-yl)ethanol **(23)**[a]



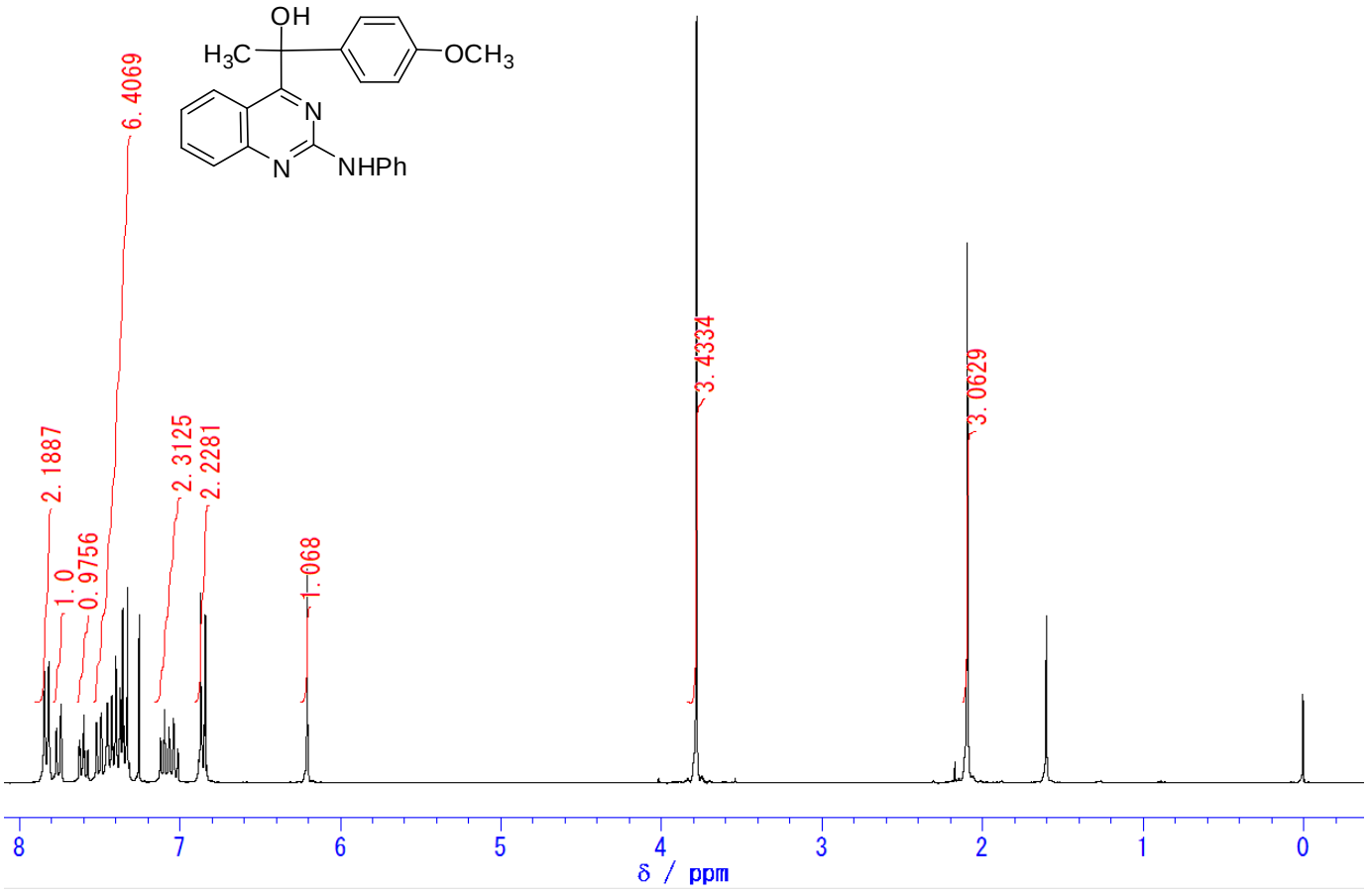
1-(4-Methoxyphenyl)-1-(2-methylthioquinazoline-4-yl)ethanol **(24)**[b]



