

Synthesis of Novel 1,4-Disubstituted 1,2,3-Triazolo-Bosentan Derivatives – Evaluation of Antimicrobial, Anticancer activities and Molecular Docking

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Supplementary Information

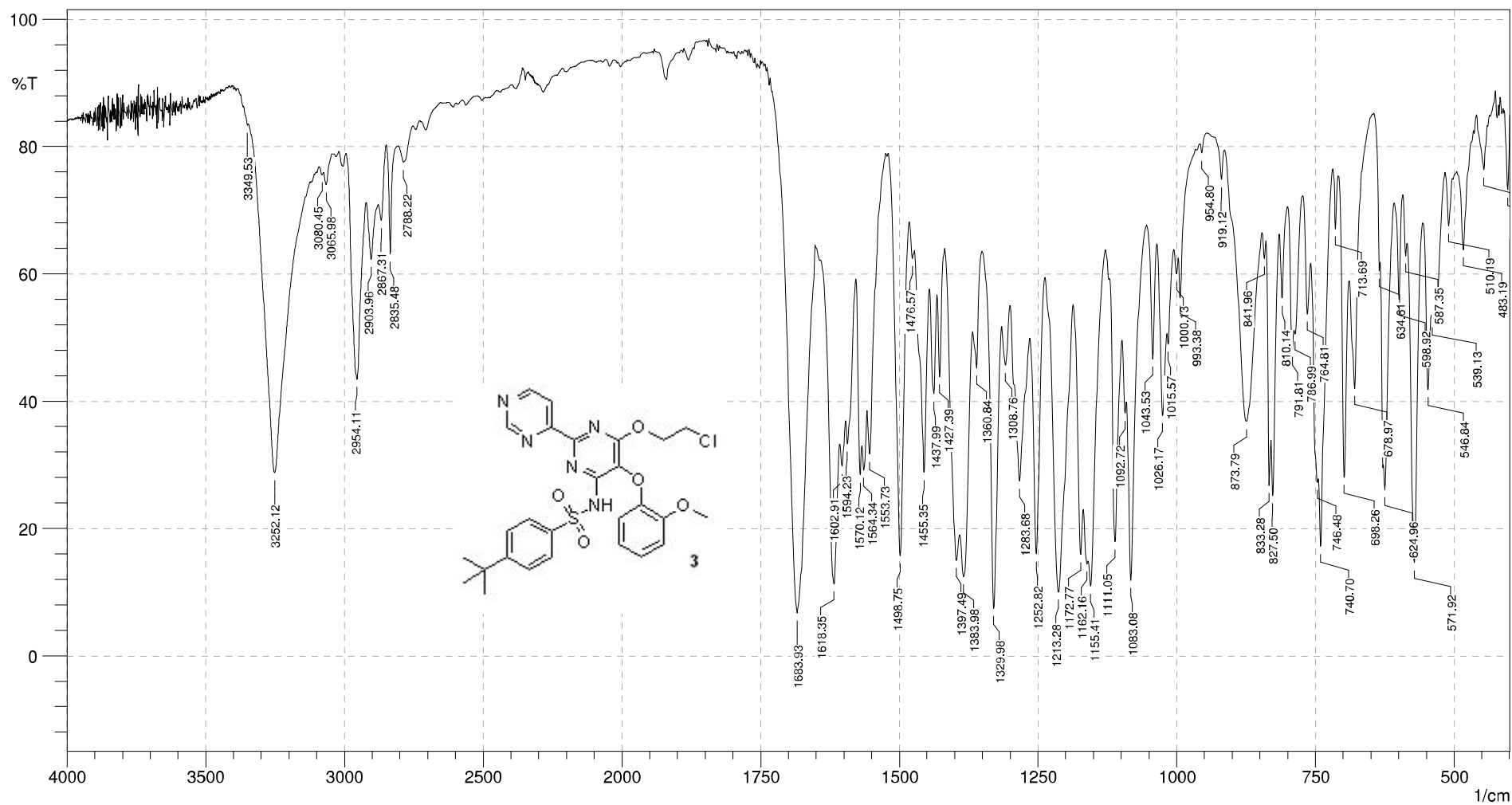
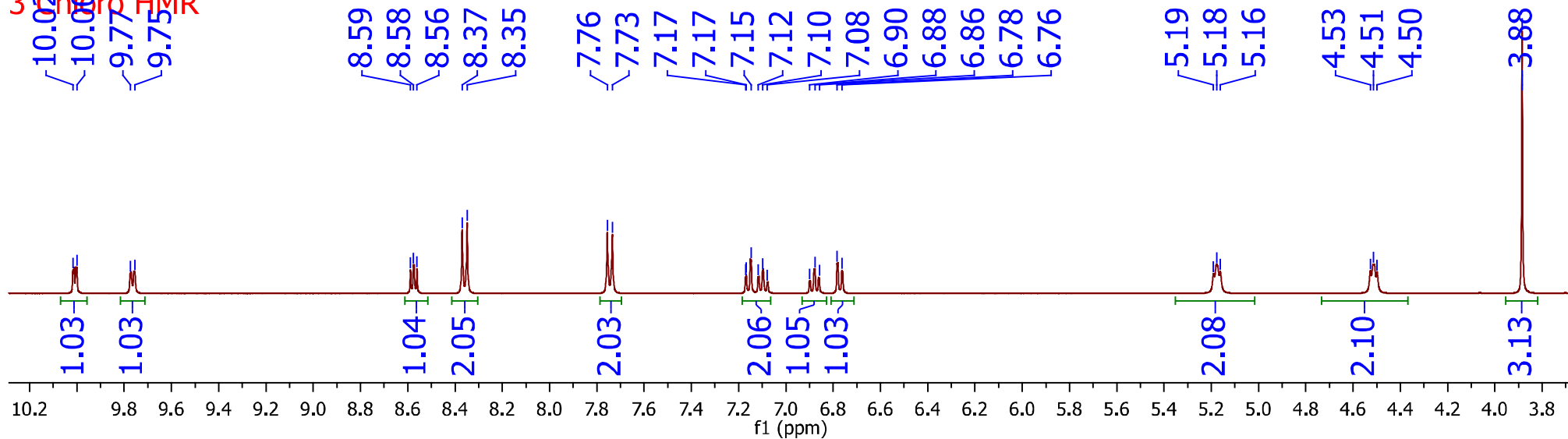


Figure 1: IR Spectrum of 4-tert-Butyl-N-(6-(2-chloroethoxy)-5-(2-methoxyphenoxy)-2,2'-bipyrimidin-4-yl)benzene-sulfonamide (**3**)

3 HMR



3 Chloro HMR

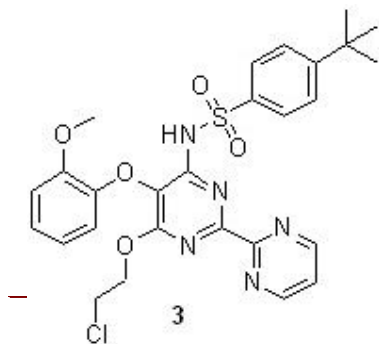
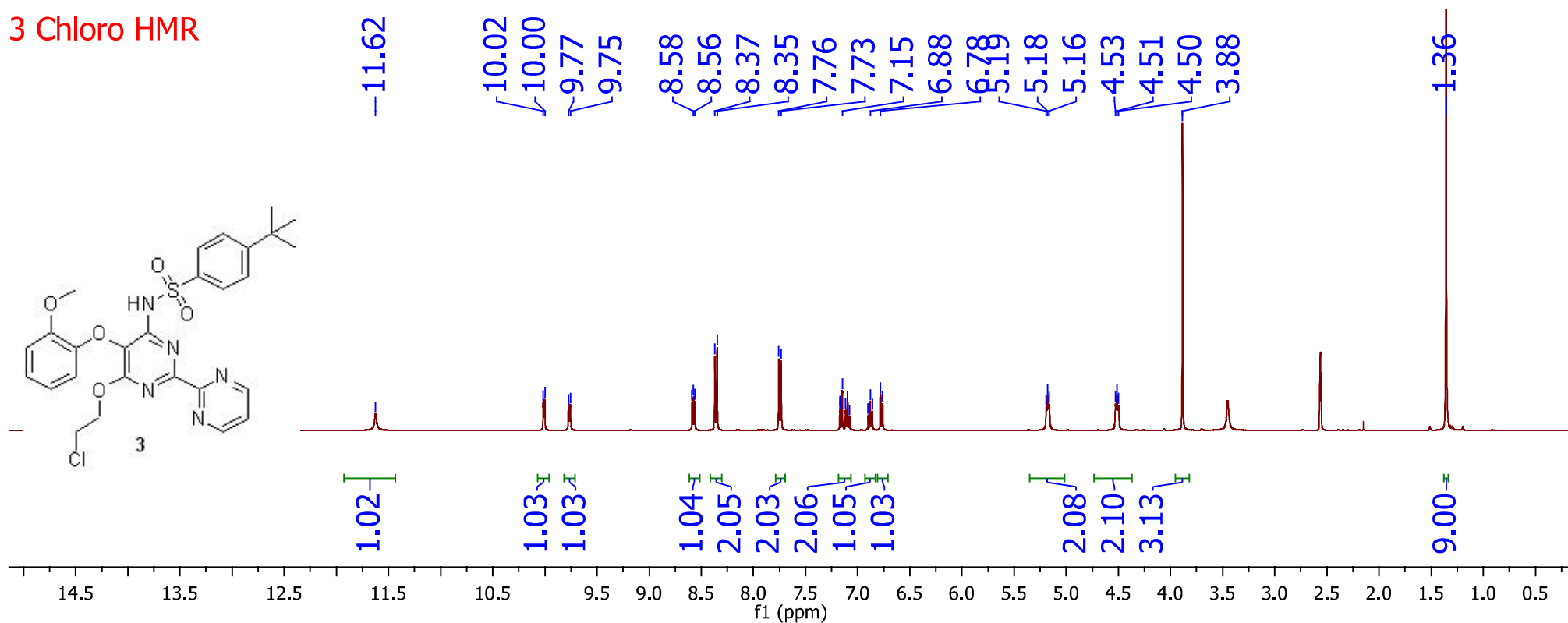


Figure 2: ^1H -NMR Spectrum of 4-tert-Butyl-N-(6-(2-chloroethoxy)-5-(2-methoxyphenoxy)-2,2'-bipyrimidin-4-yl)benzene-sulfonamide (**3**)

3 Chloro CMR

165.98
156.59
155.09
153.73
149.52
149.26
147.01
145.71
141.61
138.24
129.15
127.33
126.04
124.58
123.86
120.76
115.93
113.48

~56.27

~52.59

37.73

~35.41

31.33

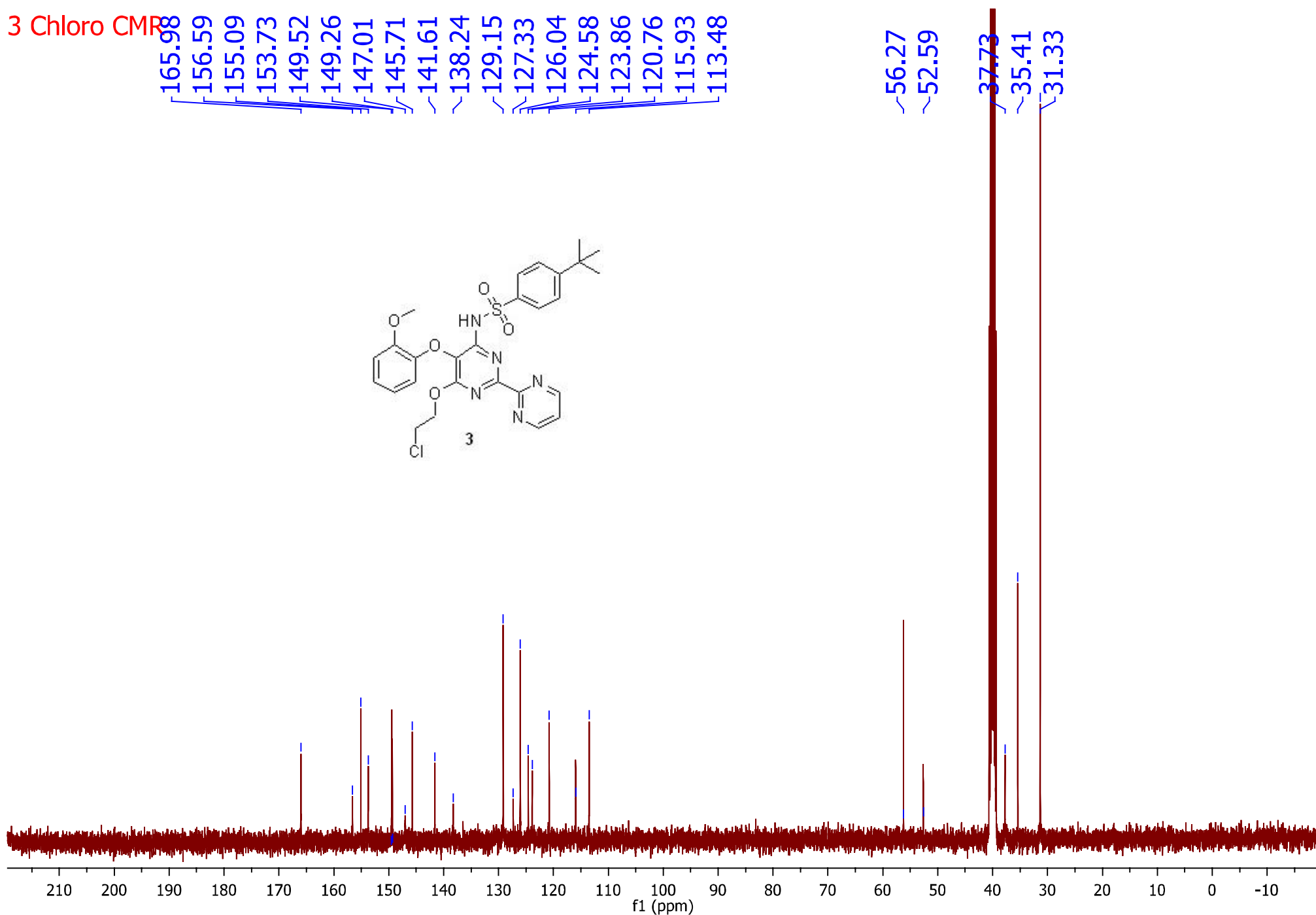
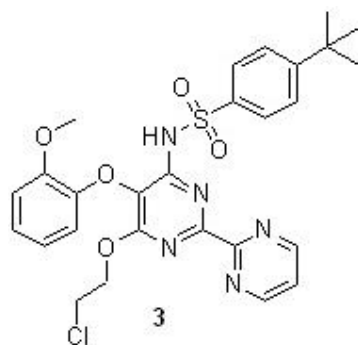


Figure 3: ¹³C-NMR Spectrum of 4-tert-Butyl-N-(6-(2-chloroethoxy)-5-(2-methoxyphenoxy)-2,2'-bipyrimidin-4-yl)benzene-sulfonamide (**3**)

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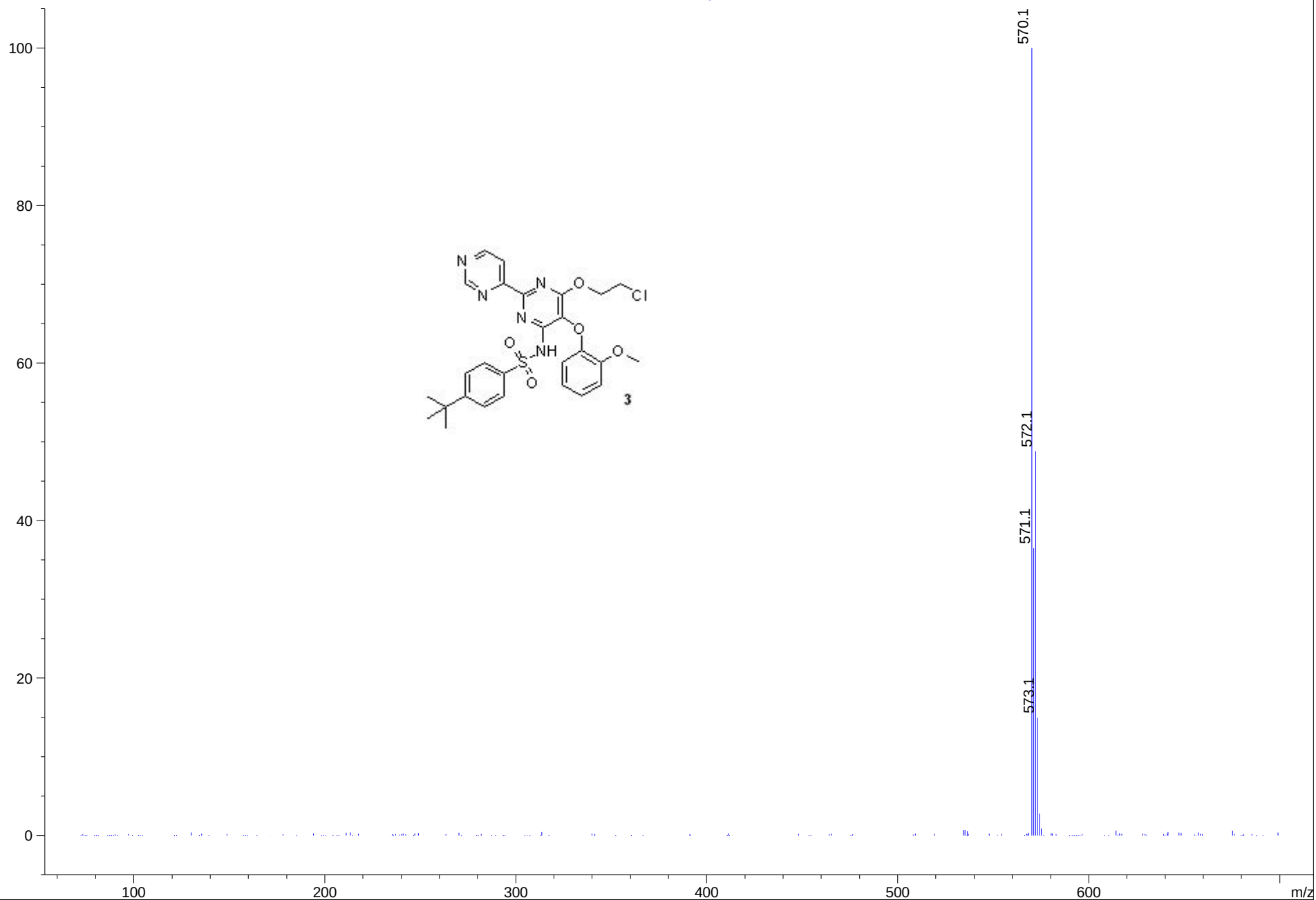
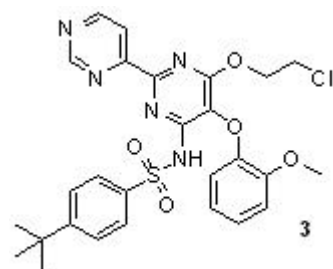


Figure 4: MS Spectrum of 4-tert-Butyl-N-(6-(2-chloroethoxy)-5-(2-methoxyphenoxy)-2,2'-bipyrimidin-4-yl)benzene-sulfonamide (**3**)

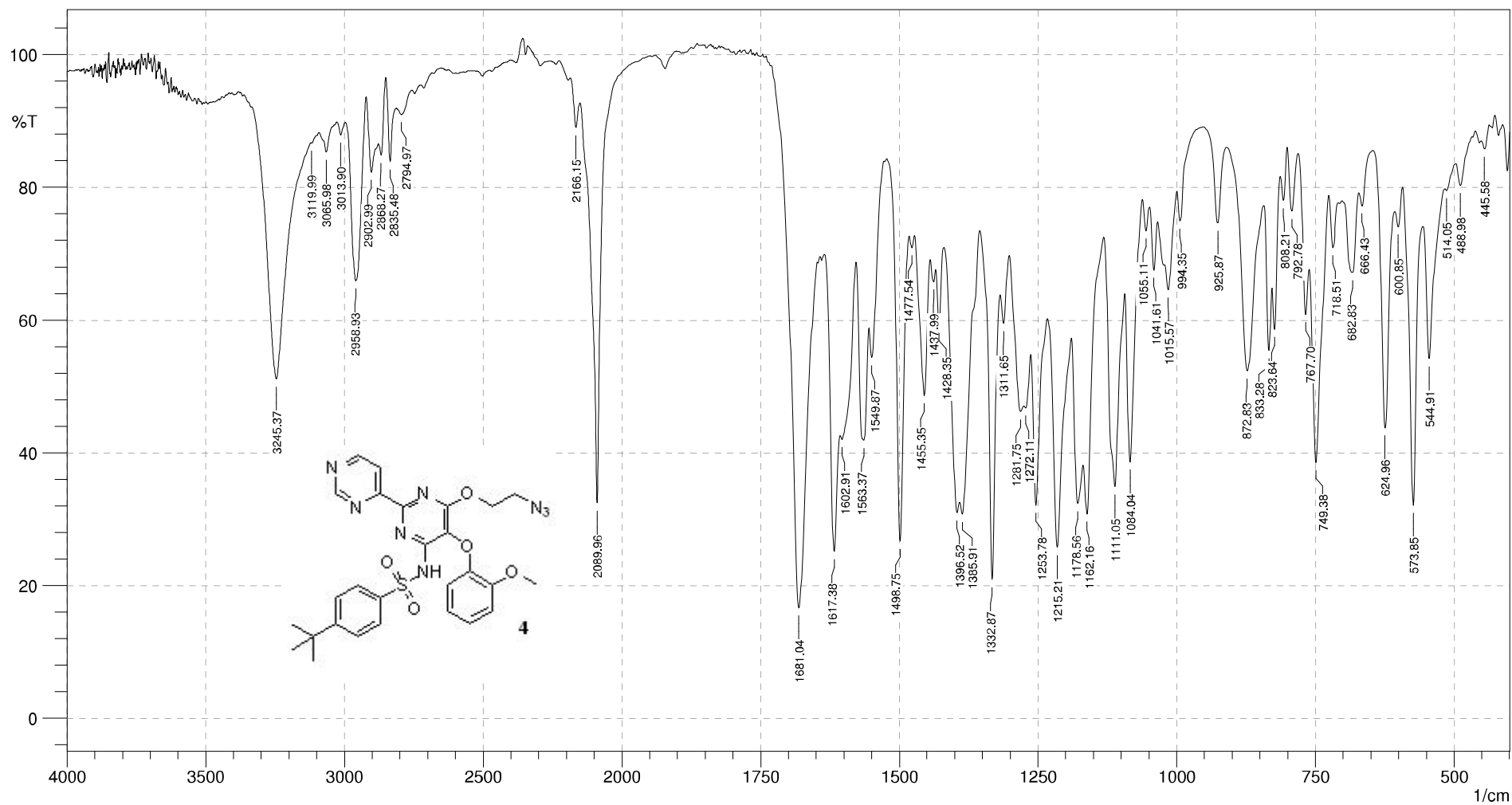


Figure 5: IR Spectrum of N-(6-(2-Azidoethoxy)-5-(2-methoxyphenoxy)-2,2'-bipyrimidin-4-yl)-4-tert-butylbenzene-sulfonamide (**4**)