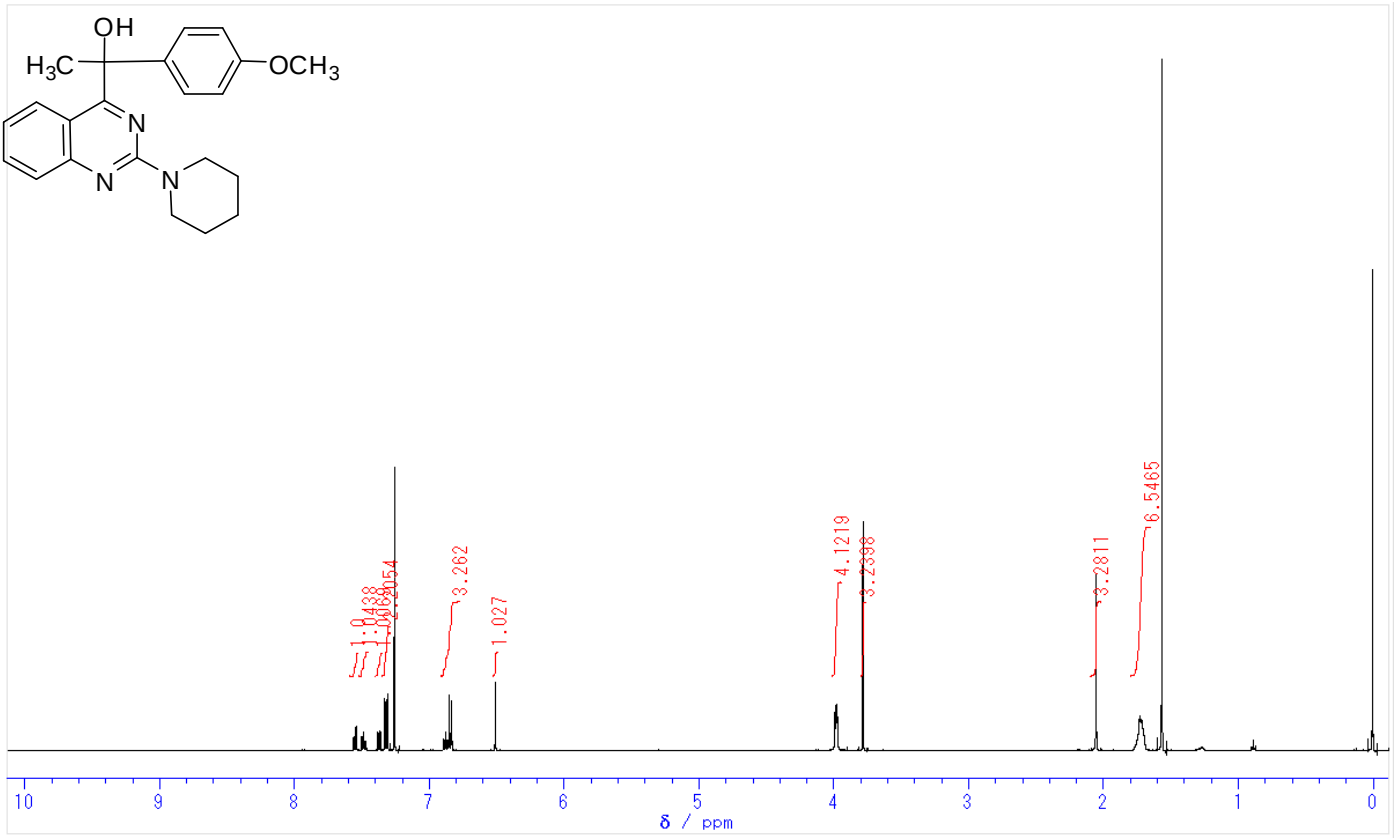
1-(2-Dimethylaminoquinazoline-4-yl)-1-(4-methoxyphenyl)ethanol **(25)**[a]



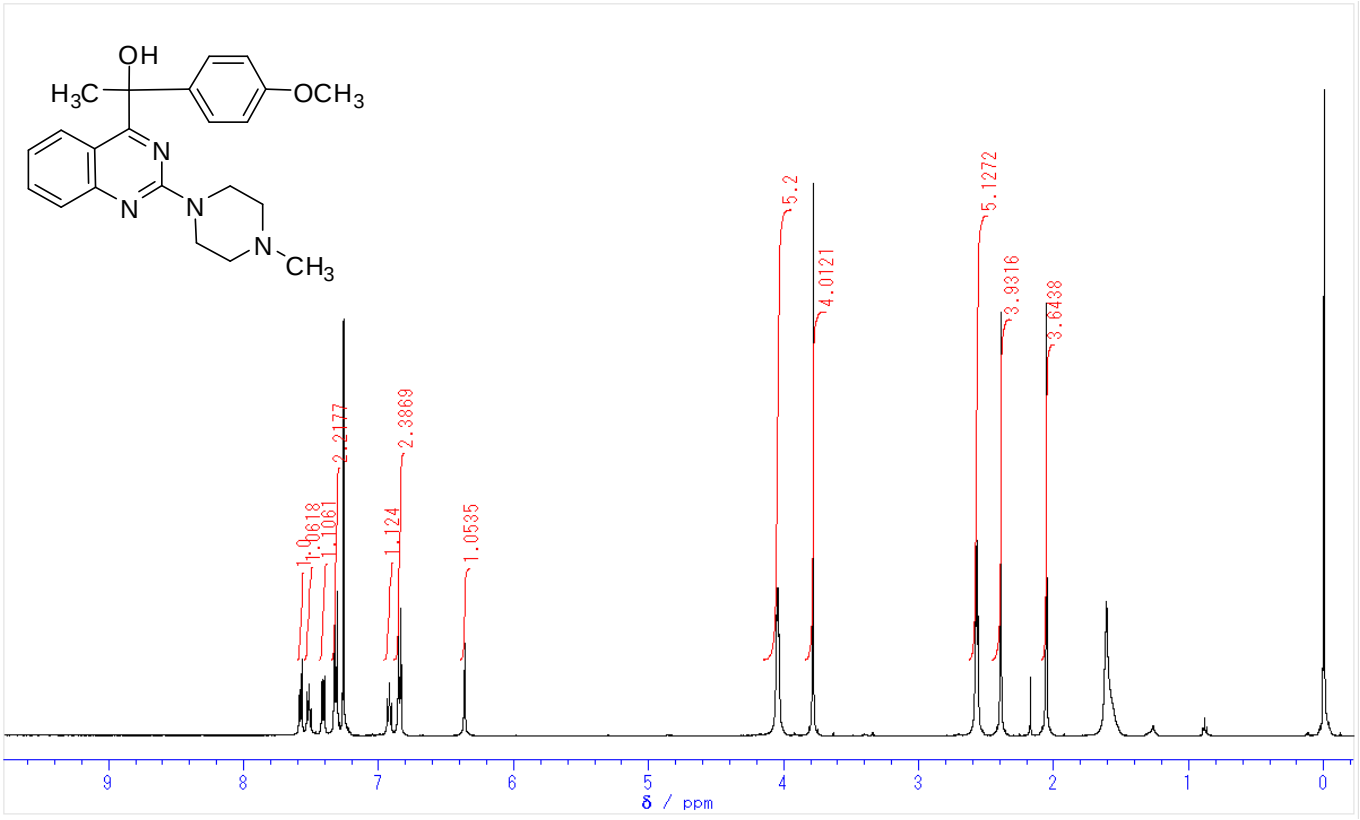
1-(4-Methoxyphenyl)-1-(2-phenylaminoquinazoline-4-yl)ethanol (**26**)[b]



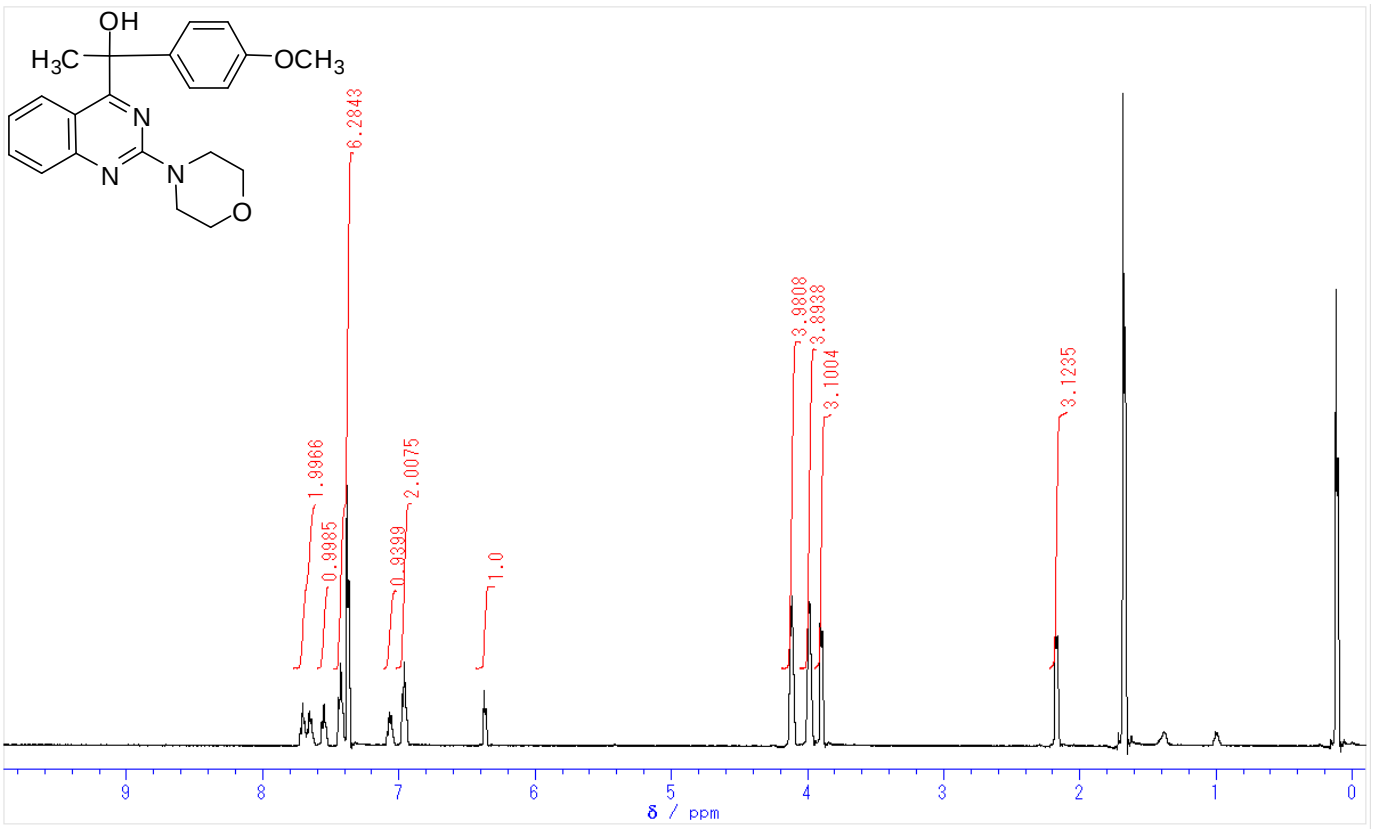
1-(4-Methoxyphenyl)-1-[2-(piperidine-1-yl)quinazoline-4-yl]ethanol (**27**)[a]