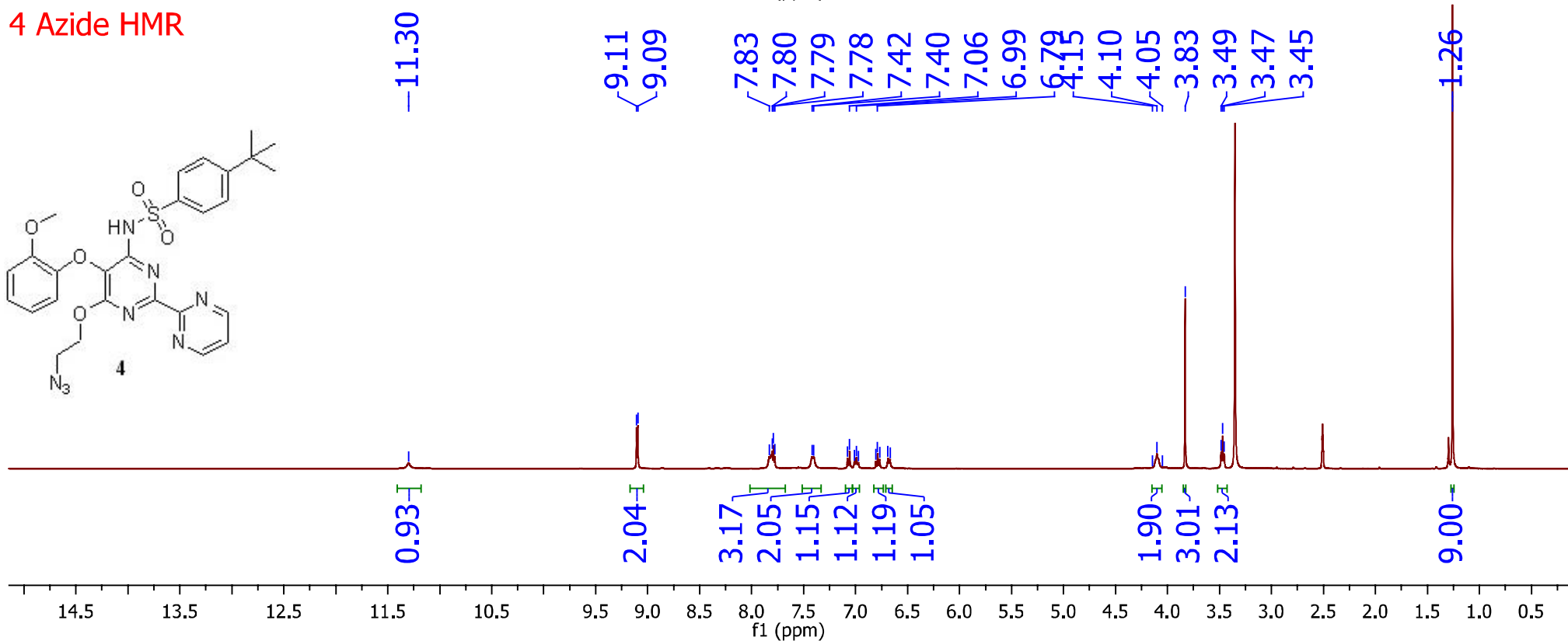
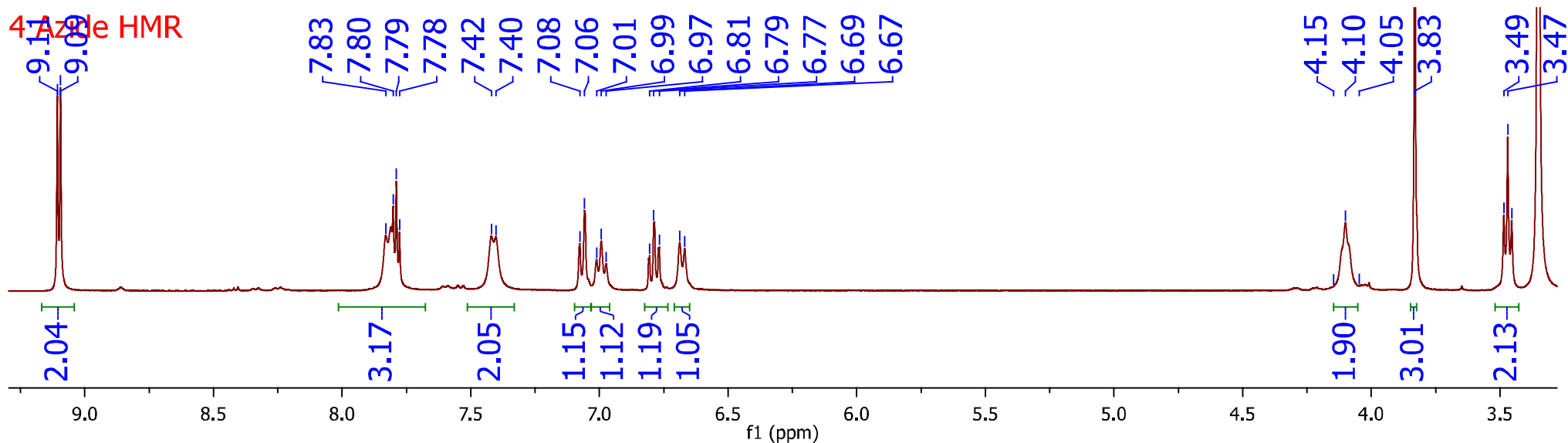


Figure 6: ^1H -NMR Spectrum of N-(6-(2-Azidoethoxy)-5-(2-methoxyphenoxy)-2,2'-bipyrimidin-4-yl)-4-tert-butylbenzene-sulfonamide (**4**)

4 Azide

159.58
158.38
157.27
156.26
151.31
149.33
146.92
146.14
138.48
128.53
125.60
124.33
123.29
122.84
120.85
115.33
113.35

~56.18
~49.06
~44.34
35.24
31.23

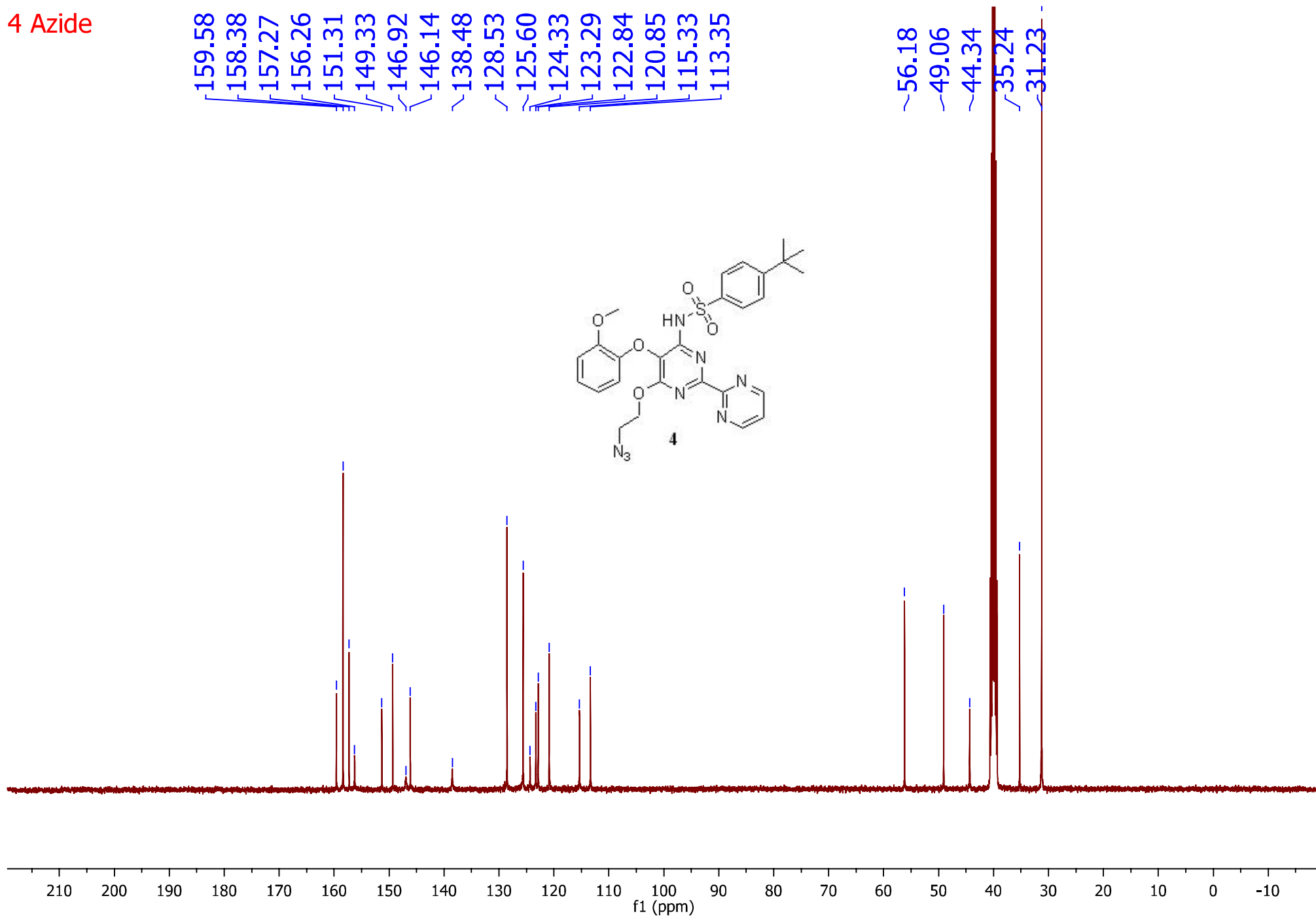
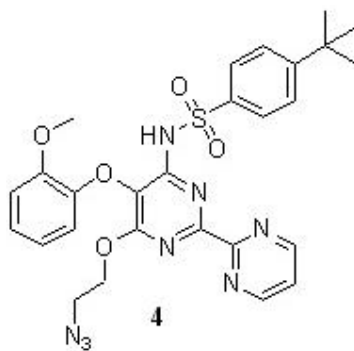


Figure 7: ¹³C-NMR Spectrum of N-(6-(2-Azidoethoxy)-5-(2-methoxyphenoxy)-2,2'-bipyrimidin-4-yl)-4-tert-butylbenzene-sulfonamide (**4**)

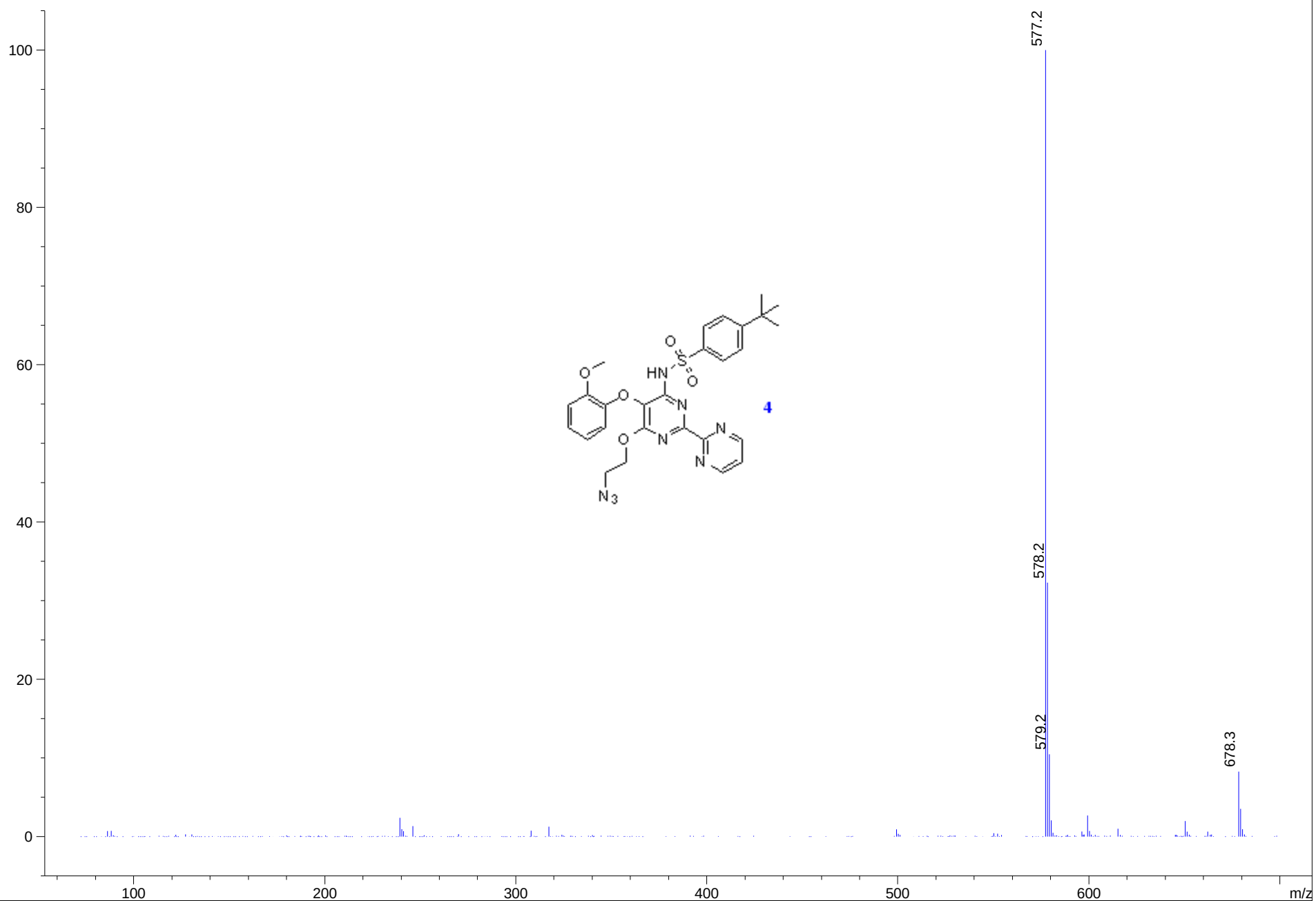


Figure 8: MS Spectrum of N-(6-(2-Azidoethoxy)-5-(2-methoxyphenoxy)-2,2'-bipyrimidin-4-yl)-4-tert-butylbenzene-sulfonamide (**4**)

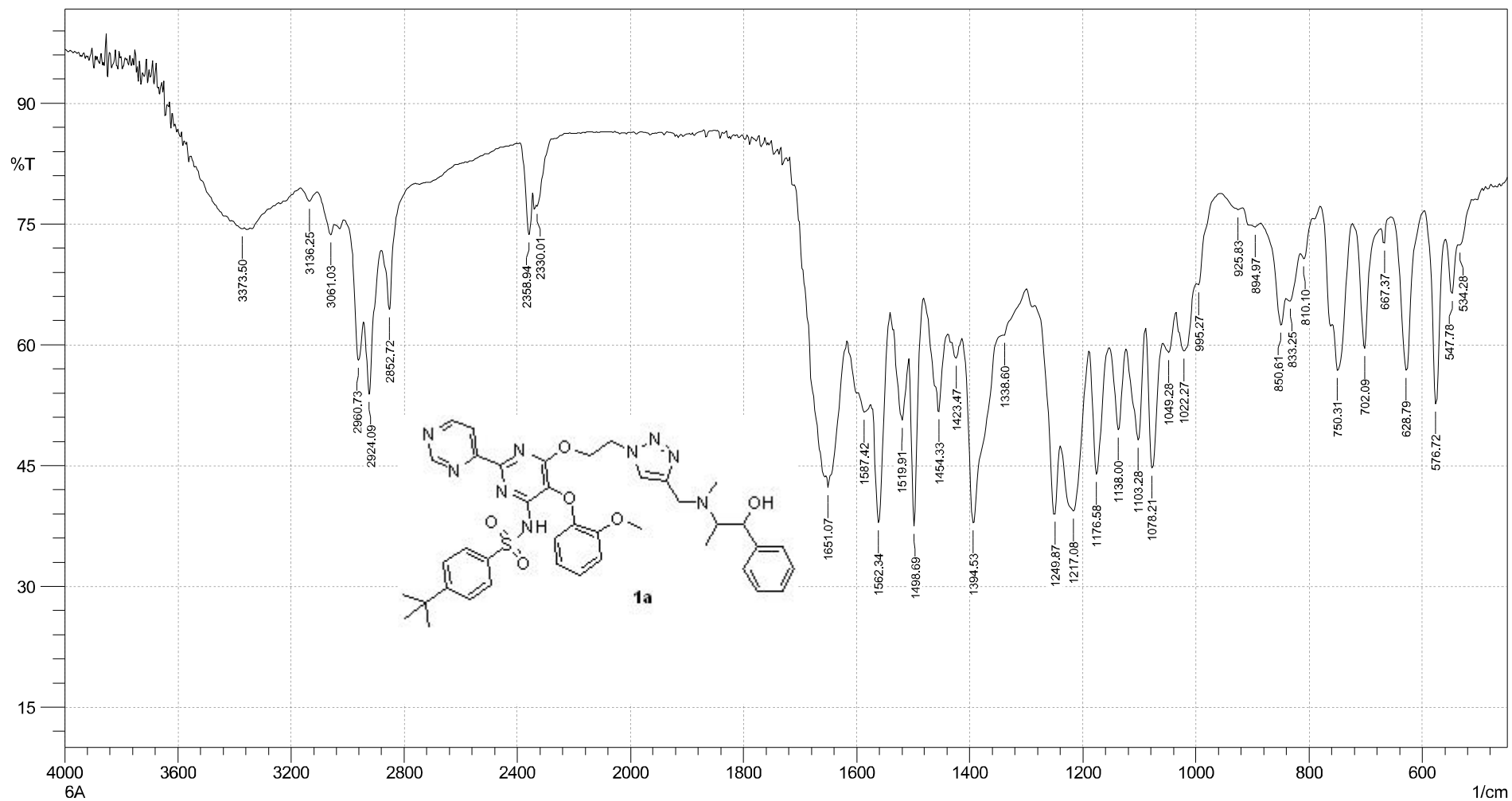


Figure 9: IR Spectrum of 4-tert-Butyl-N-(6-(2-(4-(((1S,2R)-1-hydroxy-1-phenyl-2-propyl)(methyl)amino)methyl)-1H-1,2,3-triazol-1-yl)ethoxy)-5-(2-methoxyphenoxy)-2,2'-bipyrimidin-4-yl)benzenesulfonamide (**1a**)

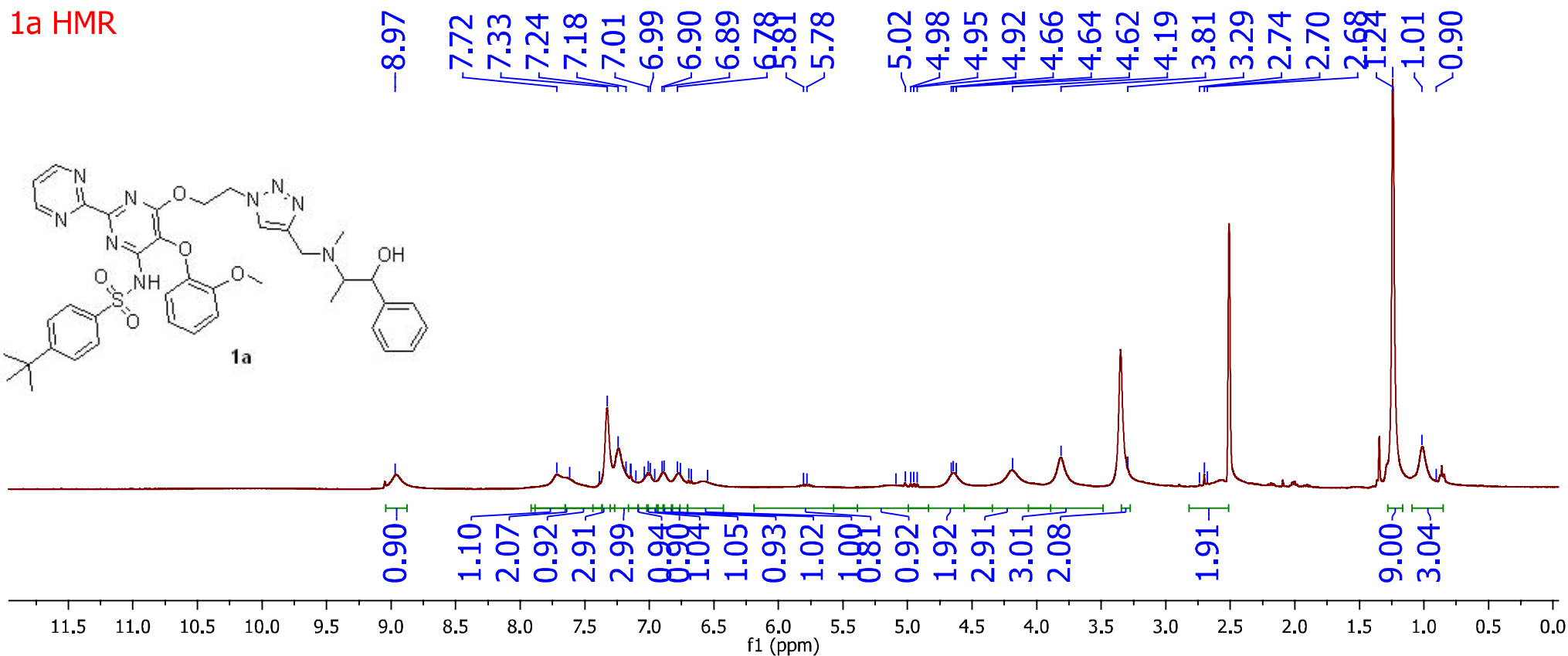
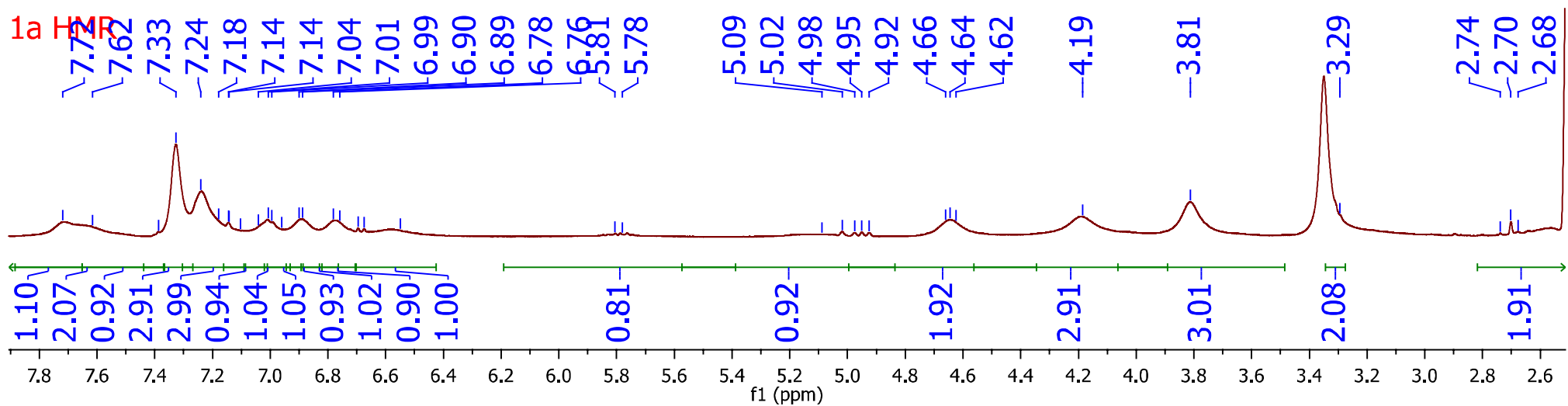


Figure 10: ^1H -NMR Spectrum of 4-tert-Butyl-N-(6-(2-(4-(((1S,2R)-1-hydroxy-1-phenyl-2-propyl)(methyl)amino)methyl)-1H-1,2,3-triazol-1-yl)ethoxy)-5-(2-methoxyphenoxy)-2,2'-bipyrimidin-4-yl)benzenesulfonamide (**1a**)

1a CMR

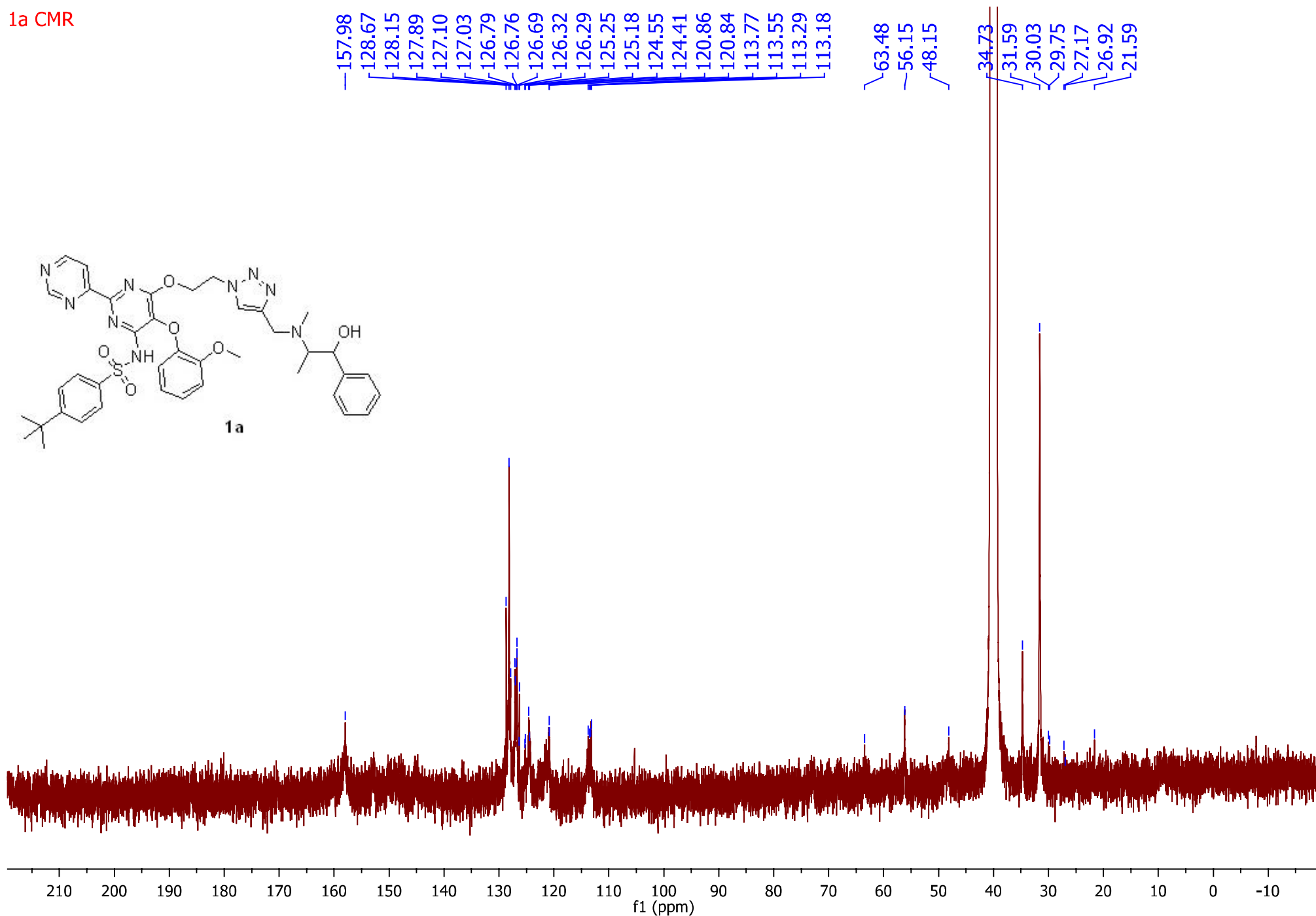


Figure 11: ¹³C-NMR Spectrum of 4-tert-Butyl-N-(6-(2-(4-(((1S,2R)-1-hydroxy-1-phenyl-2-propyl)(methyl)amino)methyl)-1H-1,2,3-triazol-1-yl)ethoxy)-5-(2-methoxyphenoxy)-2,2'-bipyrimidin-4-yl)benzenesulfonamide (**1a**)

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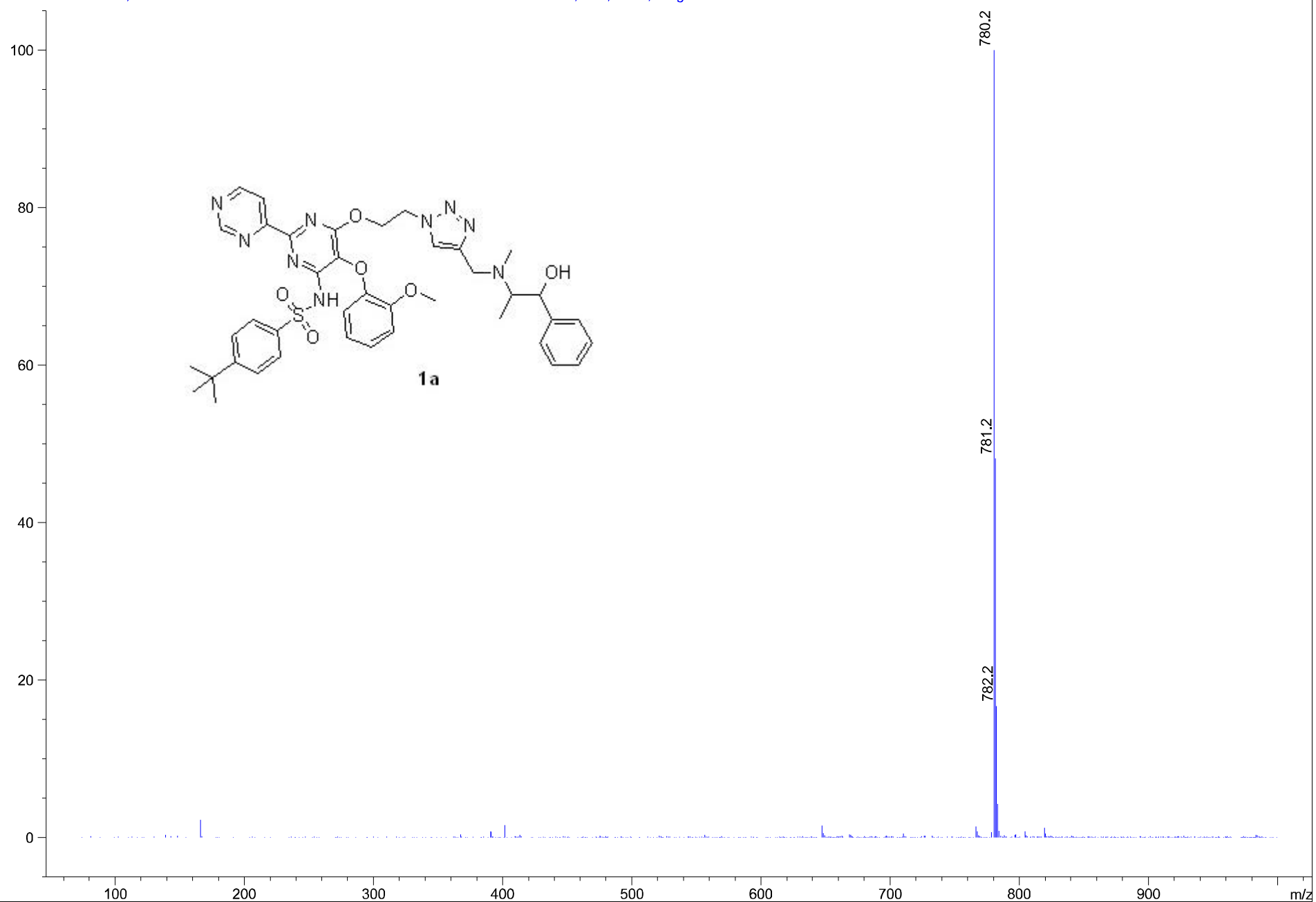


Figure 12: ¹³C-NMR Spectrum of 4-tert-Butyl-N-(6-(2-(4-(((1S,2R)-1-hydroxy-1-phenyl-2-propyl)(methyl)amino)methyl)-1H-1,2,3-triazol-1-yl)ethoxy)-5-(2-methoxyphenoxy)-2,2'-bipyrimidin-4-yl)benzenesulfonamide (**1a**)

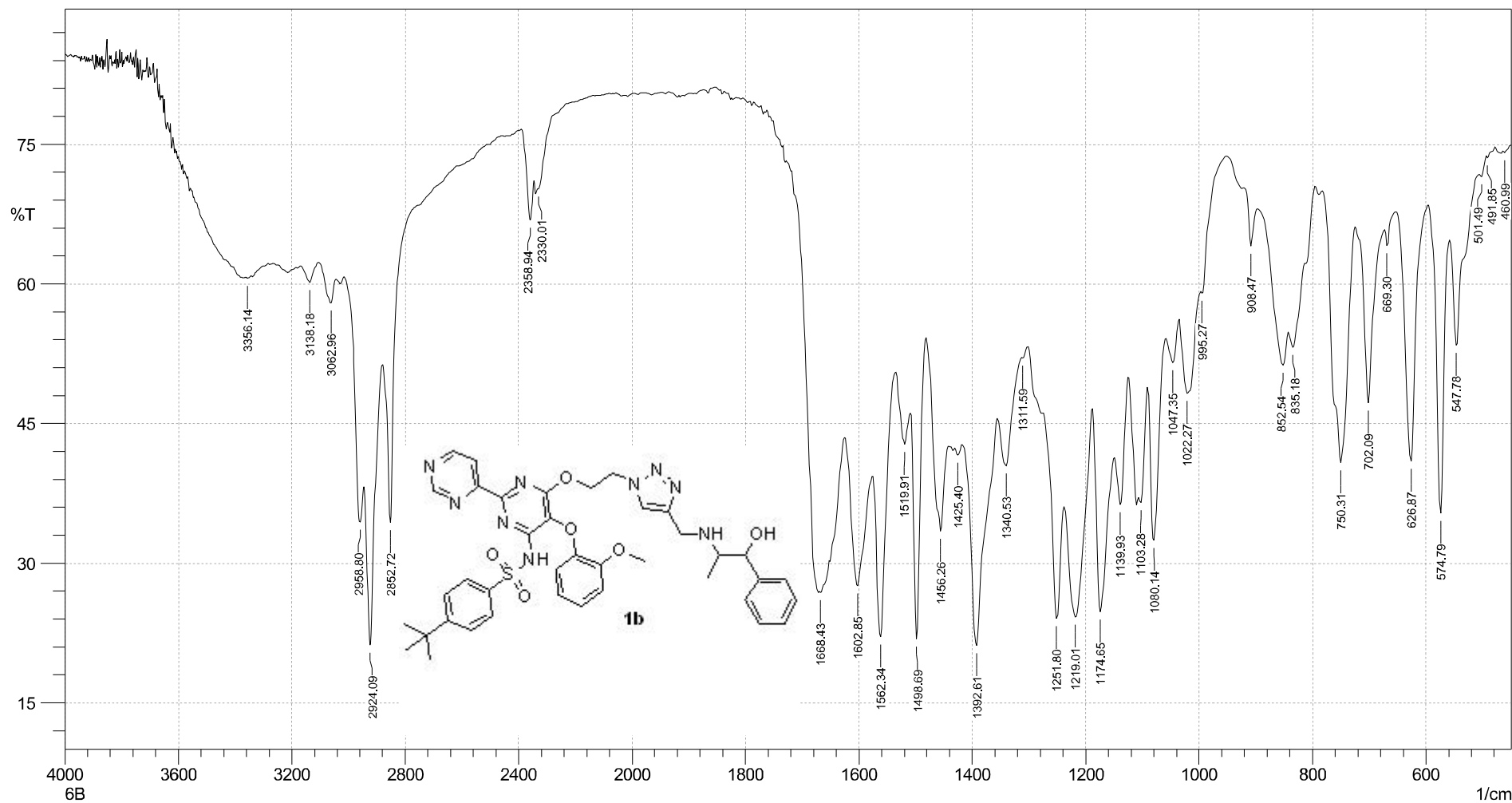


Figure 13: IR Spectrum of 4-tert-Butyl-N-(6-(2-(4-(((1S,2R)-1-hydroxy-1-phenyl-2-propylamino)methyl)-1H-1,2,3-triazol-1-yl)ethoxy)-5-(2-methoxyphenoxy)-2,2'-bipyrimidin-4-yl)benzenesulfonamide (**1b**)

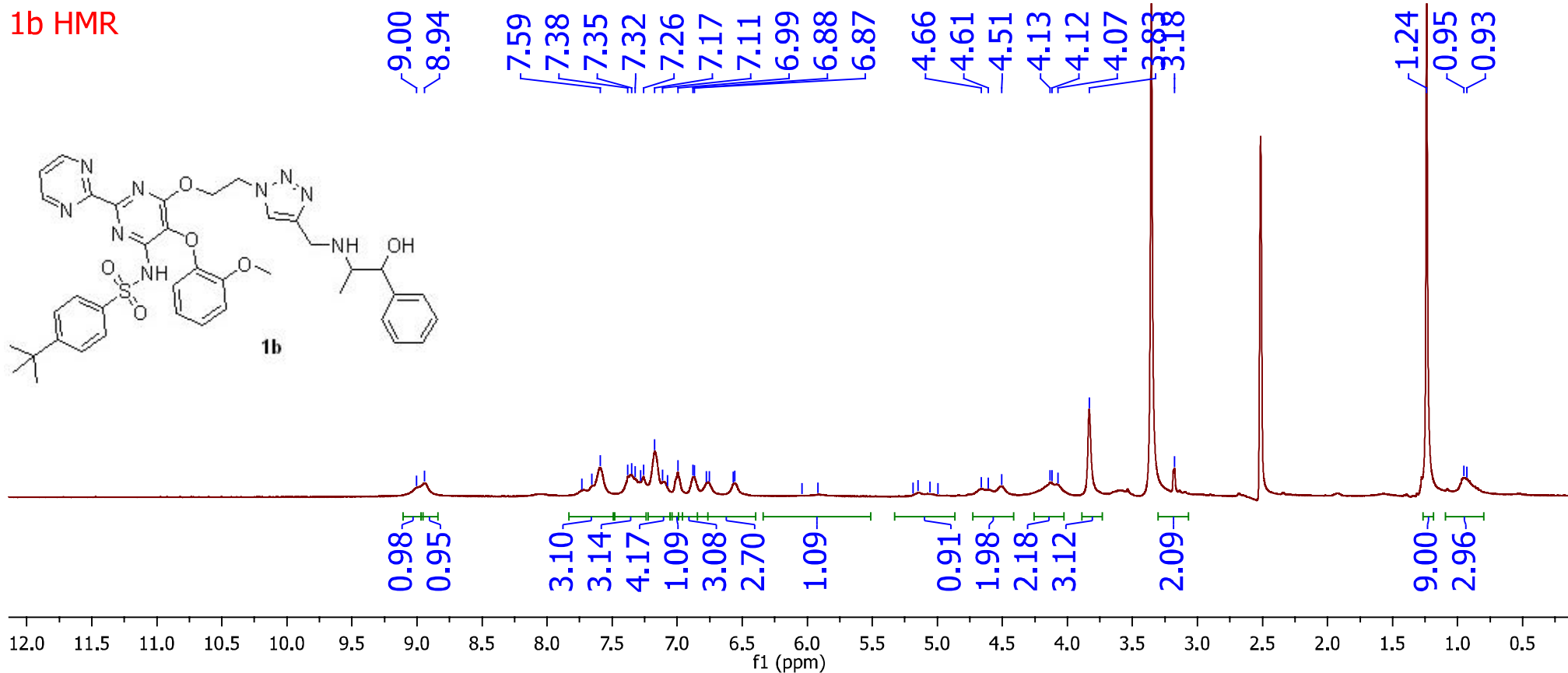
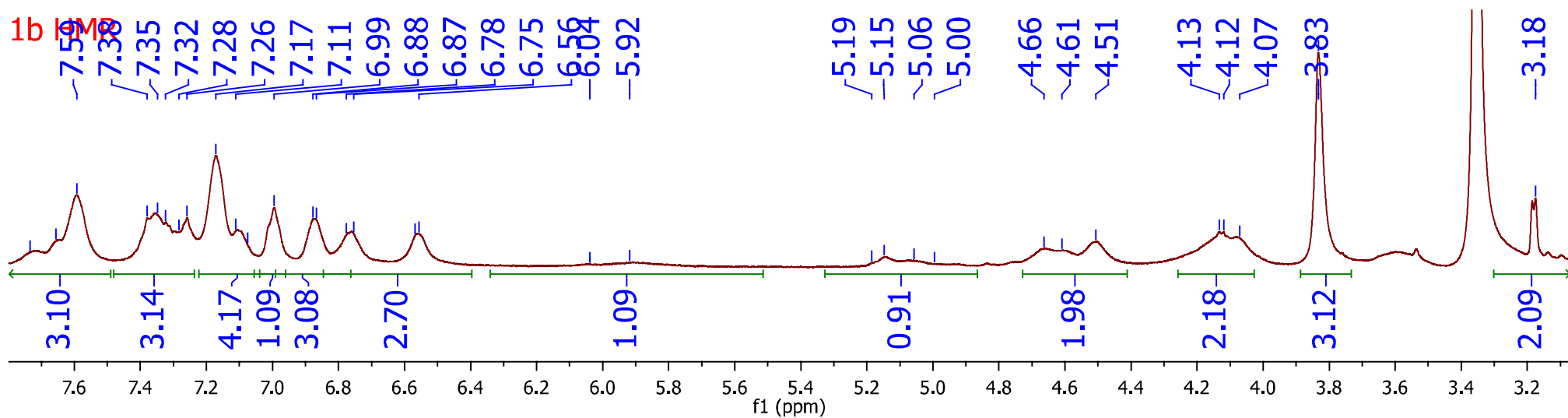


Figure 14: ^1H -NMR Spectrum of 4-tert-Butyl-N-(6-(2-(4-(((1S,2R)-1-hydroxy-1-phenyl-2-propylamino)methyl)-1H-1,2,3-triazol-1-yl)ethoxy)-5-(2-methoxyphenoxy)-2,2'-bipyrimidin-4-yl)benzenesulfonamide (**1b**)

1b CMR

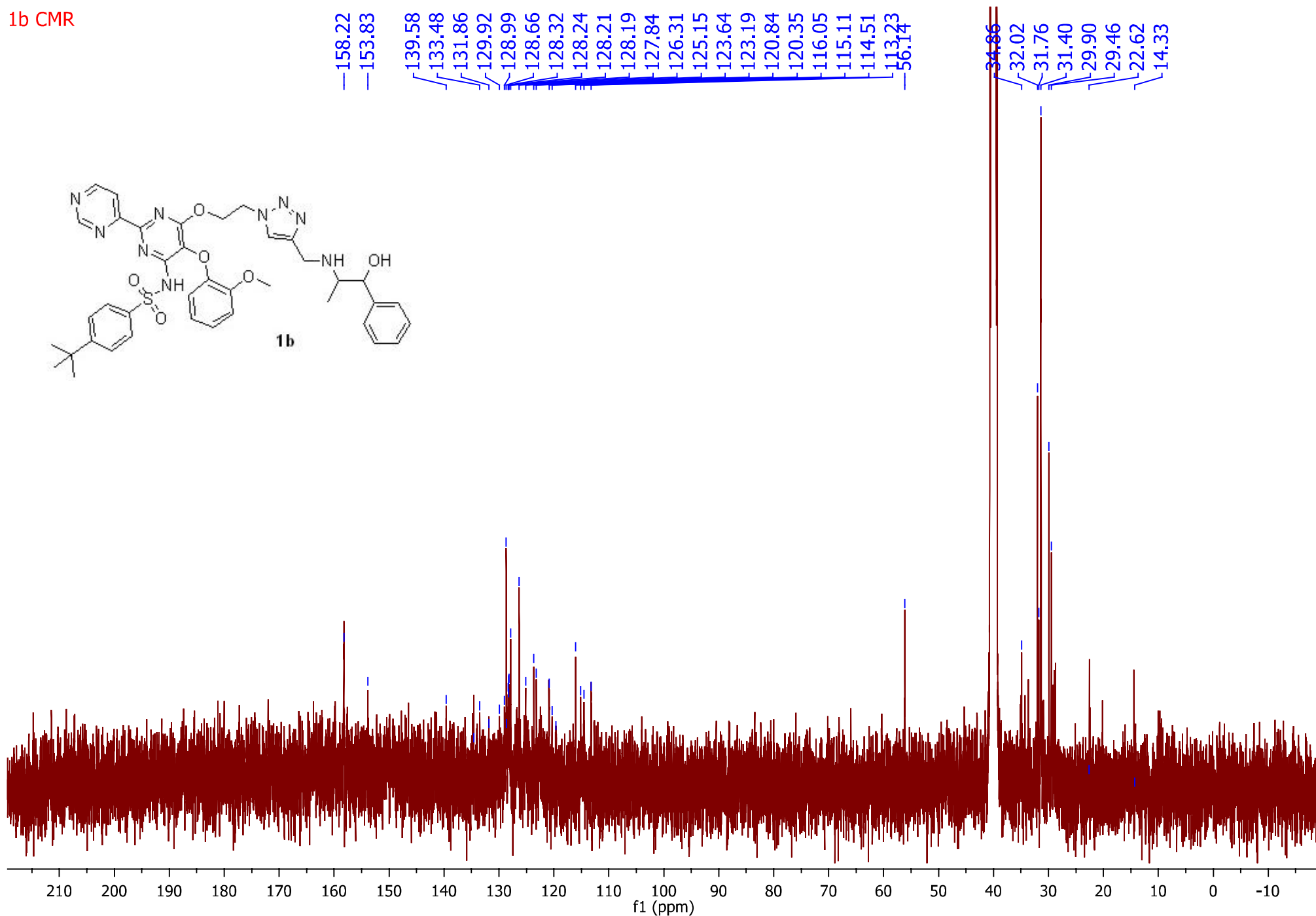


Figure 15: ¹³C-NMR Spectrum of 4-tert-Butyl-N-(6-(2-(4-(((1S,2R)-1-hydroxy-1-phenyl-2-propylamino)methyl)-1H-1,2,3-triazol-1-yl)ethoxy)-5-(2-methoxyphenoxy)-2,2'-bipyrimidin-4-yl)benzenesulfonamide (**1b**)

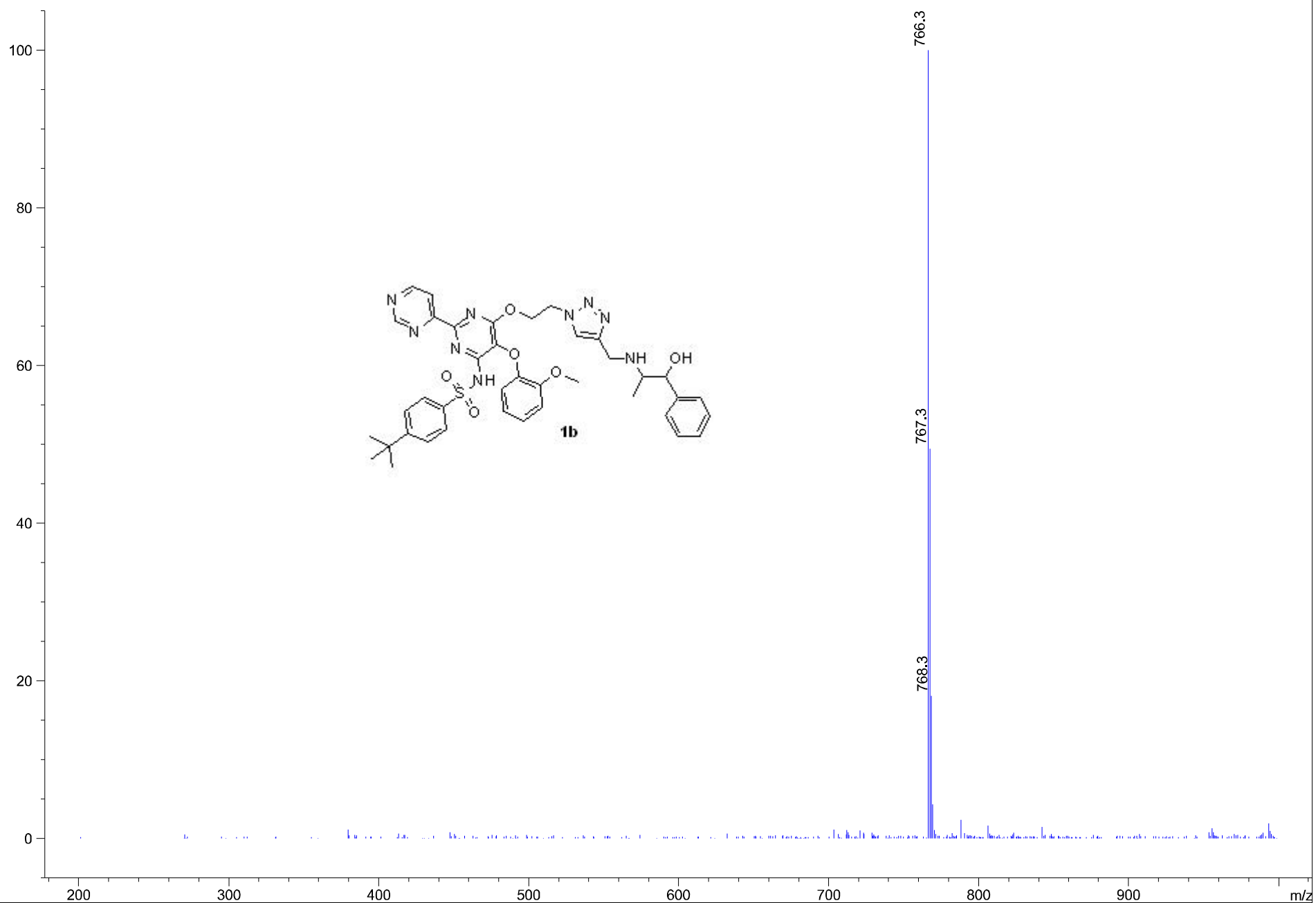


Figure 16: Mass Spectrum of 4-tert-Butyl-N-(6-(2-(4-(((1S,2R)-1-hydroxy-1-phenyl-2-propylamino)methyl)-1H-1,2,3-triazol-1-yl)ethoxy)-5-(2-methoxyphenoxy)-2,2'-bipyrimidin-4-yl)benzenesulfonamide (**1b**)