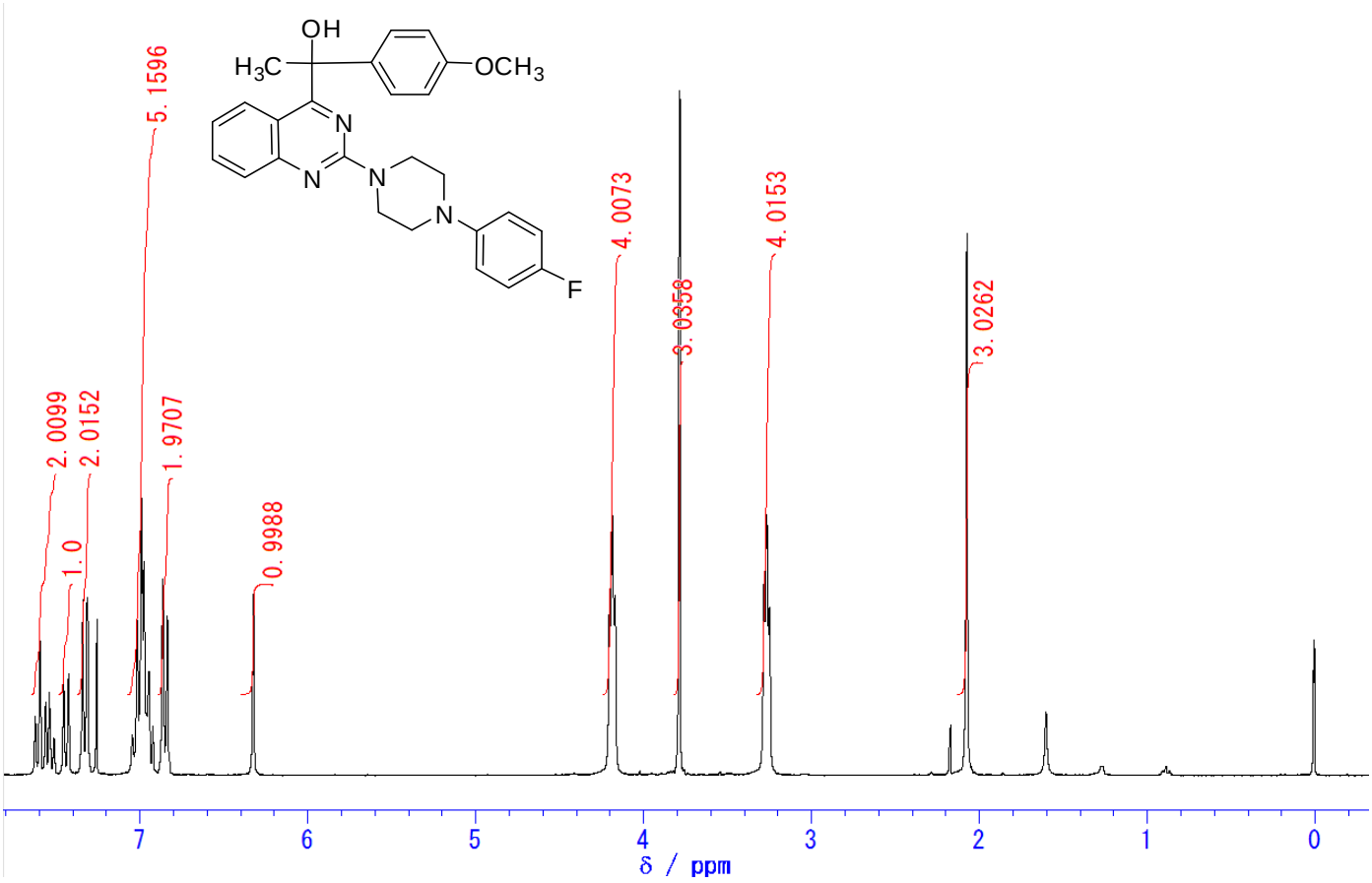
1-(4-Methoxyphenyl)-1-[2-(4-piperadine-1-yl)quinazoline-4-yl]ethanol (**28**)[a]