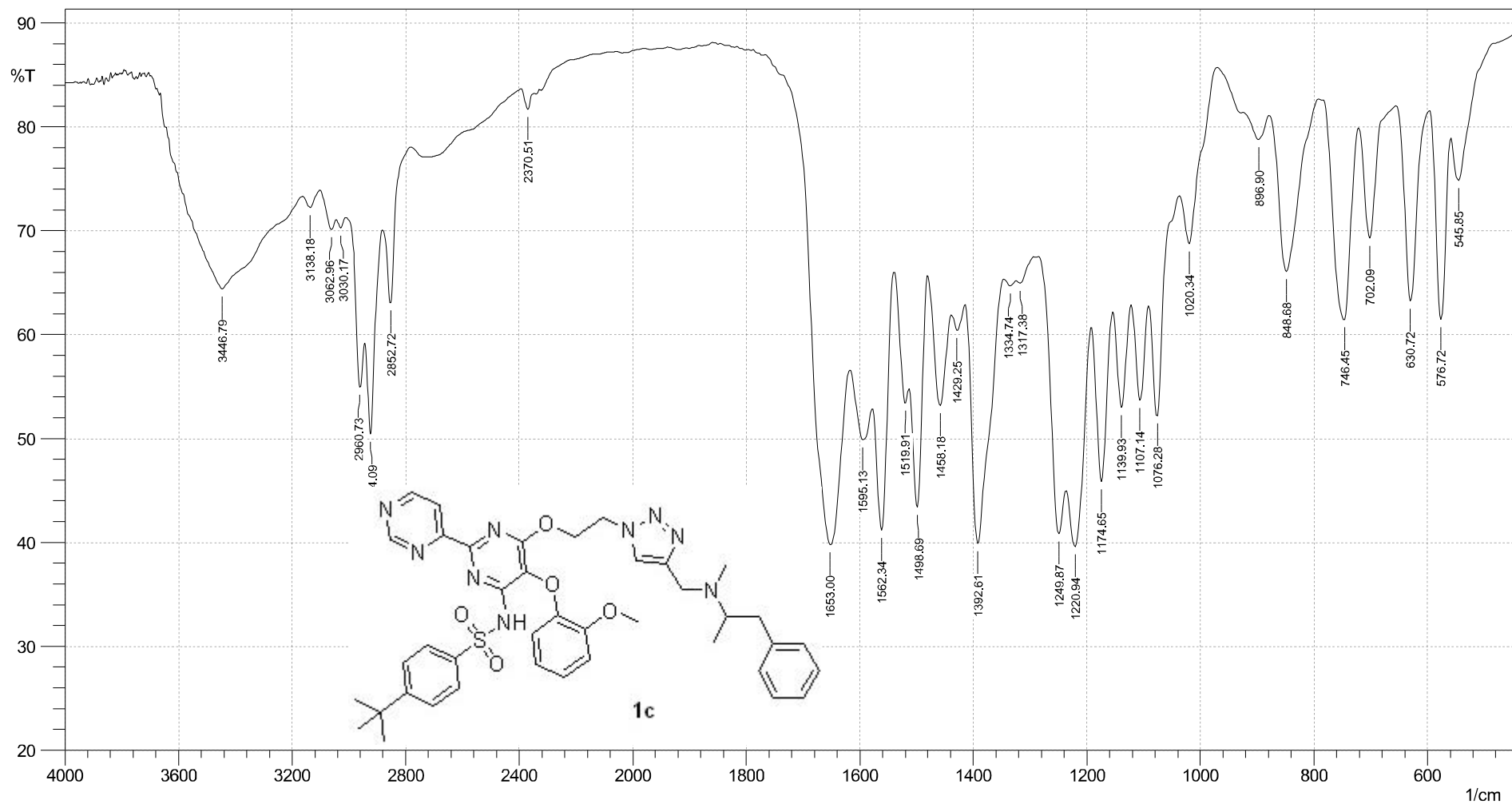


Figure 17: IR Spectrum of 4-tert-Butyl-N-(5-(2-methoxyphenoxy)-6-(2-(4-((methyl(1-phenylpropan-2-yl)-amino)-methyl)-1H-1,2,3-triazol-1-yl)ethoxy)-2,2'-bipyrimidin-4-yl)benzenesulfonamide (**1c**)

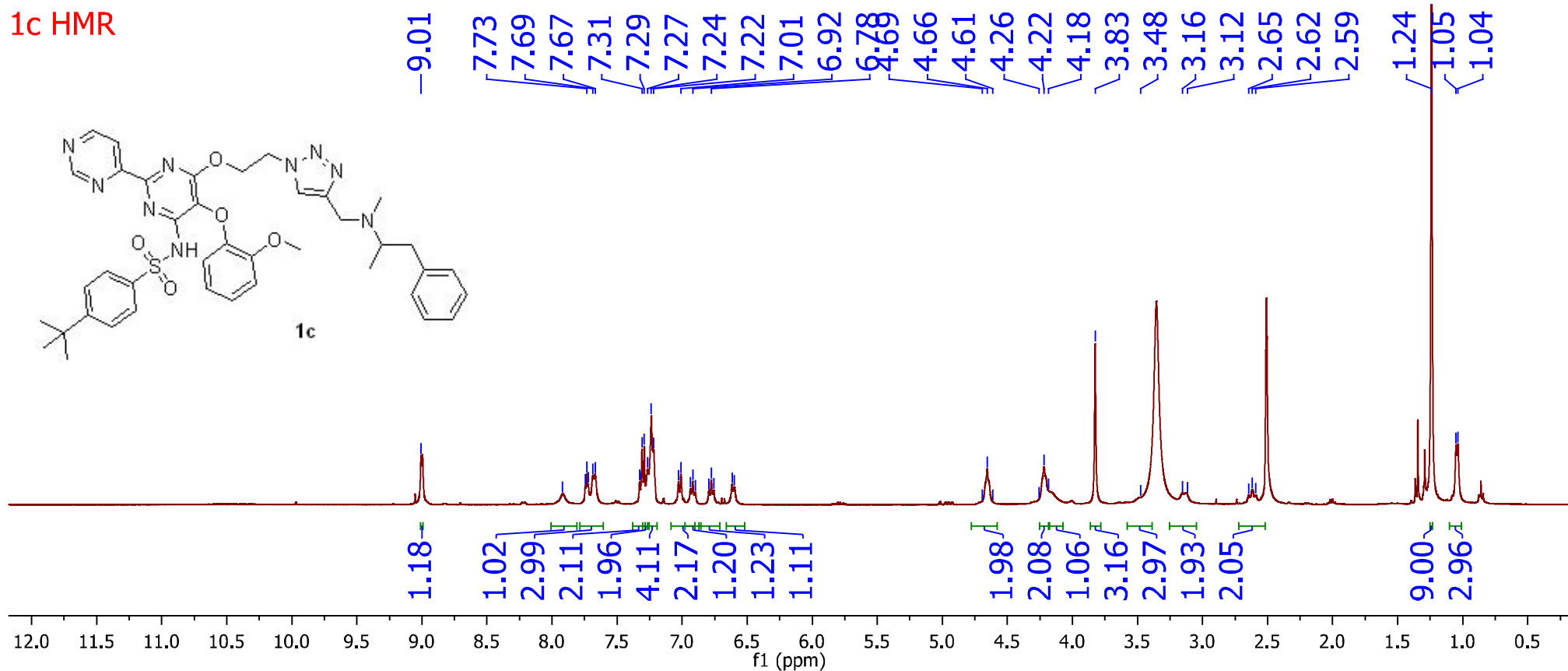
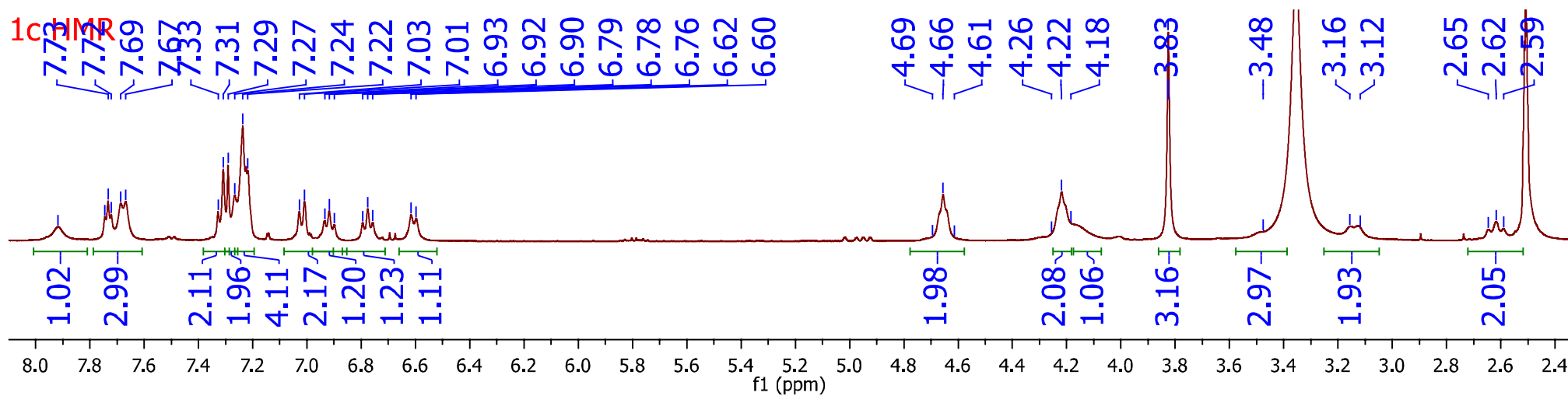


Figure 18: ^1H -NMR Spectrum of 4-tert-Butyl-N-(5-(2-methoxyphenoxy)-6-(2-(4-((methyl(1-phenylpropan-2-yl)-amino)-methyl)-1H-1,2,3-triazol-1-yl)ethoxy)-2,2'-bipyrimidin-4-yl)benzenesulfonamide (**1c**)

1c CMR

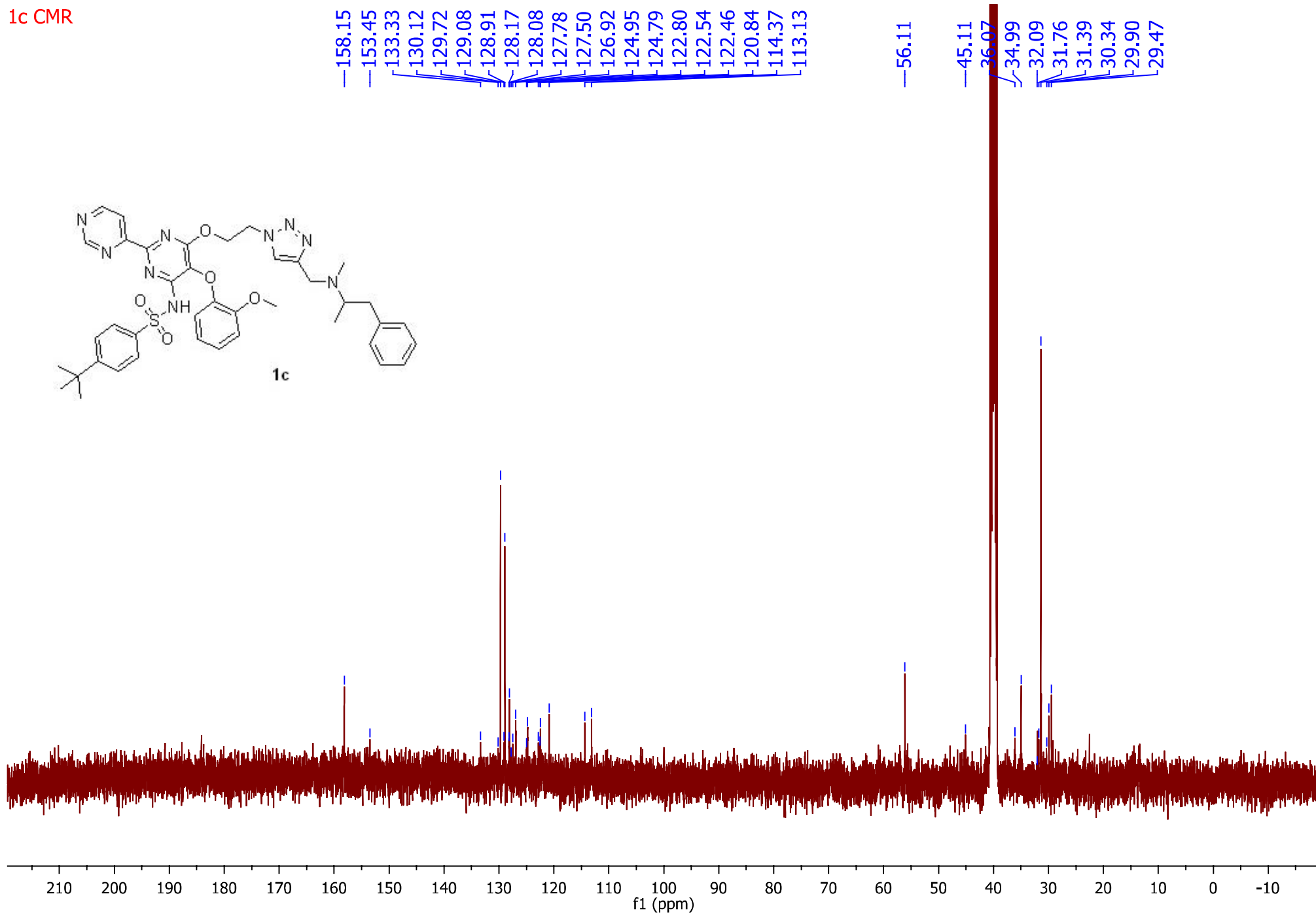


Figure 19: ¹³C-NMR Spectrum of 4-tert-Butyl-N-(5-(2-methoxyphenoxy)-6-(2-(4-((methyl(1-phenylpropan-2-yl)-amino)-methyl)-1H-1,2,3-triazol-1-yl)ethoxy)-2,2'-bipyrimidin-4-yl)benzenesulfonamide (**1c**)

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Figure 20: ^{13}C -NMR Spectrum of 4-tert-Butyl-N-(5-(2-methoxyphenoxy)-6-(2-(4-((methyl(1-phenylpropan-2-yl)amino)methyl)-1H-1,2,3-triazol-1-yl)ethoxy)-2,2'-bipyrimidin-4-yl)benzenesulfonamide (**1c**)

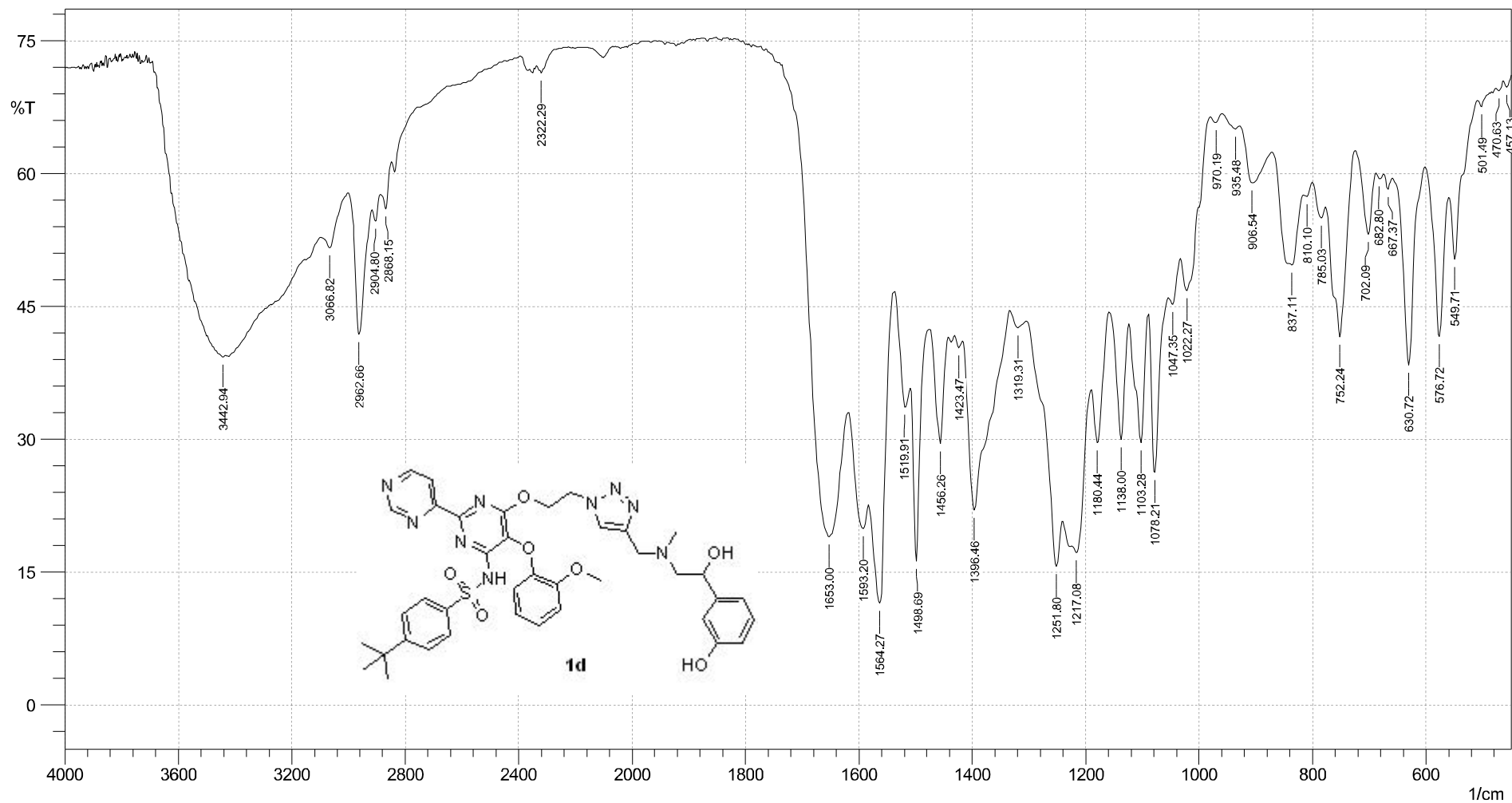


Figure 21: IR Spectrum of 4-tert-Butyl-N-(6-(2-(4-(((2-hydroxy-2-(3-hydroxyphenyl)ethyl)(methyl)amino)-methyl)-1H-1,2,3-triazol-1-yl)ethoxy)-5-(2-methoxyphenoxy)-2,2'-bipyrimidin-4-yl)-benzene-sulfonamide (**1d**)

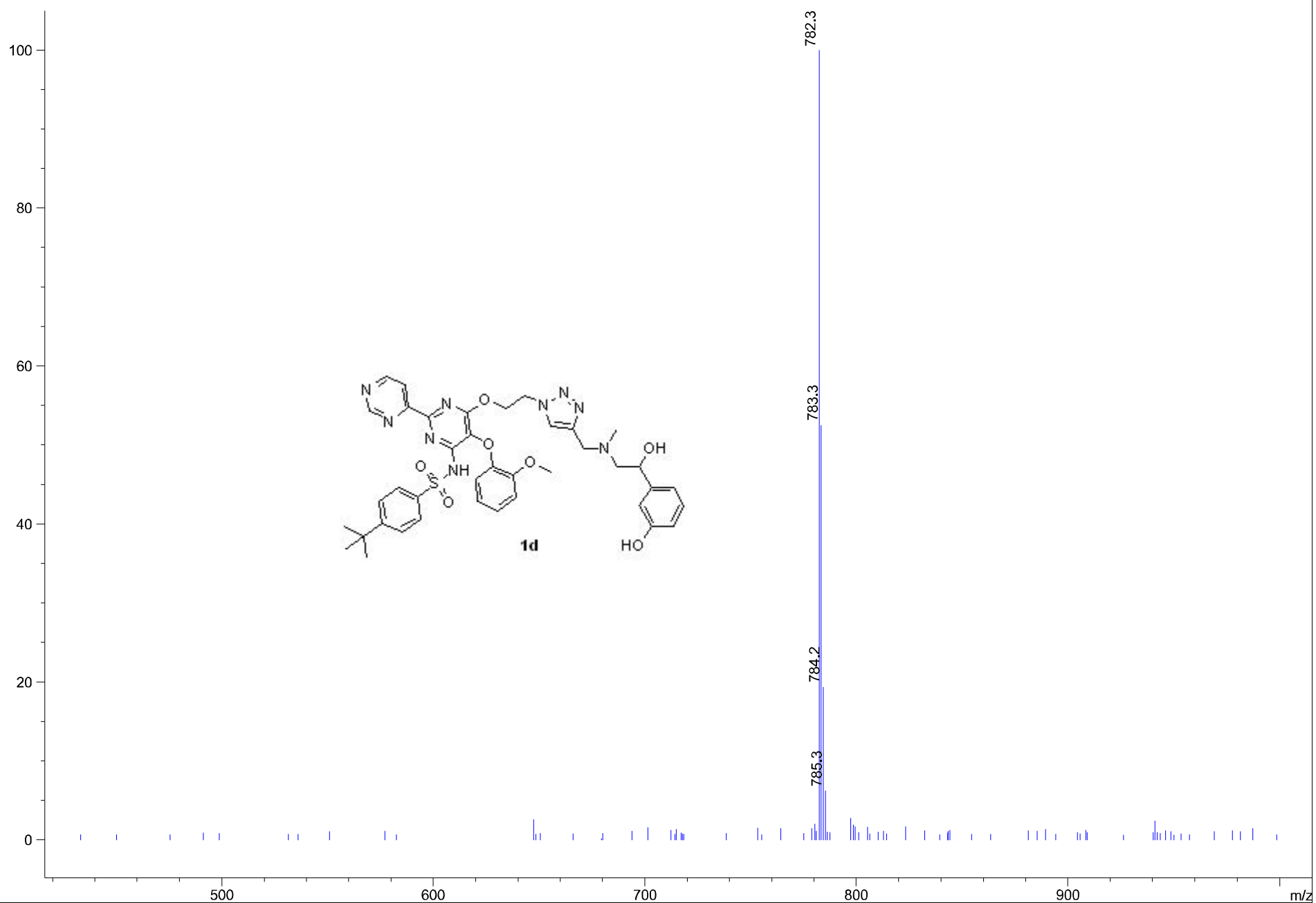


Figure 22: Mass Spectrum of 4-tert-Butyl-N-(6-(2-(4-(((2-hydroxy-2-(3-hydroxyphenyl)ethyl)(methyl)amino)-methyl)-1H-1,2,3-triazol-1-yl)ethoxy)-5-(2-methoxyphenoxy)-2,2'-bipyrimidin-4-yl)-benzene-sulfonamide (**1d**)