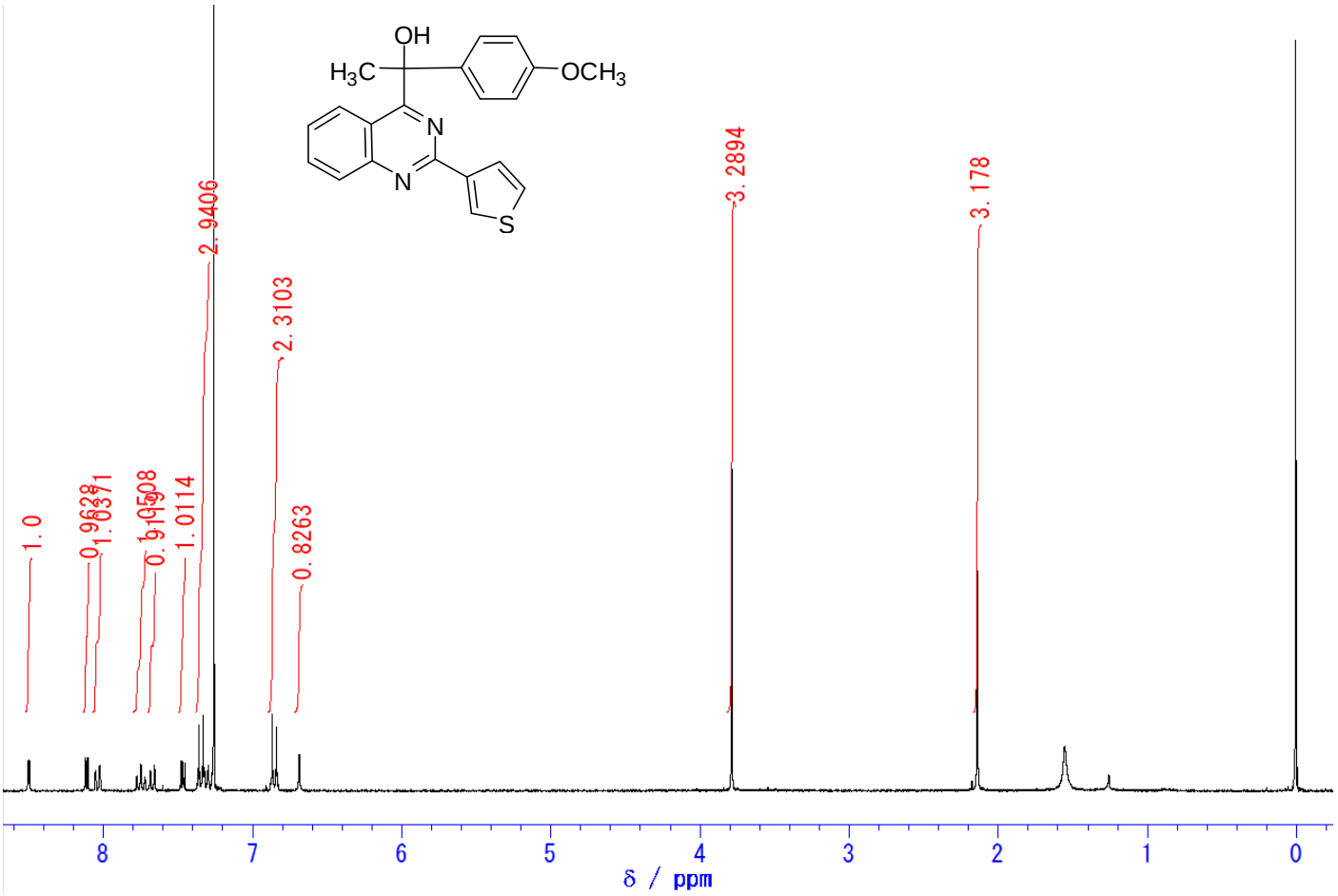
1-(4-Methoxyphenyl)-1-(2-morpholinoquinazoline-4-yl)ethanol (**29**)[a]



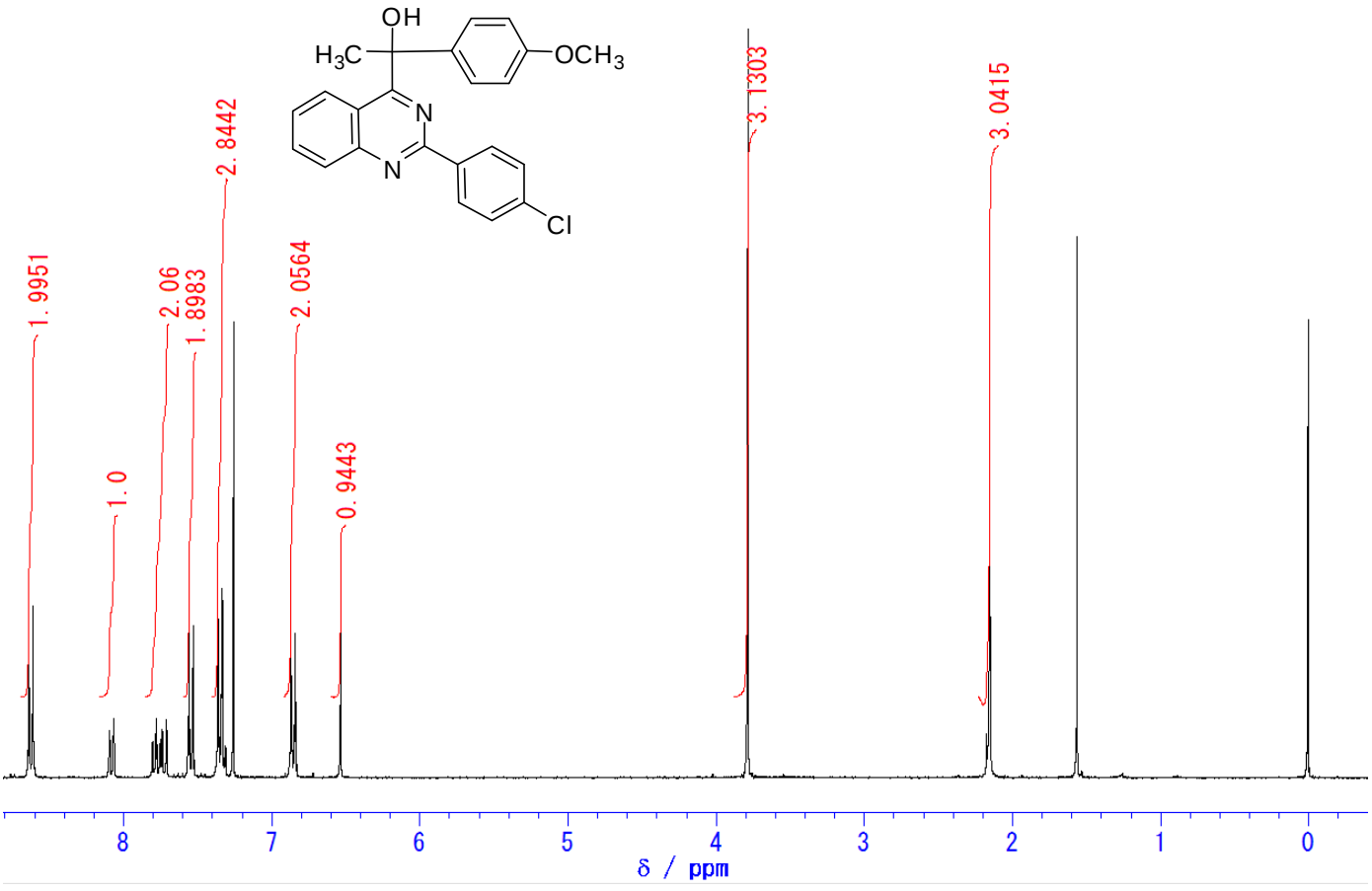
1-(4-Methoxyphenyl)-1-{2-[4-(4-fluorophenyl)piperadine-1-yl]quinazoline-4-yl}ethanol (**30**)[b]