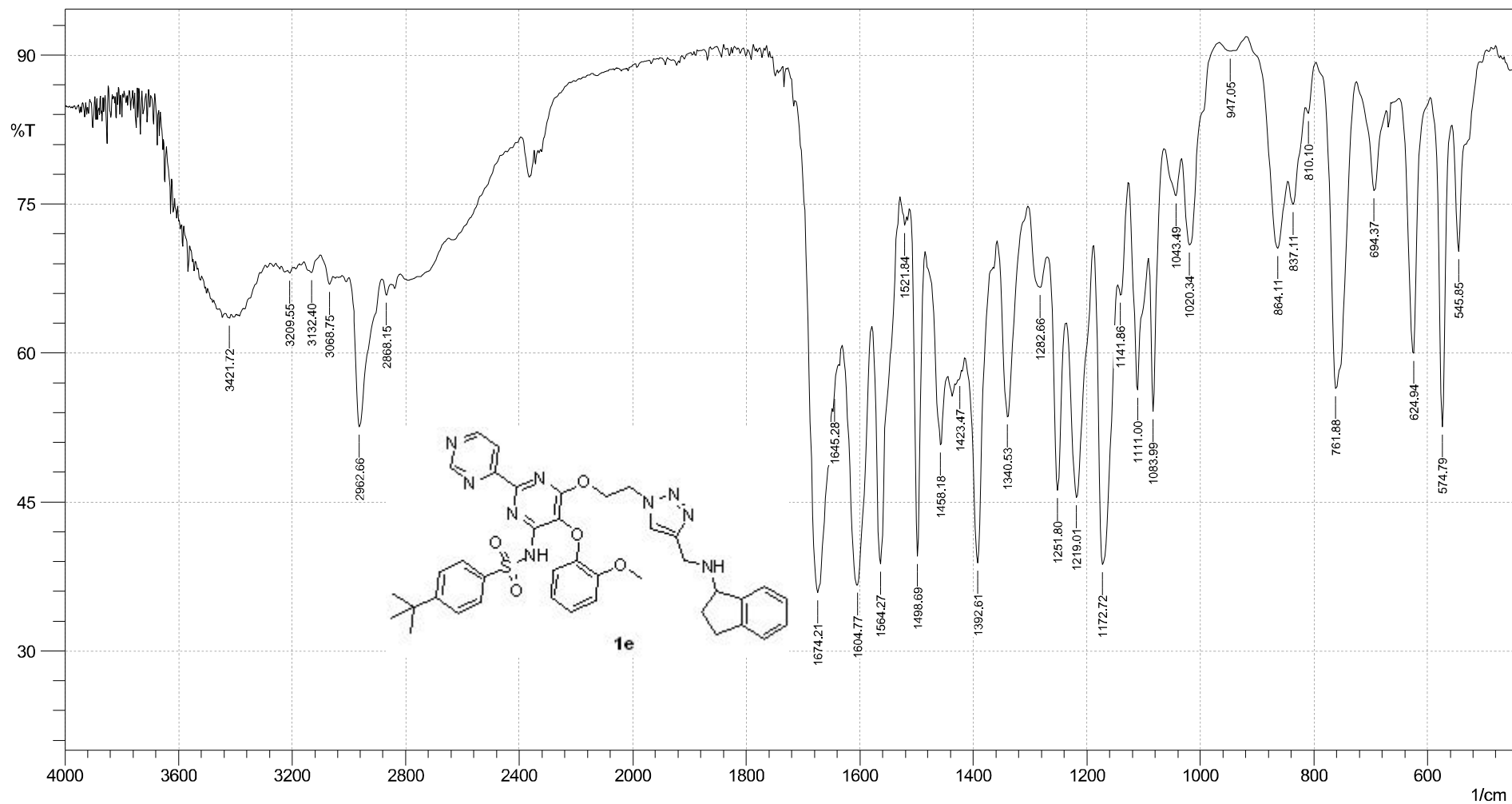


Figure 23: IR Spectrum of 4-tert-butyl-N-(6-(2-(4-((2,3-dihydro-1H-inden-1-ylamino)methyl)-1H-1,2,3-triazol-1-yl)-ethoxy)-5-(2-methoxyphenoxy)-2,2'-bipyrimidin-4-yl)benzenesulfonamide (**1e**)

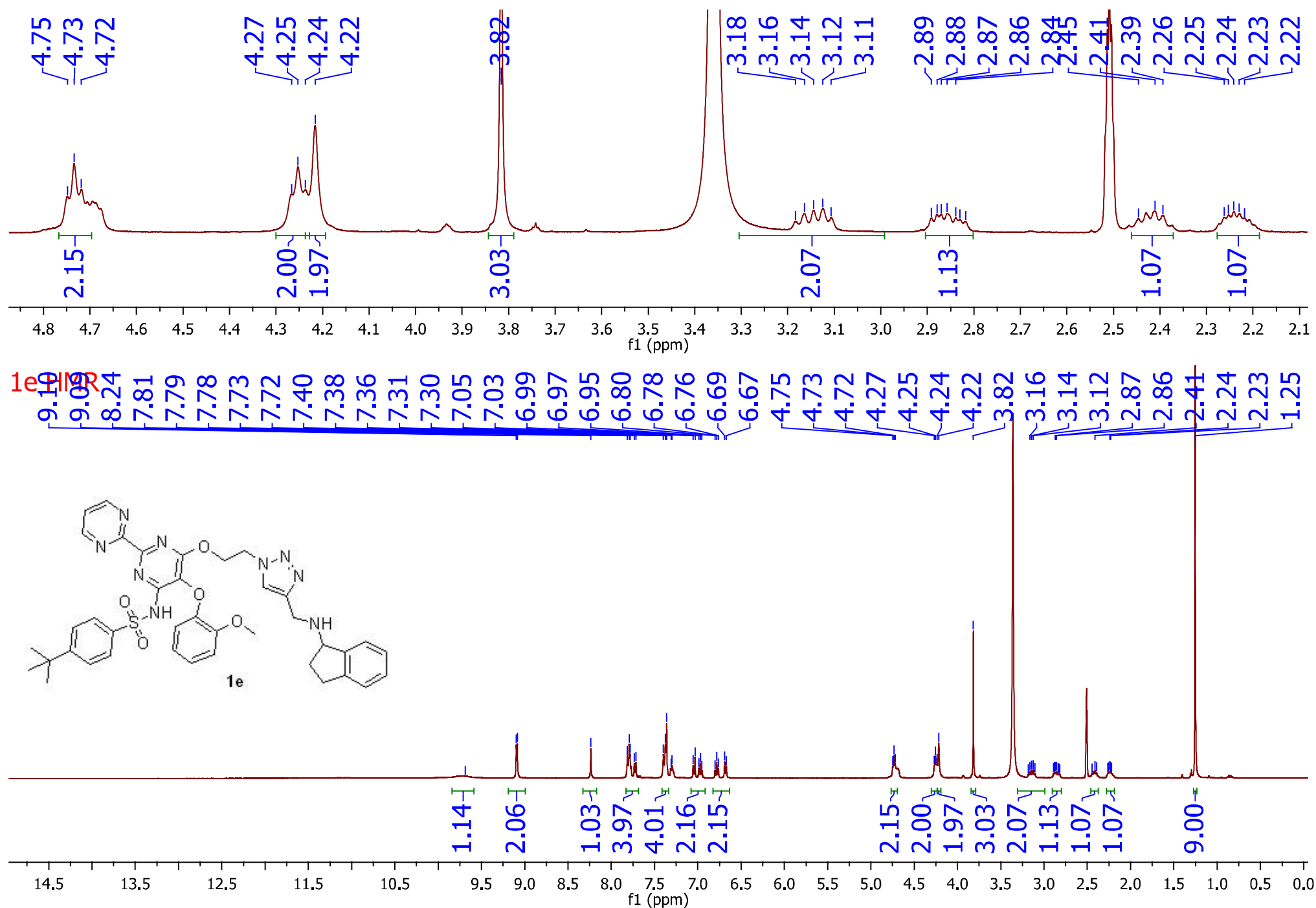


Figure 24: ¹H-NMR Spectrum of 4-tert-butyl-N-(6-(2-(4-((2,3-dihydro-1H-inden-1-ylamino)methyl)-1H-1,2,3-triazol-1-yl)ethoxy)-5-(2-methoxyphenoxy)-2,2'-bipyrimidin-4-yl)benzenesulfonamide (**1e**)

1e CMR

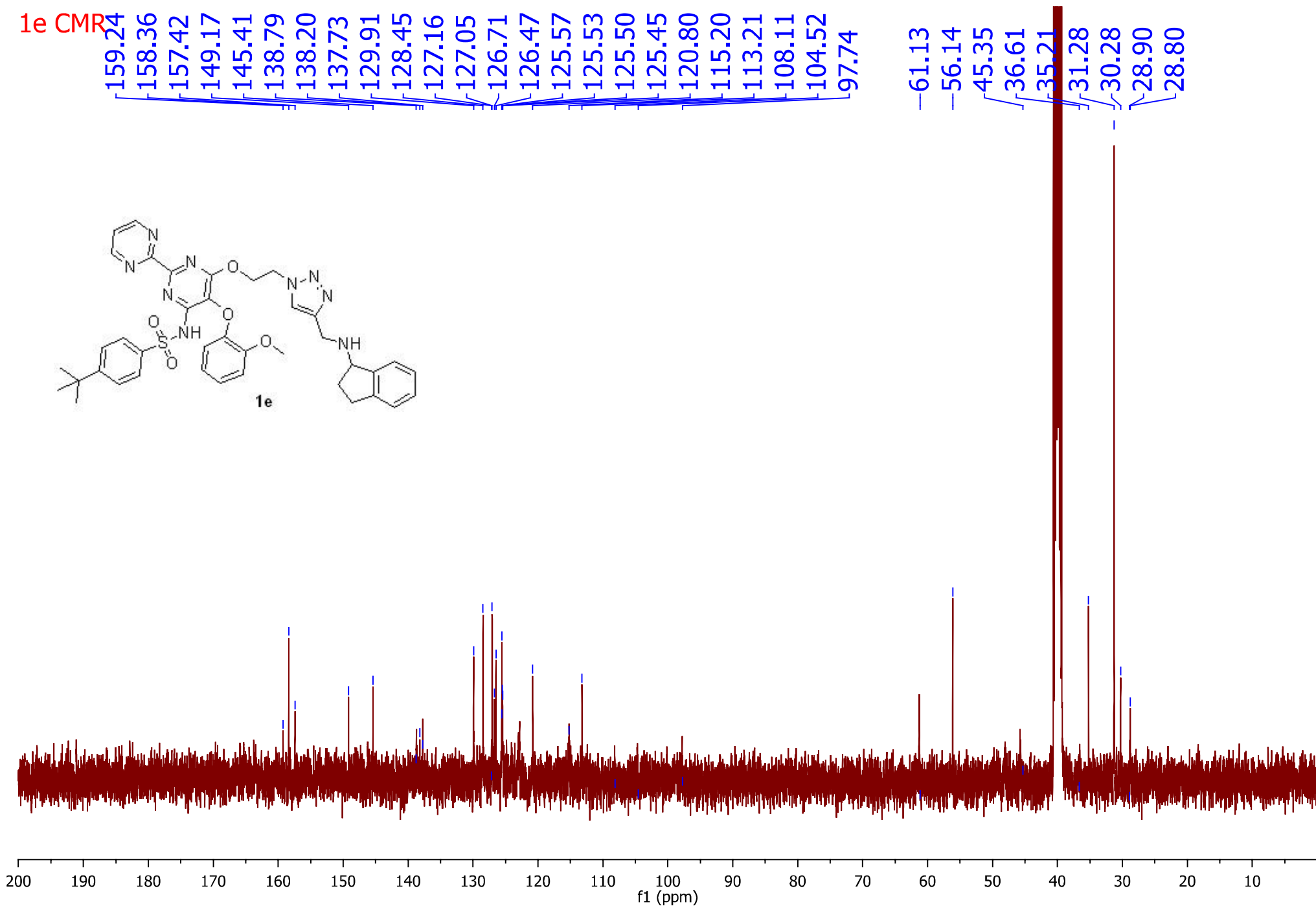


Figure 25: ¹³C-NMR Spectrum of 4-tert-butyl-N-(6-(2-(4-((2,3-dihydro-1H-inden-1-ylamino)methyl)-1H-1,2,3-triazol-1-yl)ethoxy)-5-(2-methoxyphenoxy)-2,2'-bipyrimidin-4-yl)benzenesulfonamide (**1e**)

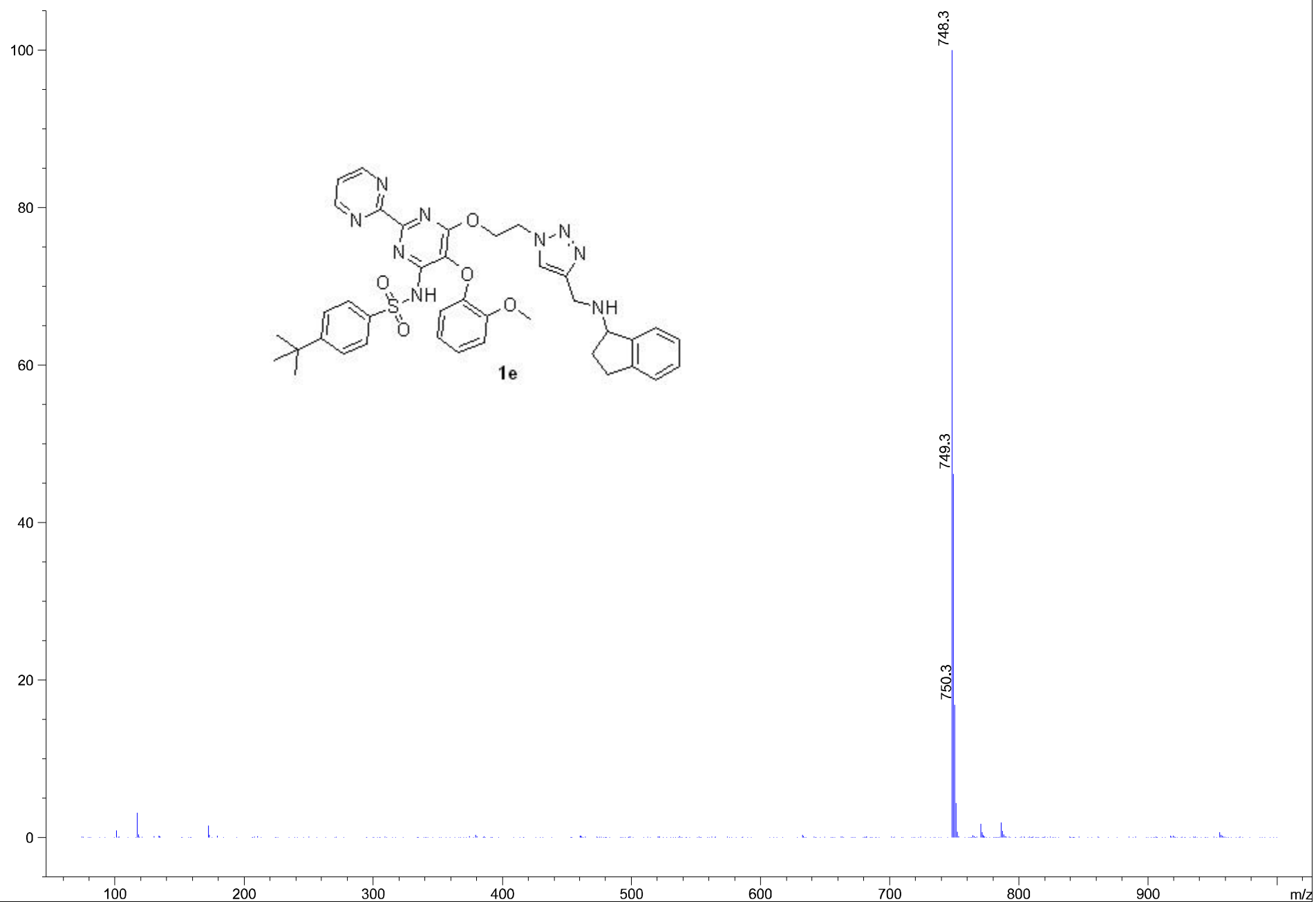


Figure 26: Mass Spectrum of 4-tert-butyl-N-(6-(2-(4-((2,3-dihydro-1H-inden-1-ylamino)methyl)-1H-1,2,3-triazol-1-yl)ethoxy)-5-(2-methoxyphenoxy)-2,2'-bipyrimidin-4-yl)benzenesulfonamide (**1e**)

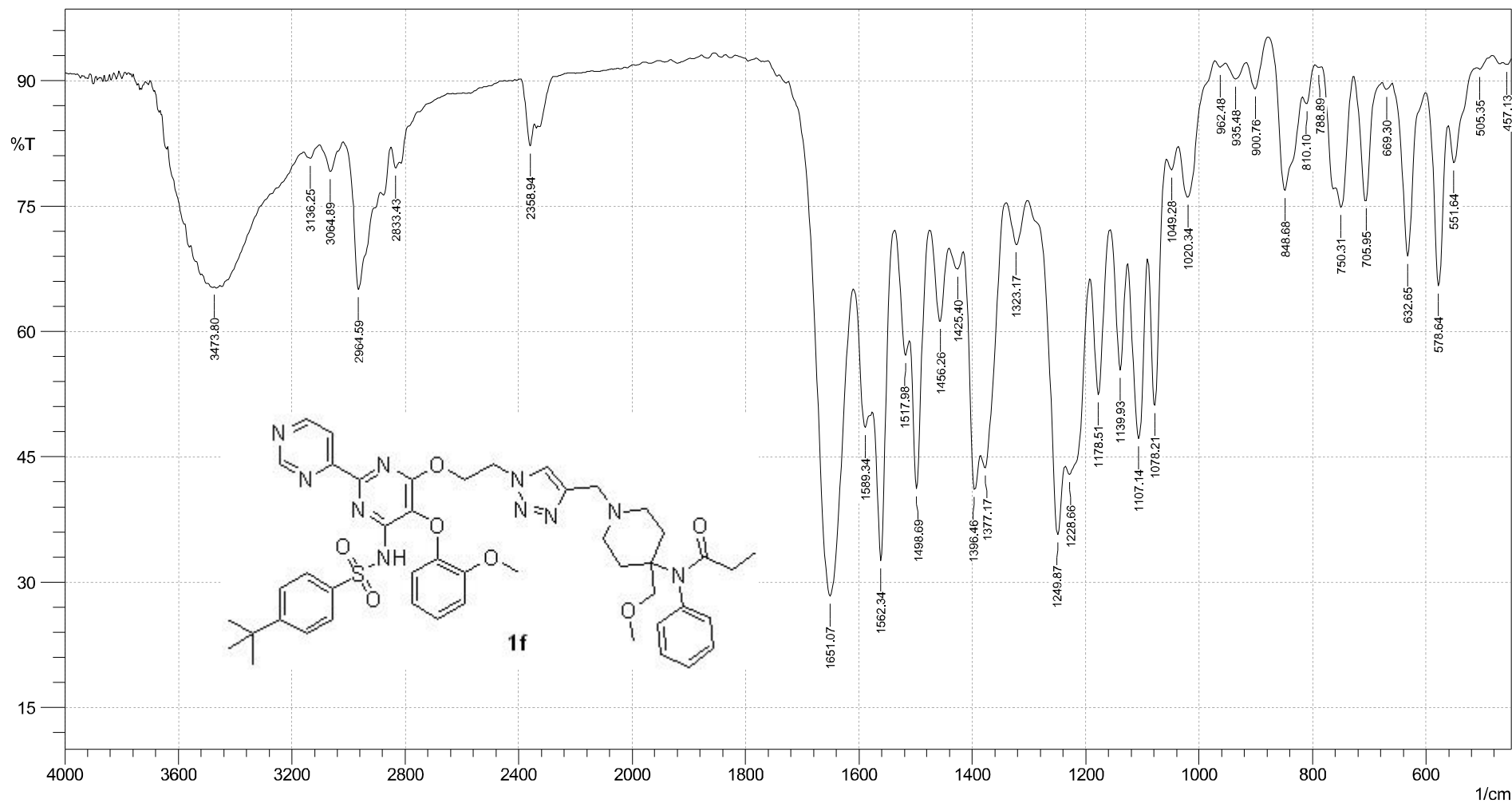


Figure 27: IR Spectrum of N-(1-(2-(1-((6-(4-tert-Butylphenyl)sulfonamido)-5-(2-methoxyphenoxy)-2,2'-bipyrimidin-4-yl)methyl)-1H-1,2,3-triazol-4-yloxy)ethyl)-4-(methoxymethyl)piperidin-4-yl)-N-phenyl-propionamide (**1f**)

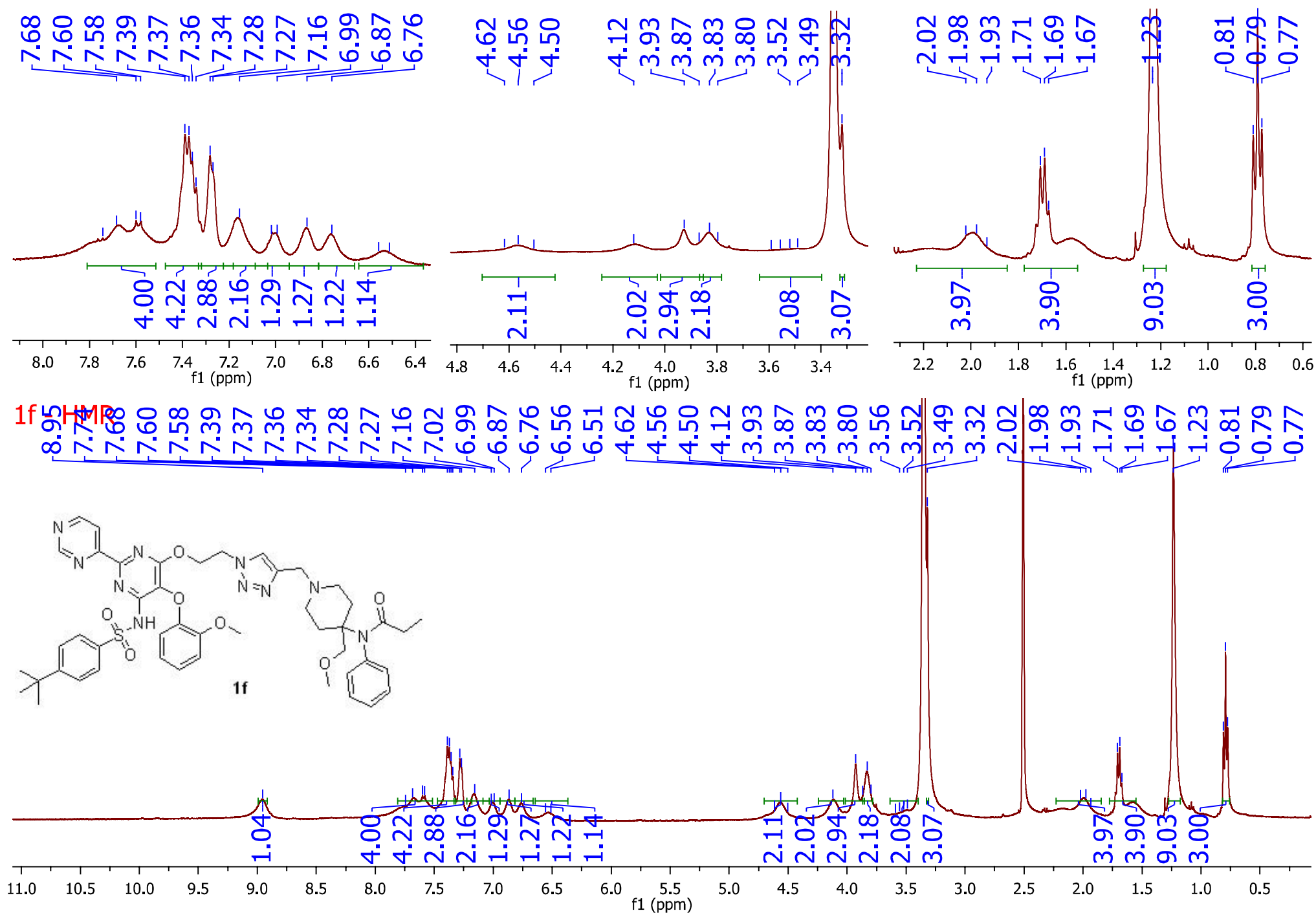


Figure 28: ¹H-NMR Spectrum of N-(1-(2-(1-((6-(4-tert-Butylphenylsulfonamido)-5-(2-methoxyphenoxy)-2,2'-bipyrimidin-4-yl)methyl)-1H-1,2,3-triazol-4-yloxy)ethyl)-4-(methoxymethyl)piperidin-4-yl)-N-phenyl-propionamide (**1f**)

1f

—168.34
—152.92
—150.32
—149.15
—146.09
—141.35
—140.51
—139.18
—136.29
—135.10
—134.01
—133.47
—131.52
—129.13
—124.47
—122.40
—120.86
—113.80