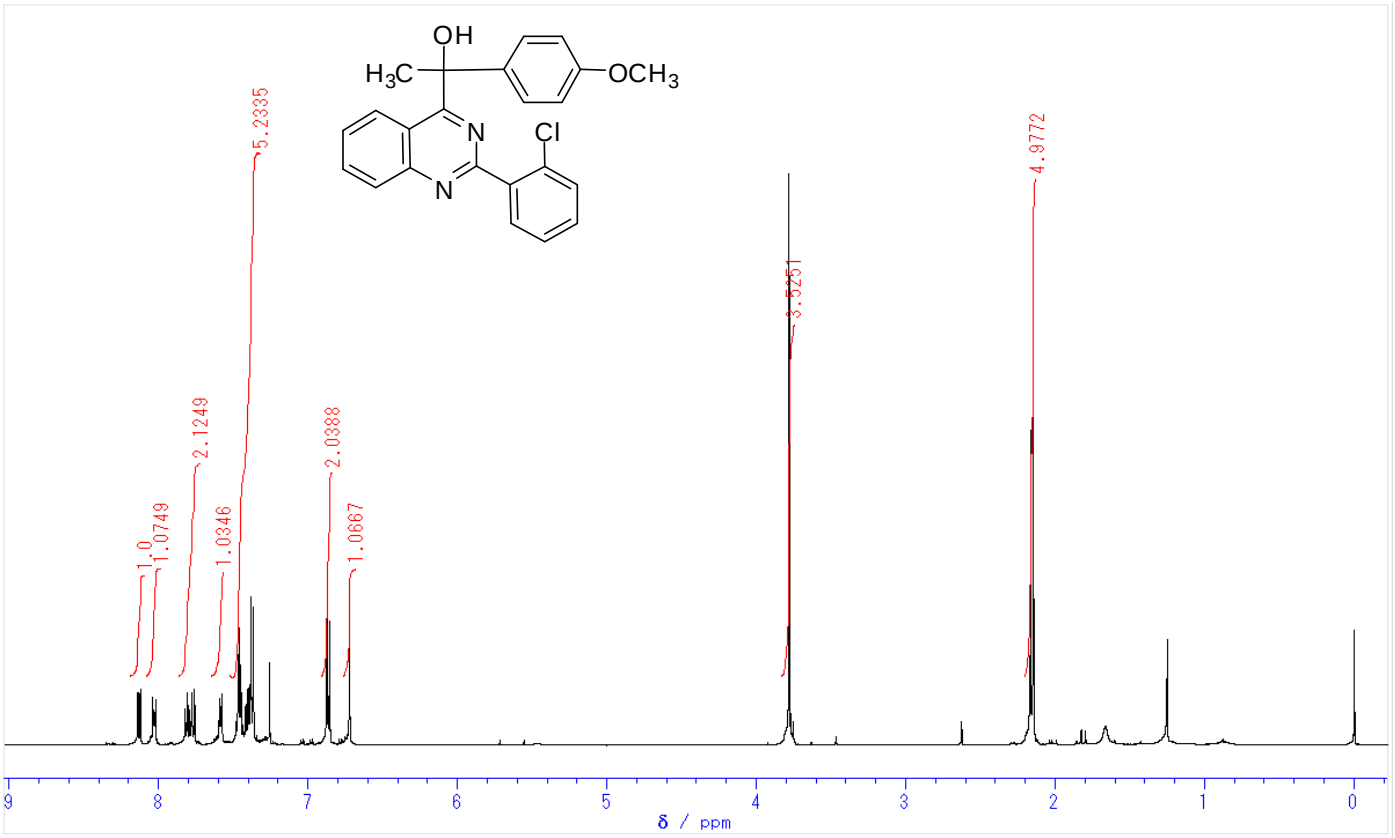
1-(4-Methoxyphenyl)-1-(3-thienylquinazoline-4-yl)ethanol **(31)**[b]



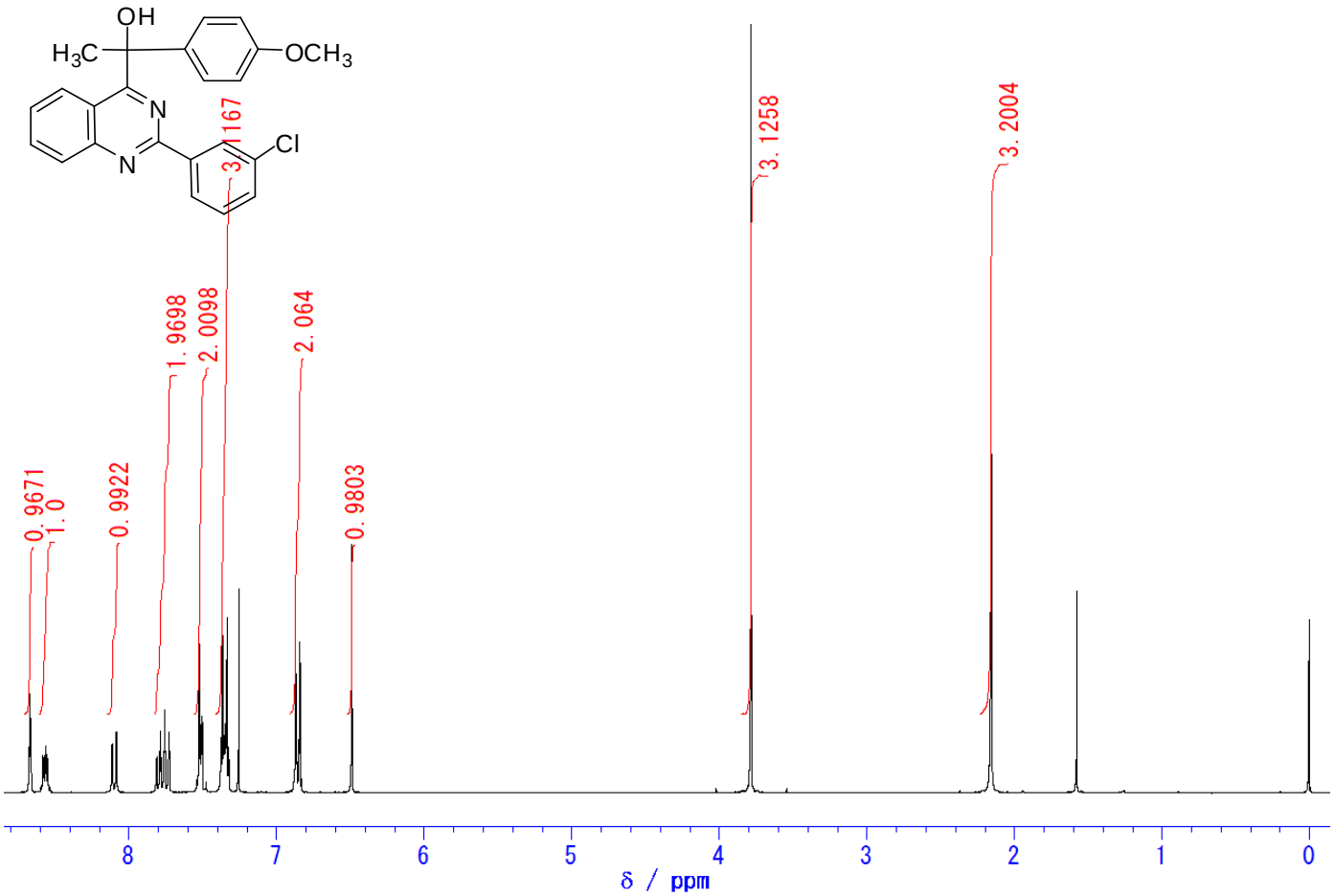
1-[2-(4-Chlorophenyl)quinazoline-4-yl]-1-(4-methoxyphenyl)ethanol **(32)**[b]



1-[2-(2-Chlorophenyl)quinazoline-4-yl]-1-(4-methoxyphenyl)ethanol **(33)**[a]

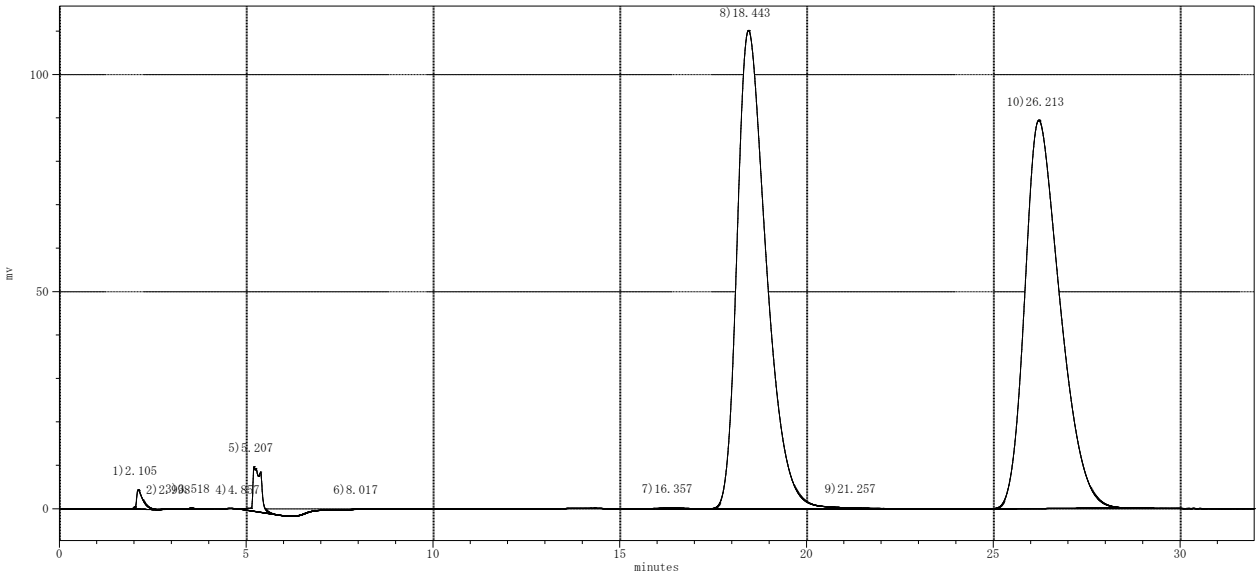


1-[2-(3-Chlorophenyl)quinazoline-4-yl]-1-(4-methoxyphenyl)ethanol **(34)**[b]