—89.08

—79.46

—76.57

—59.28

—34.80

—31.59

—31.53

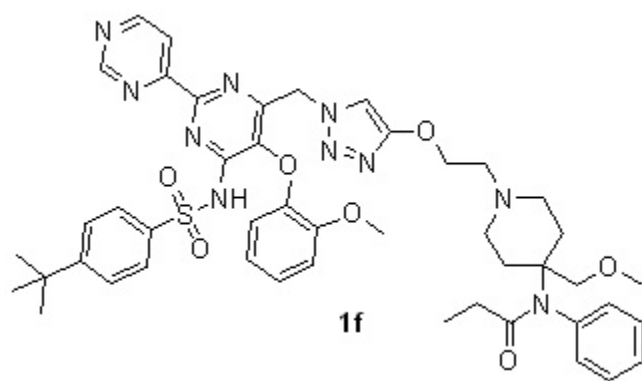
—30.47

—28.70

—28.29

—23.30

—9.97



1f

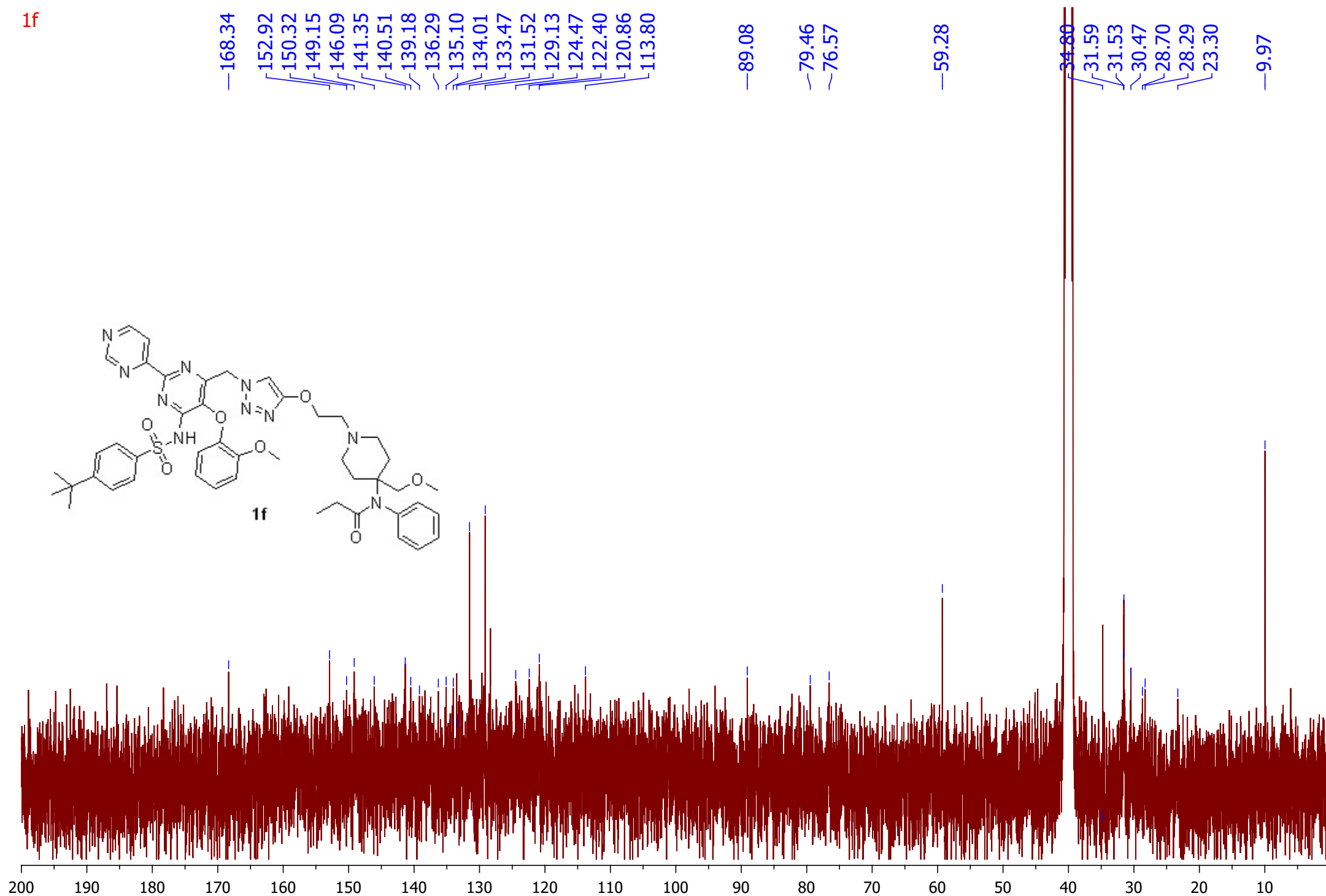


Figure 29: MS Spectrum of N-(1-(2-(1-((4-tert-Butylphenyl)sulfonamido)-5-(2-methoxyphenoxy)-2,2'-bipyrimidin-4-yl)methyl)-1H-1,2,3-triazol-4-yloxy)ethyl)-4-(methoxymethyl)piperidin-4-yl)-N-phenyl-propionamide (**1f**)

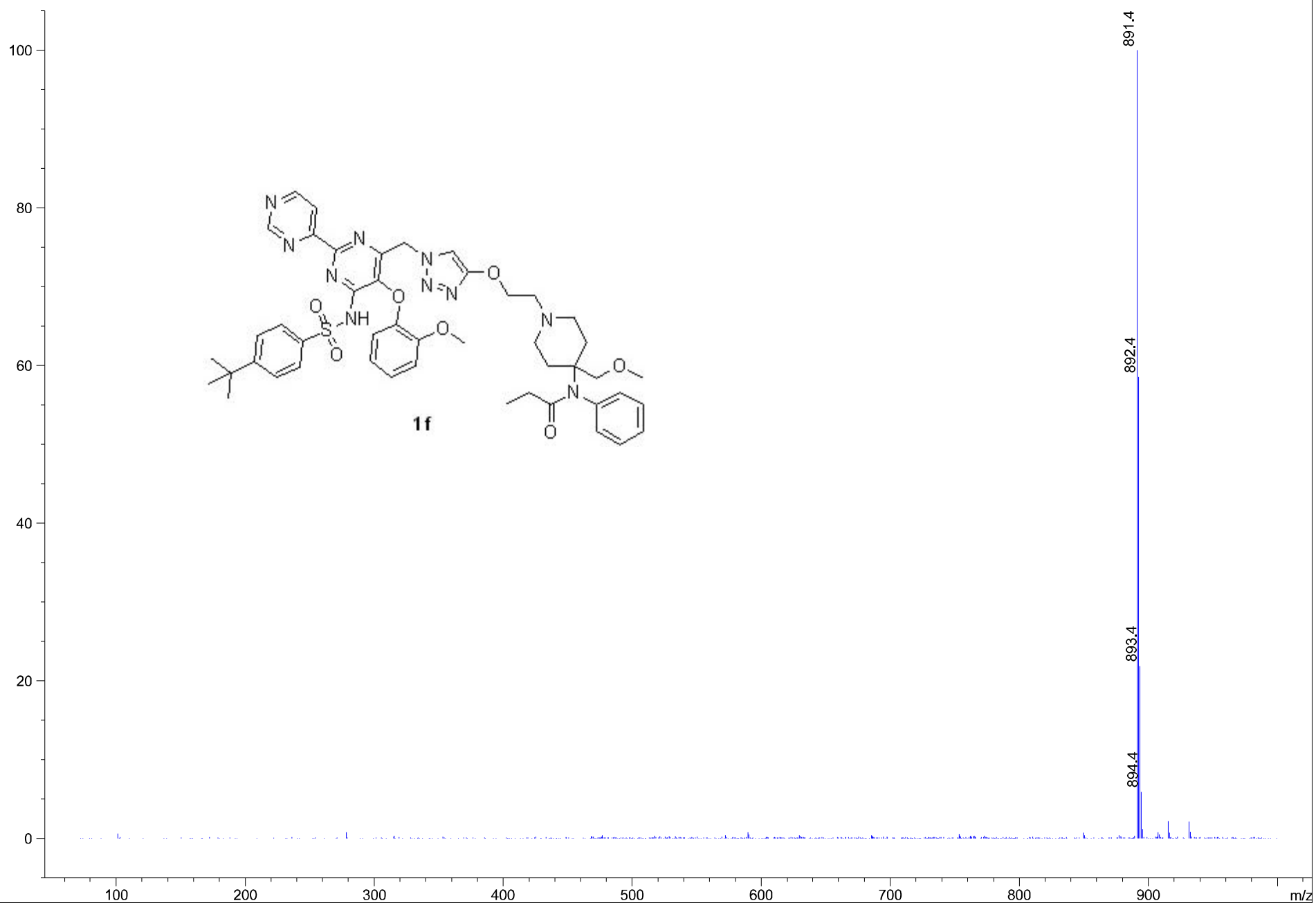


Figure 30: Mass Spectrum of N-(1-(2-(1-((6-(4-tert-Butylphenyl)sulfonamido)-5-(2-methoxyphenoxy)-2,2'-bipyrimidin-4-yl)methyl)-1H-1,2,3-triazol-4-yloxy)ethyl)-4-(methoxymethyl)piperidin-4-yl)-N-phenyl-propionamide (**1f**)

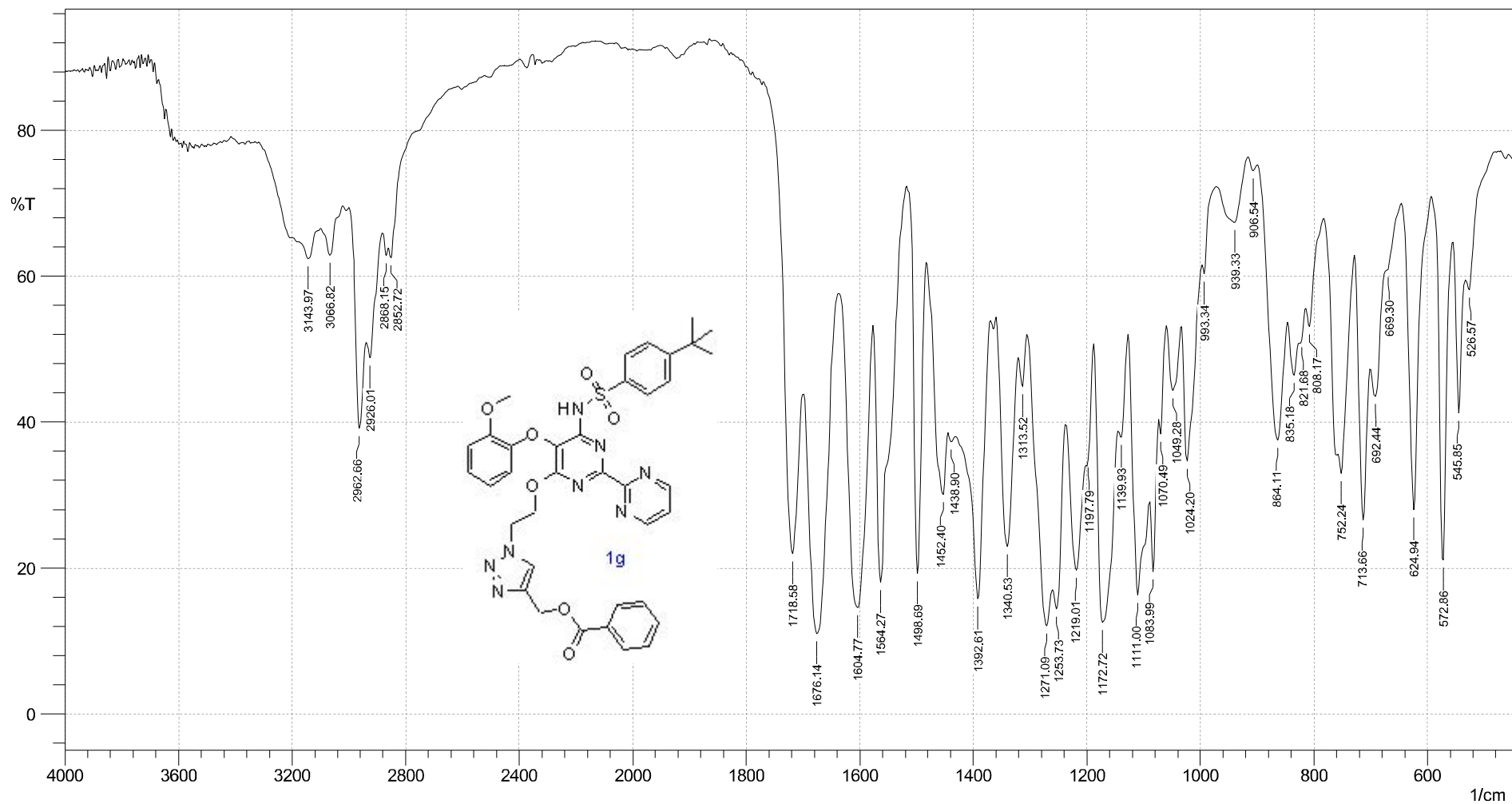


Figure 31: IR Spectrum of (1-(2-(6-(4-tert-Butylphenyl)sulfonamido)-5-(2-methoxyphenoxy)-2,2'-bipyrimidin-4-yl-oxy)ethyl)-1H-1,2,3-triazol-4-yl)methyl benzoate (**1g**)

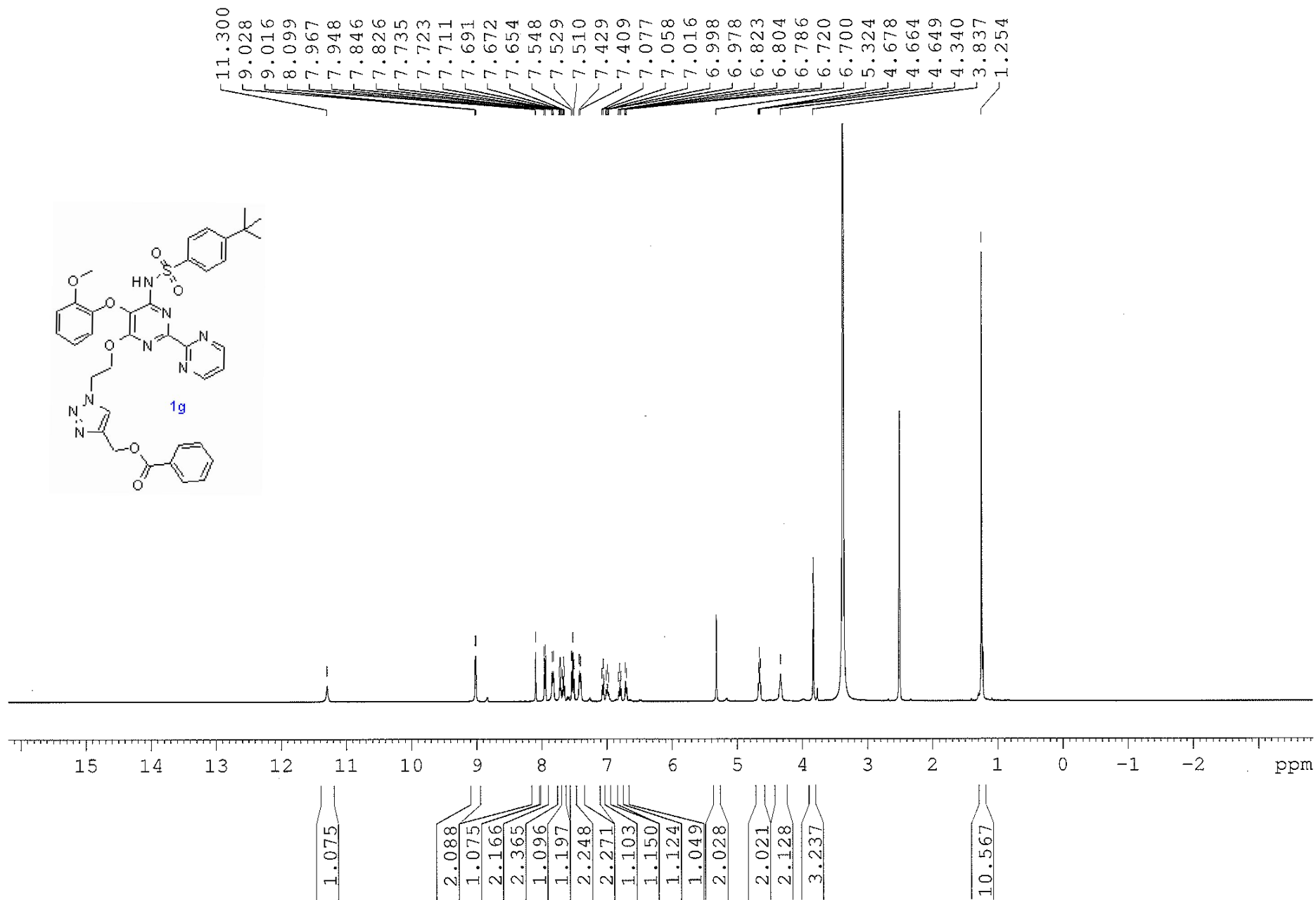


Figure 32: ¹H-NMR Spectrum of (1-(2-(6-(4-tert-Butylphenyl)sulfonamido)-5-(2-methoxyphenoxy)-2,2'-bipyrimidin-4-yl-oxy)ethyl)-1H-1,2,3-triazol-4-yl)methyl benzoate (**1g**)

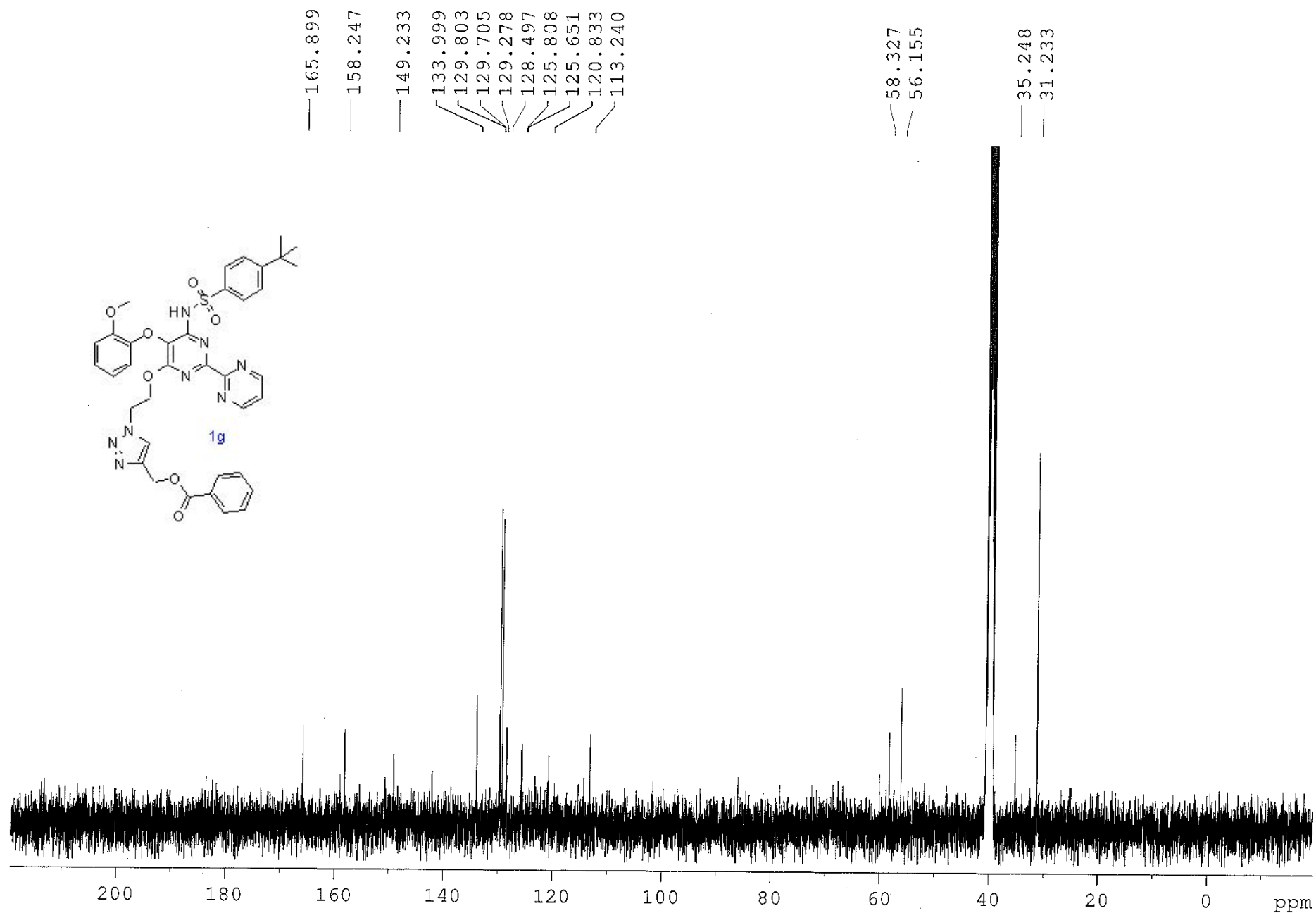


Figure 33: ¹³C-NMR Spectrum of (1-(2-(6-(4-tert-Butylphenylsulfonamido)-5-(2-methoxyphenoxy)-2,2'-bipyrimidin-4-yl-oxy)ethyl)-1H-1,2,3-triazol-4-yl)methyl benzoate (**1g**)

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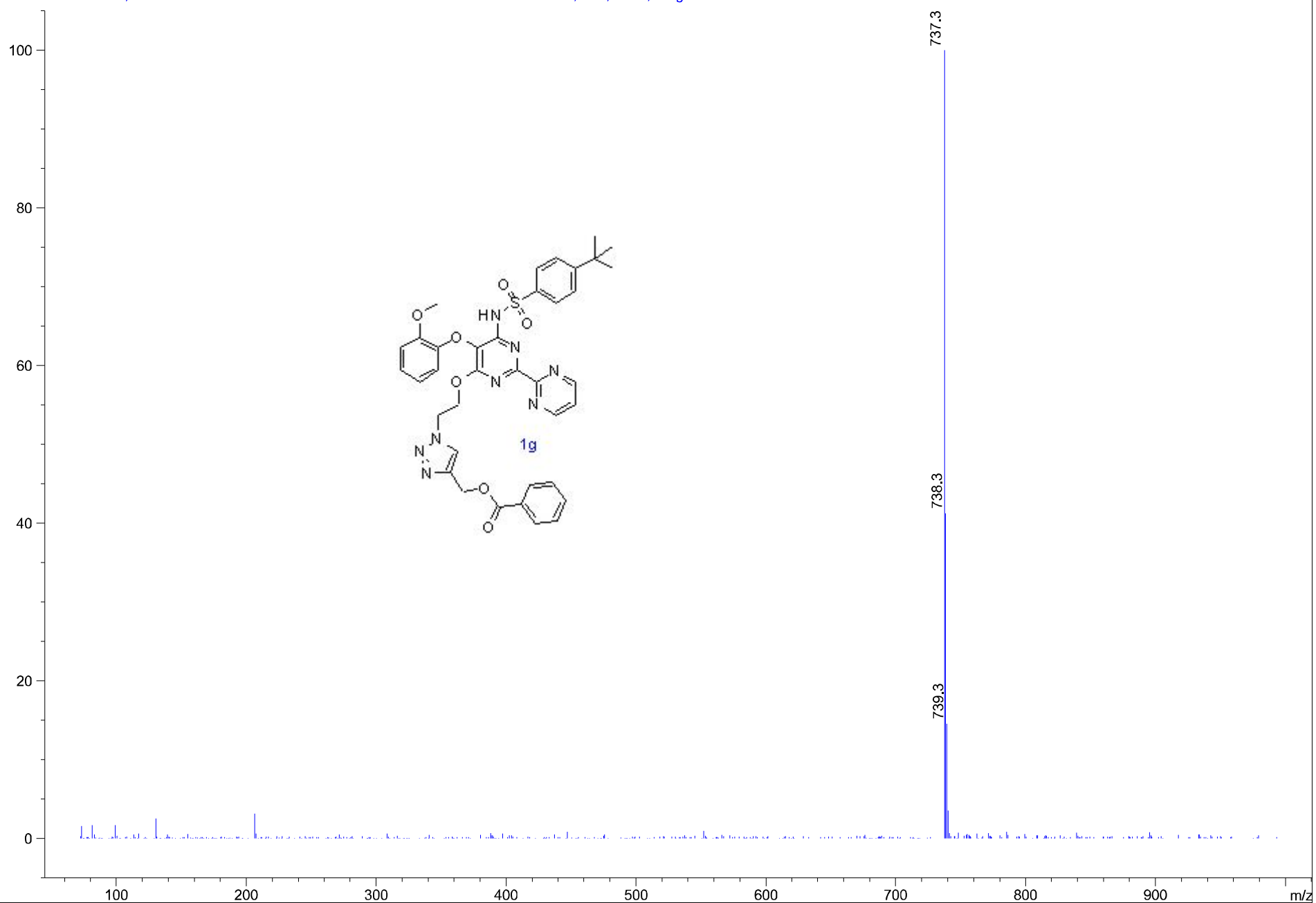