7. HPLC Chart

(±)-1a



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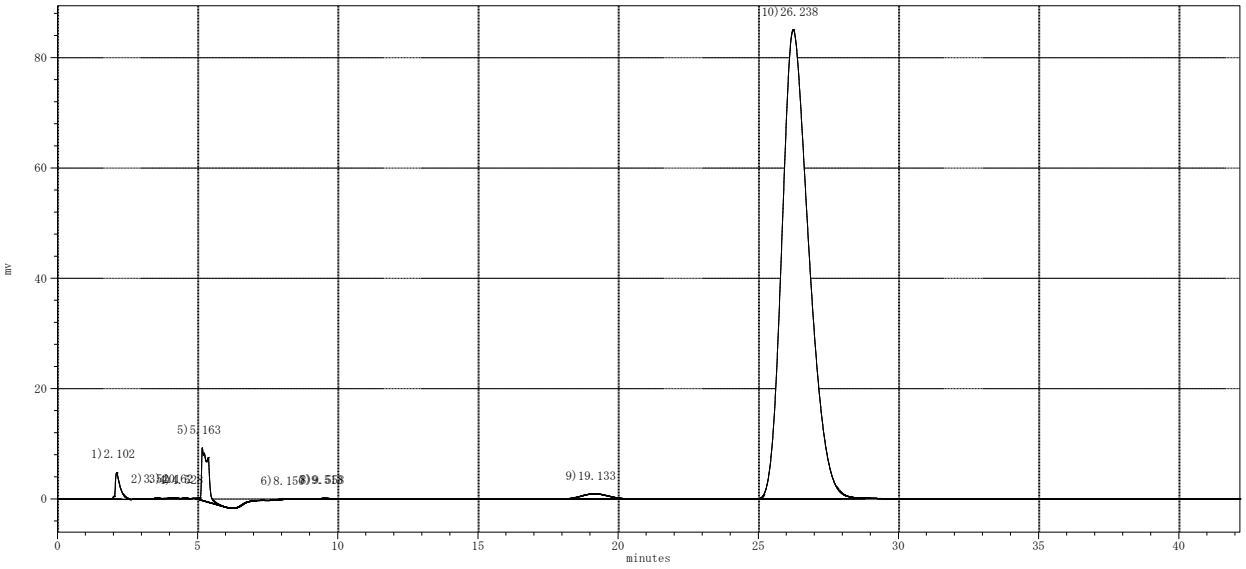

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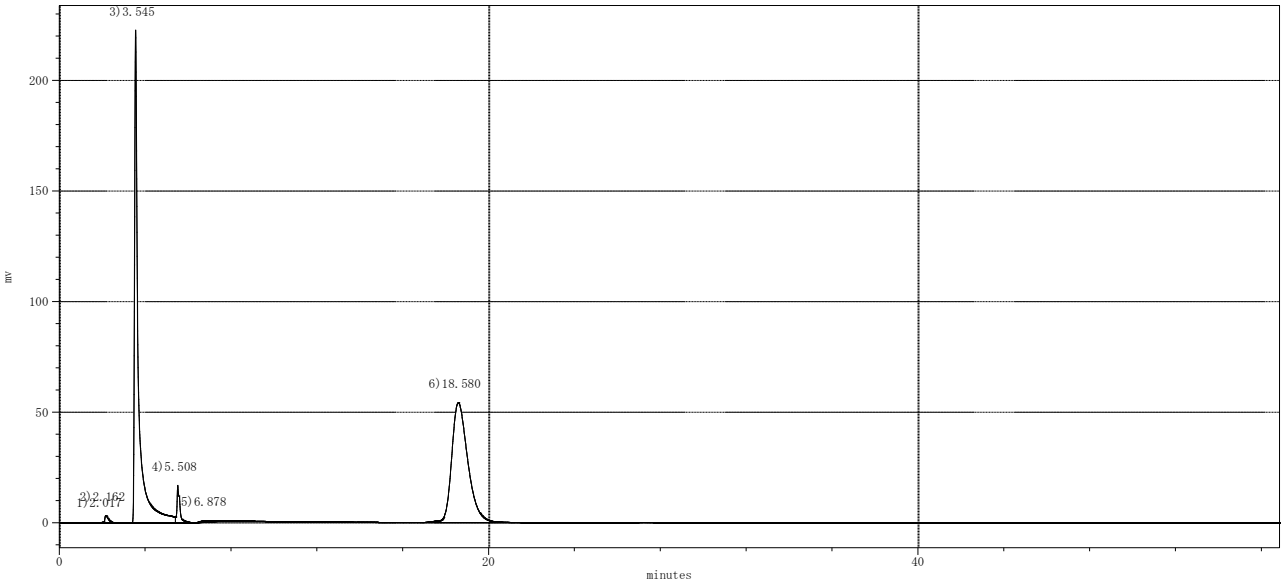

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