Figure 34: Mass Spectrum of (1-(2-(6-(4-tert-Butylphenylsulfonamido)-5-(2-methoxyphenoxy)-2,2'-bipyrimidin-4-yl-oxy)ethyl)-1H-1,2,3-triazol-4-yl)methyl benzoate (**1g**)

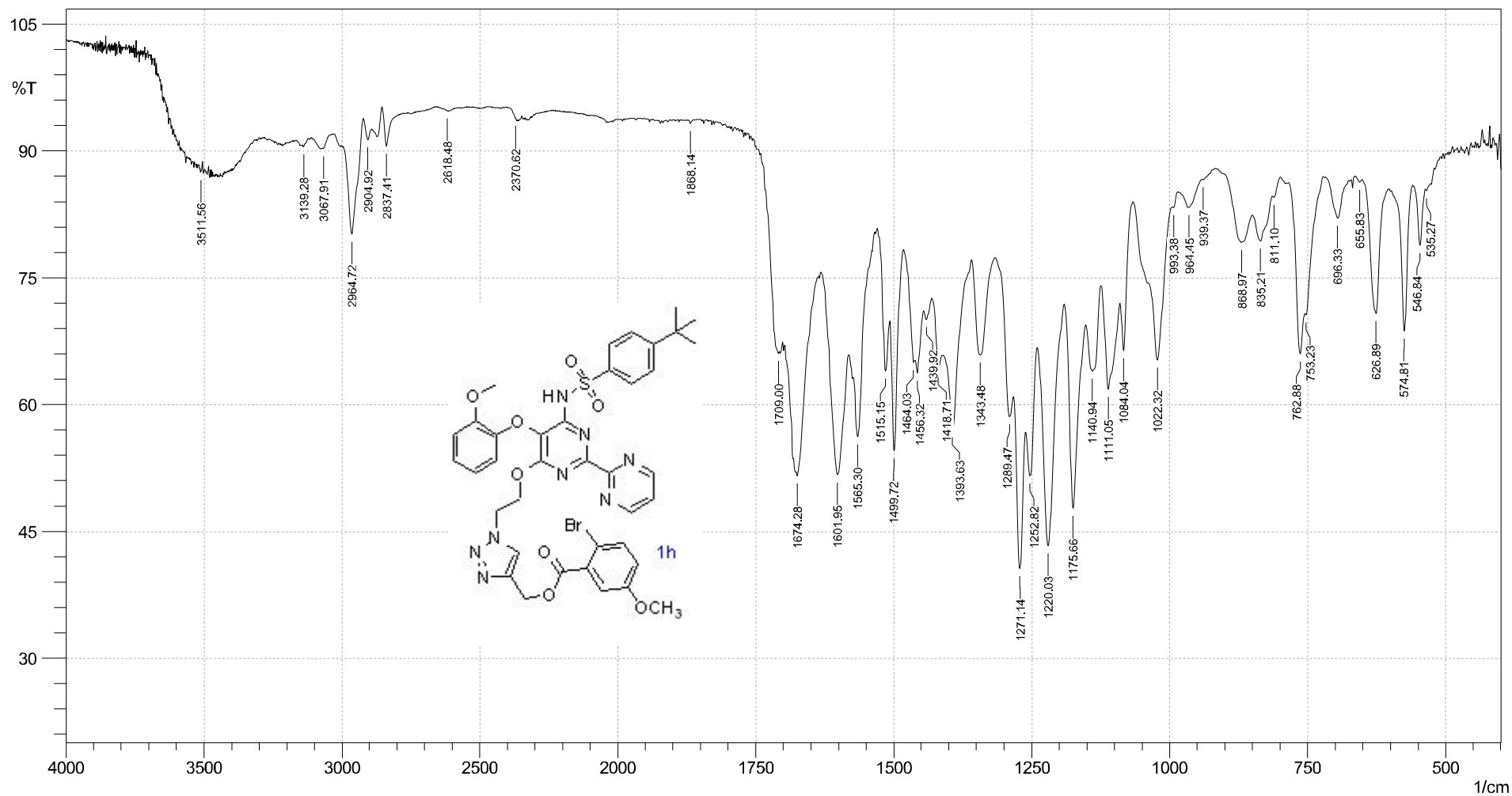


Figure 35: IR Spectrum of (1-(2-(6-(4-tert-Butylphenyl)sulfonamido)-5-(2-methoxyphenoxy)-2,2'-bipyrimidin-4-yl-oxy)ethyl)-1H-1,2,3-triazol-4-yl)methyl 2-bromo-5-methoxybenzoate (**1h**)

7e

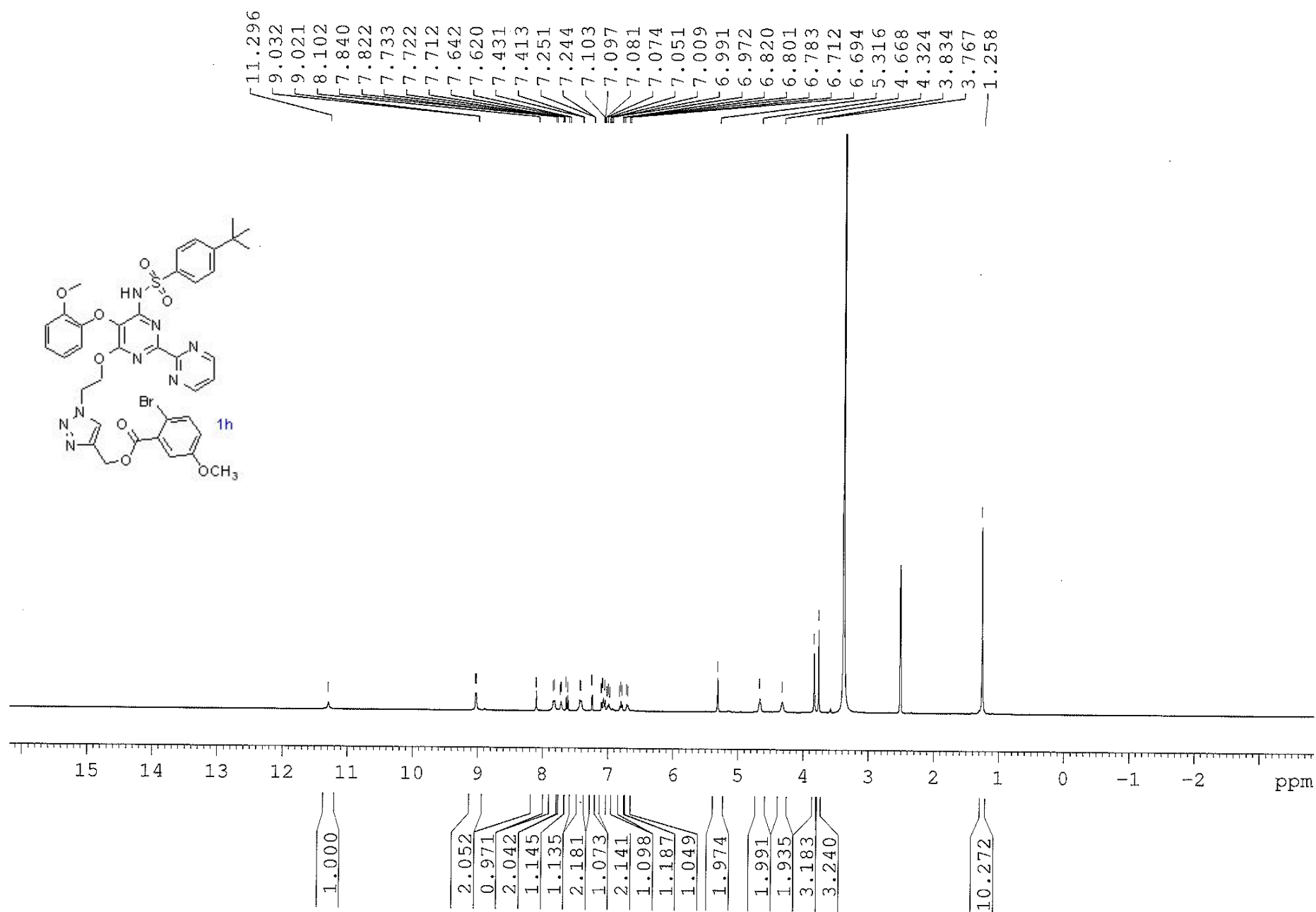


Figure 36: ¹H-NMR Spectrum of (1-(2-(6-(4-tert-Butylphenylsulfonamido)-5-(2-methoxyphenoxy)-2,2'-bipyrimidin-4-yl-oxy)ethyl)-1H-1,2,3-triazol-4-yl)methyl 2-bromo-5-methoxybenzoate (**1h**)

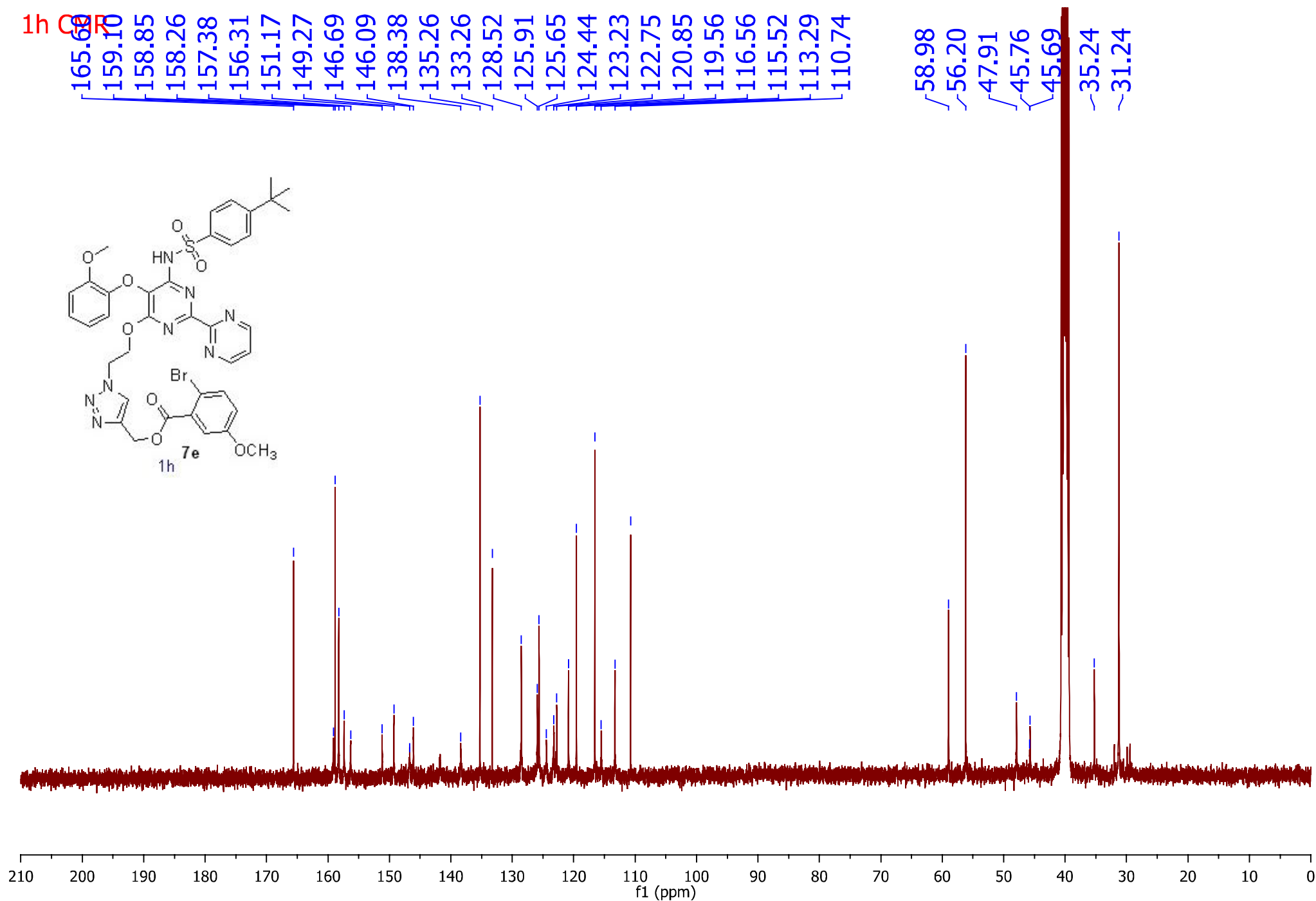


Figure 37: ^{13}C -NMR Spectrum of (1-(2-(6-(4-tert-Butylphenyl)sulfonamido)-5-(2-methoxyphenoxy)-2,2'-bipyrimidin-4-yl-oxy)ethyl)-1H-1,2,3-triazol-4-yl)methyl 2-bromo-5-methoxybenzoate (**1h**)

*MSD1 SPC, time=0.356 of D:\DATA\2014\JUNE\260614\2606201406.D ES-API, Pos, Scan, Frag: 70

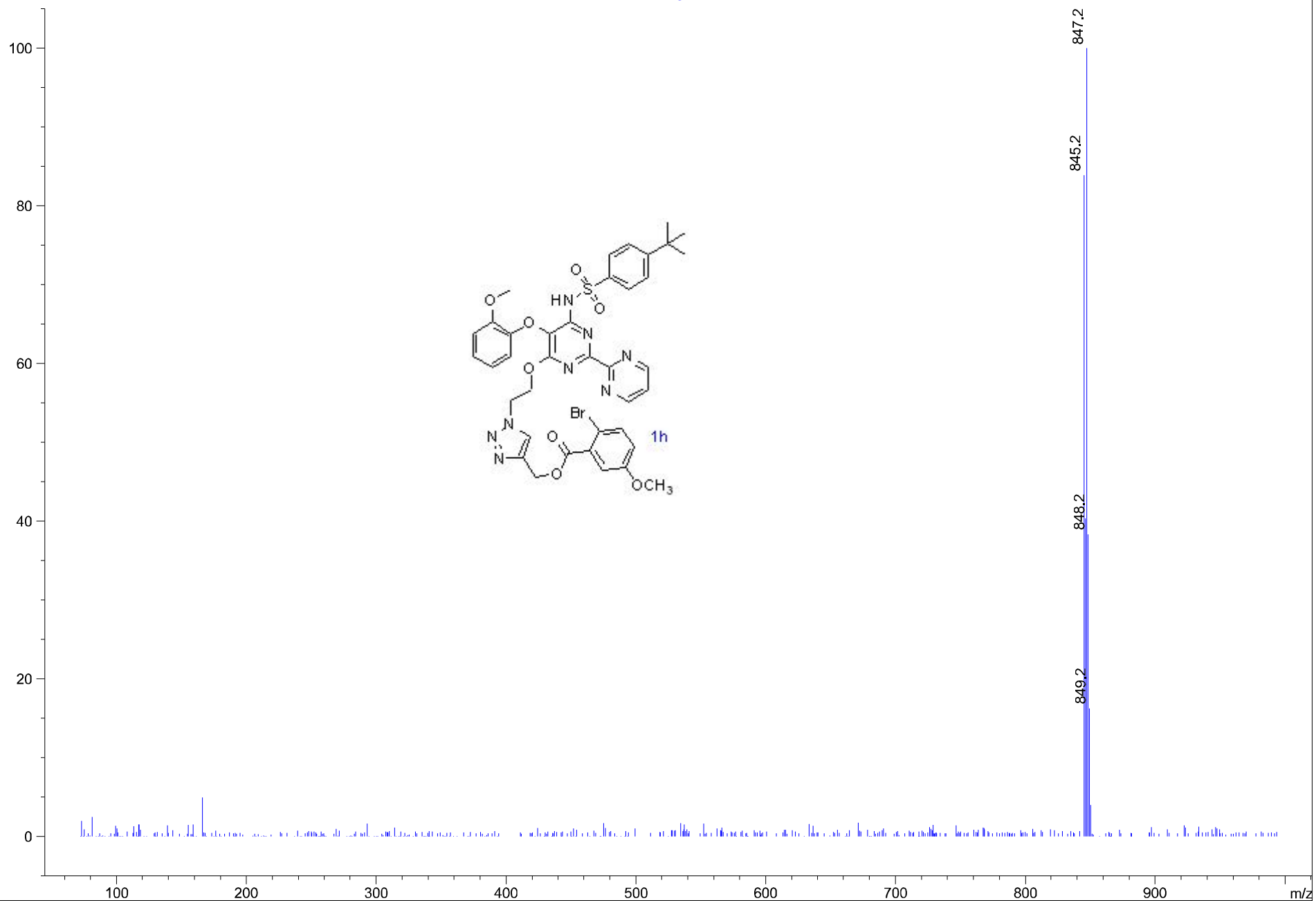


Figure 38: Mass Spectrum of (1-(2-(6-(4-tert-Butylphenylsulfonamido)-5-(2-methoxyphenoxy)-2,2'-bipyrimidin-4-yl-oxy)ethyl)-1H-1,2,3-triazol-4-yl)methyl 2-bromo-5-methoxybenzoate (**1h**)

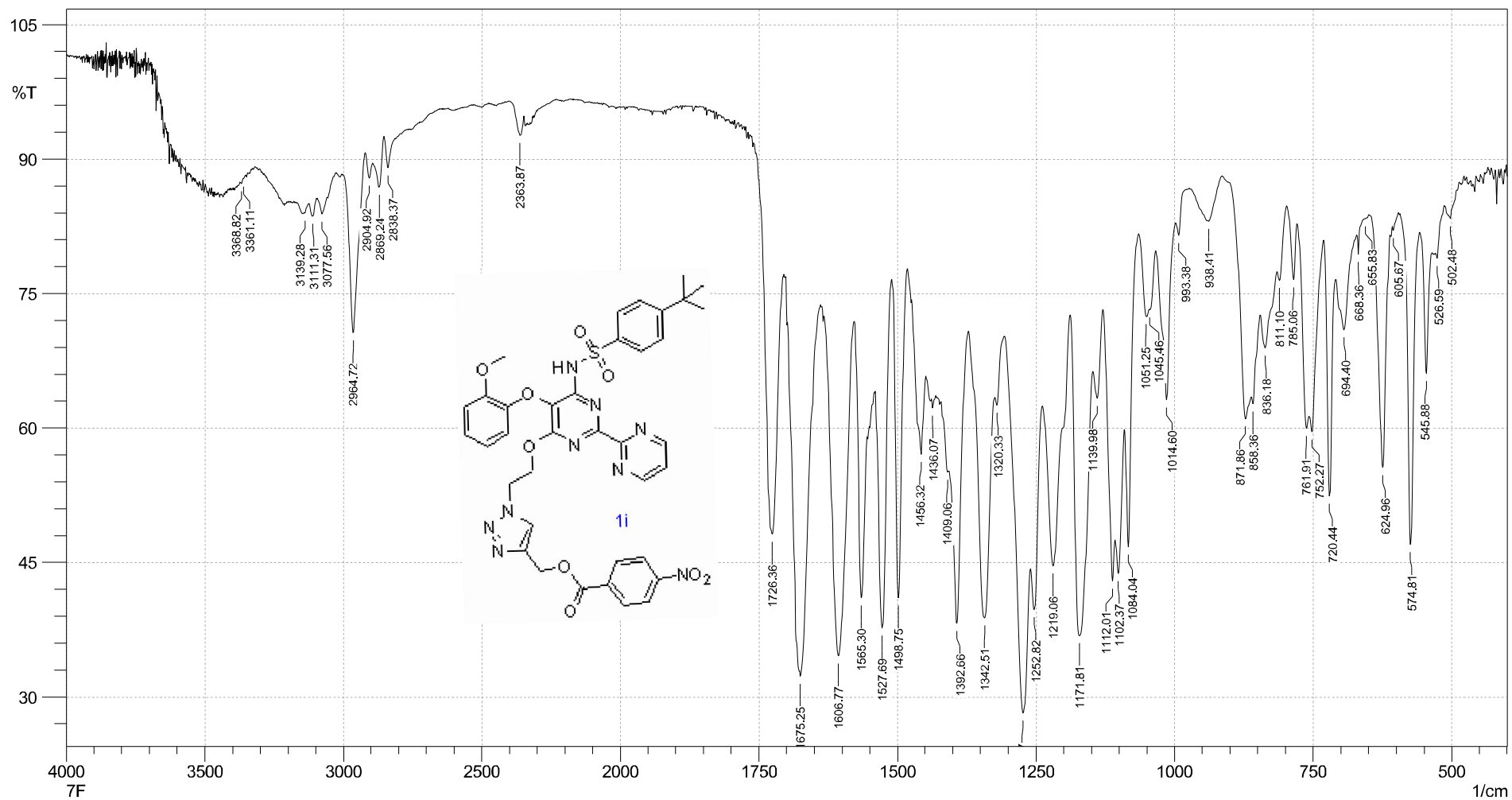


Figure 39: IR Spectrum of (1-(2-(6-(4-tert-Butylphenyl)sulfonamido)-5-(2-methoxyphenoxy)-2,2'-bipyrimidin-4-yl-oxyethyl)-1H-1,2,3-triazol-4-yl)methyl 4-nitrobenzoate (**1i**)

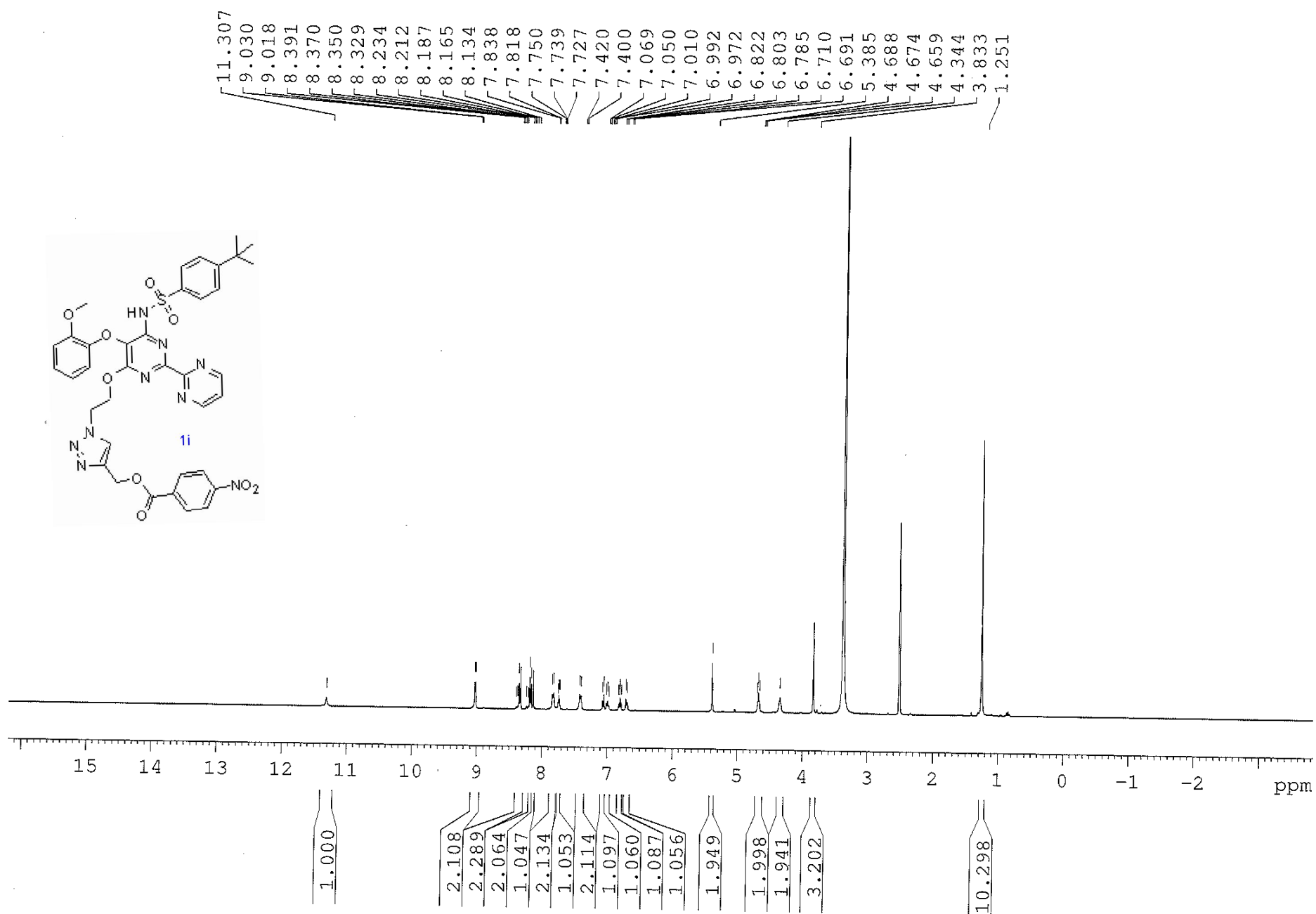


Figure 40: ¹H-NMR Spectrum of (1-(2-(6-(4-tert-Butylphenyl)sulfonamido)-5-(2-methoxyphenoxy)-2,2'-bipyrimidin-4-yl-oxyethyl)-1H-1,2,3-triazol-4-yl)methyl 4-nitrobenzoate (**1i**)

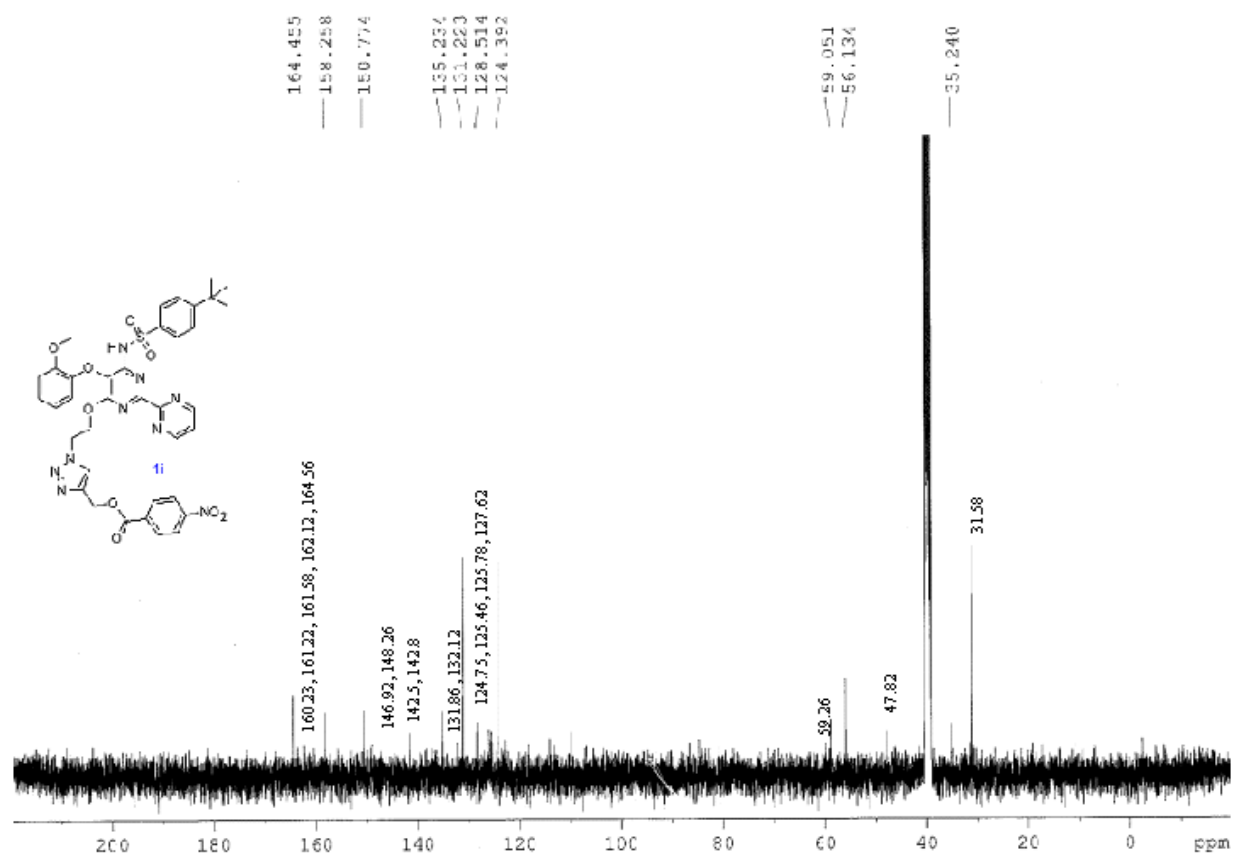


Figure 41: ¹³C-NMR Spectrum of (1-(2-(6-(4-tert-Butylphenyl)sulfonamido)-5-(2-methoxyphenoxy)-2,2'-bipyrimidin-4-yl-oxethyl)-1H-1,2,3-triazol-4-yl)methyl 4-nitrobenzoate (**1i**)

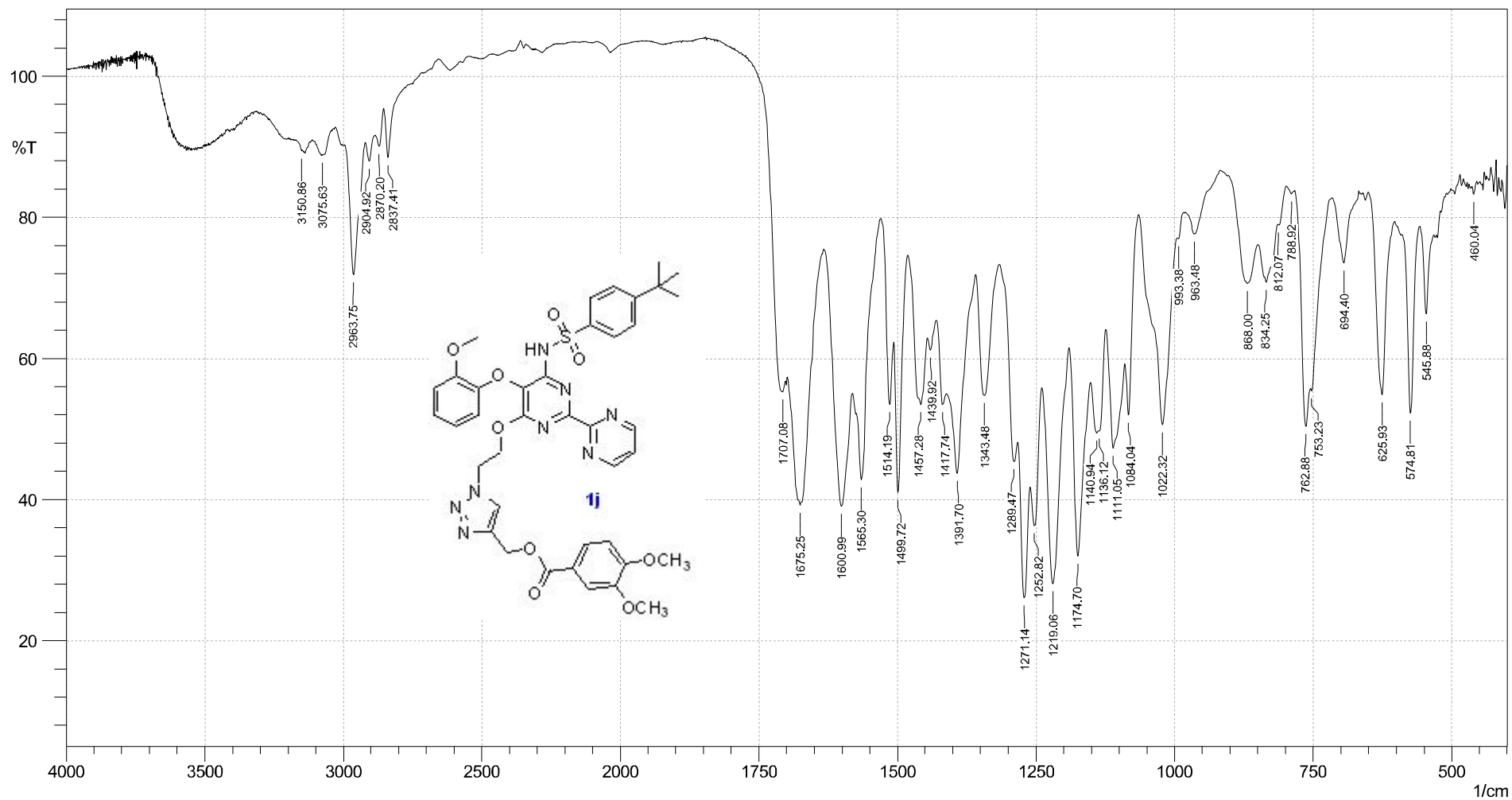


Figure 42: IR Spectrum of (1-(2-(6-(4-tert-Butylphenylsulfonamido)-5-(2-methoxyphenoxy)-2,2'-bipyrimidin-4-yl-oxyethyl)-1H-1,2,3-triazol-4-yl)methyl 3,4-dimethoxybenzoate (**1j**)

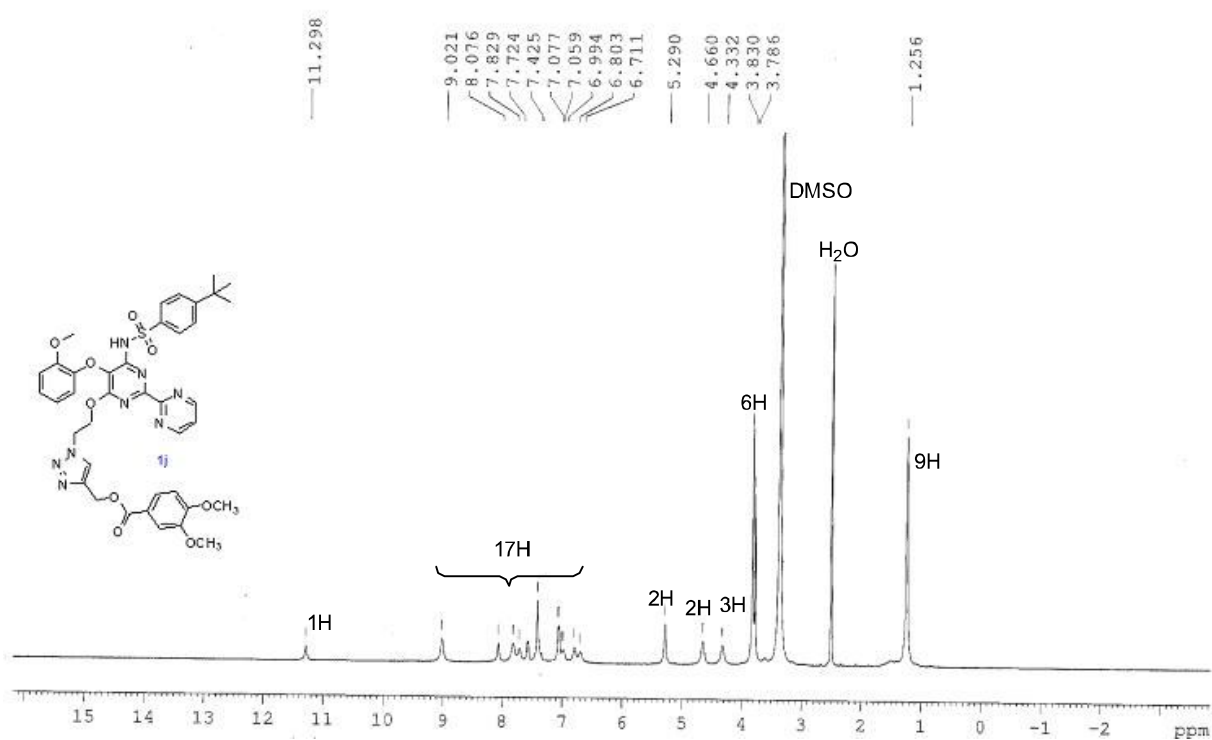


Figure 43: ¹H-NMR Spectrum of (1-(2-(6-(4-tert-Butylphenyl)sulfonamido)-5-(2-methoxyphenoxy)-2,2'-bipyrimidin-4-yl-oxyethyl)-1H-1,2,3-triazol-4-yl)methyl 3,4-dimethoxybenzoate (**1j**)

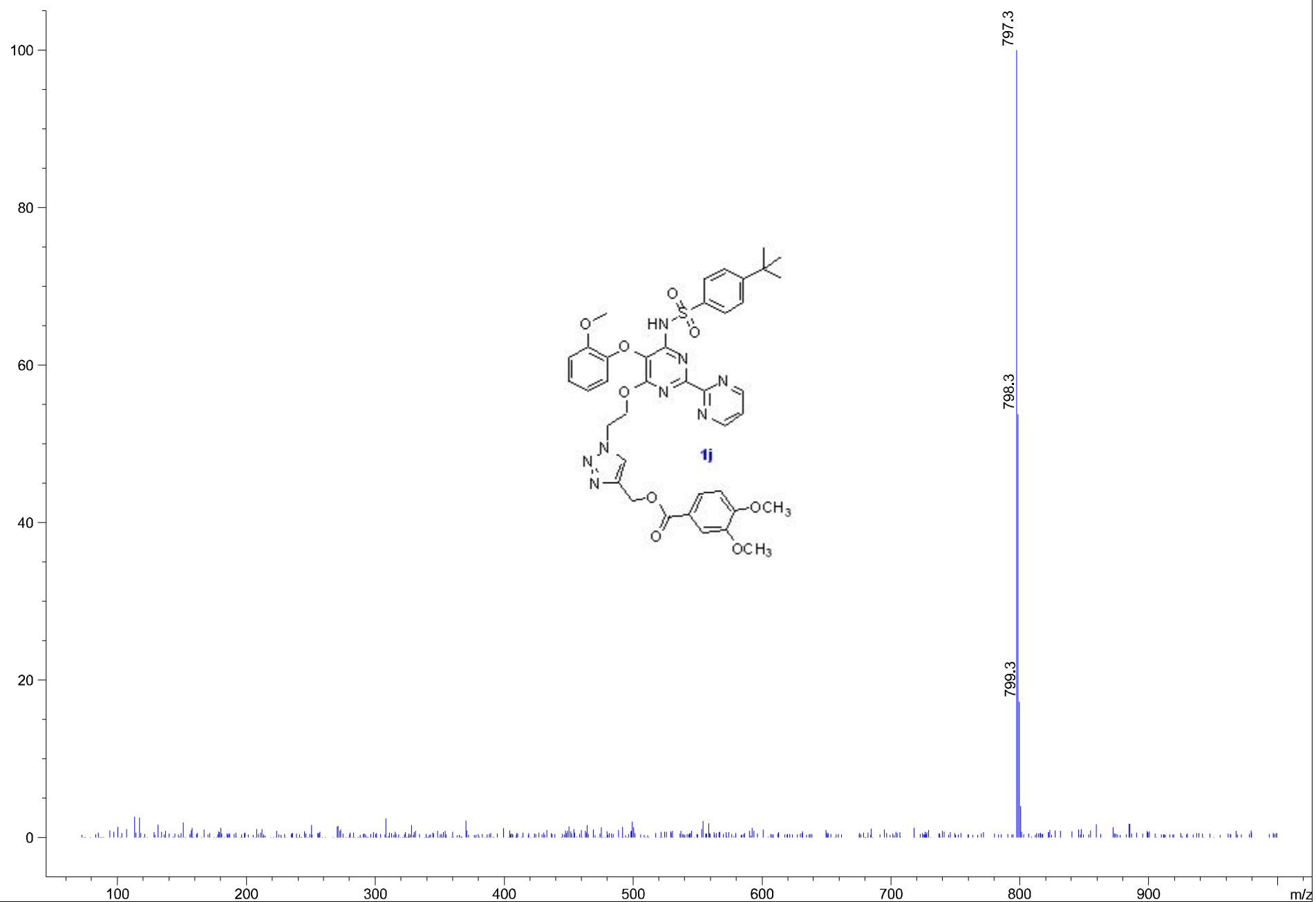


Figure 44: Mass Spectrum of (1-(2-(6-(4-tert-Butylphenylsulfonamido)-5-(2-methoxyphenoxy)-2,2'-bipyrimidin-4-yl-oxyethyl)-1H-1,2,3-triazol-4-yl)methyl 3,4-dimethoxybenzoate (**1j**)

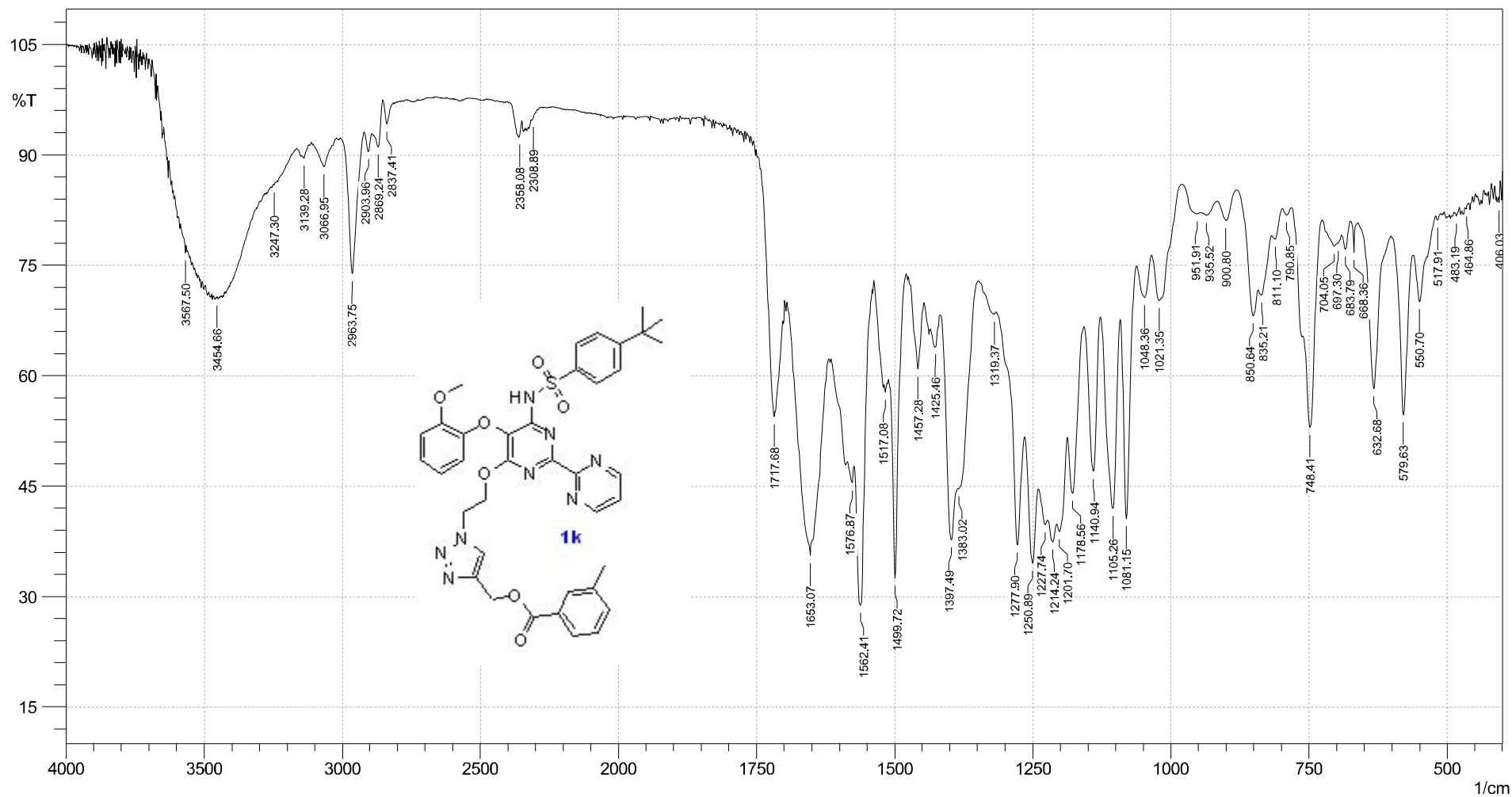


Figure 45: IR Spectrum of (1-(2-(6-(4-tert-Butylphenyl)sulfonamido)-5-(2-methoxyphenoxy)-2,2'-bipyrimidin-4-yl-oxy)ethyl)-1H-1,2,3-triazol-4-yl)methyl 3-methylbenzoate (**1k**)

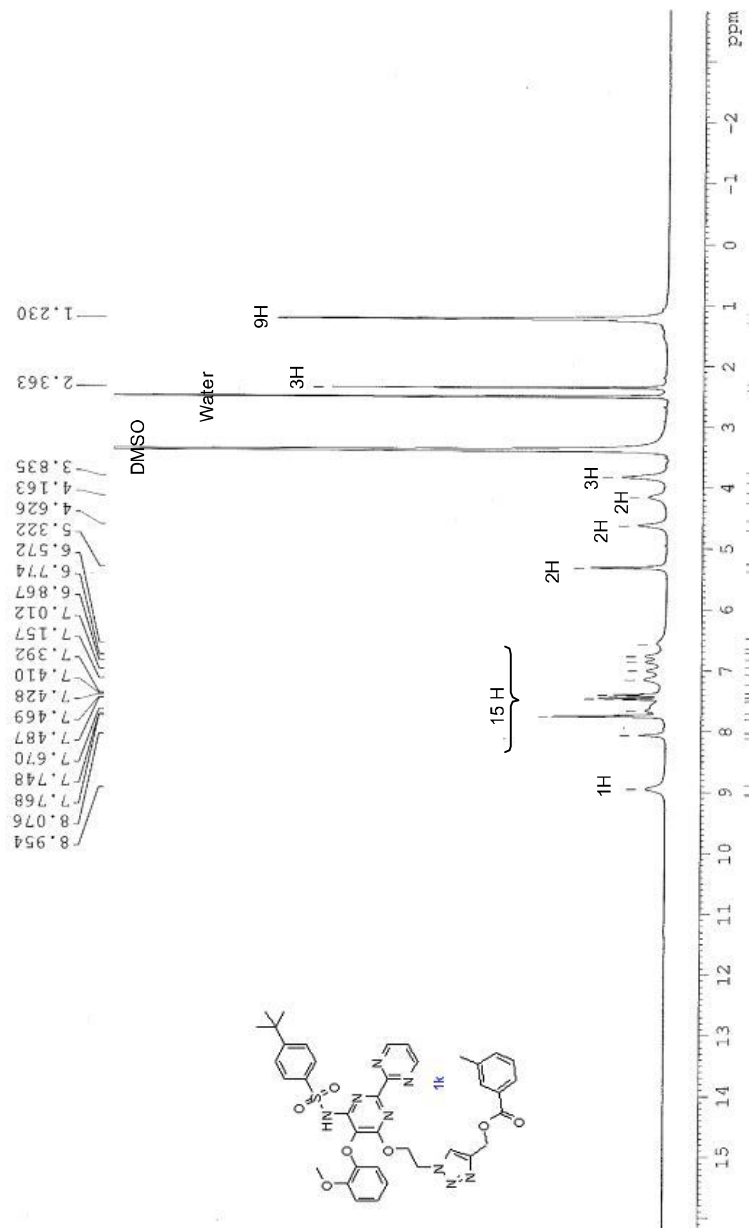


Figure 46: ^1H -NMR Spectrum of (1-(2-(6-(4-tert-Butylphenylsulfonamido)-5-(2-methoxyphenoxy)-2',2'-bipyrimidin-4-yl-oxy)ethyl)-1H-1,2,3-triazol-4-yl)methyl 3-methylbenzoate (**1k**)

*MSD1 SPC, time=0.336 of D:\DATA\2014\JUNE\260614\2606201409.D ES-API, Pos, Scan, Frag: 70

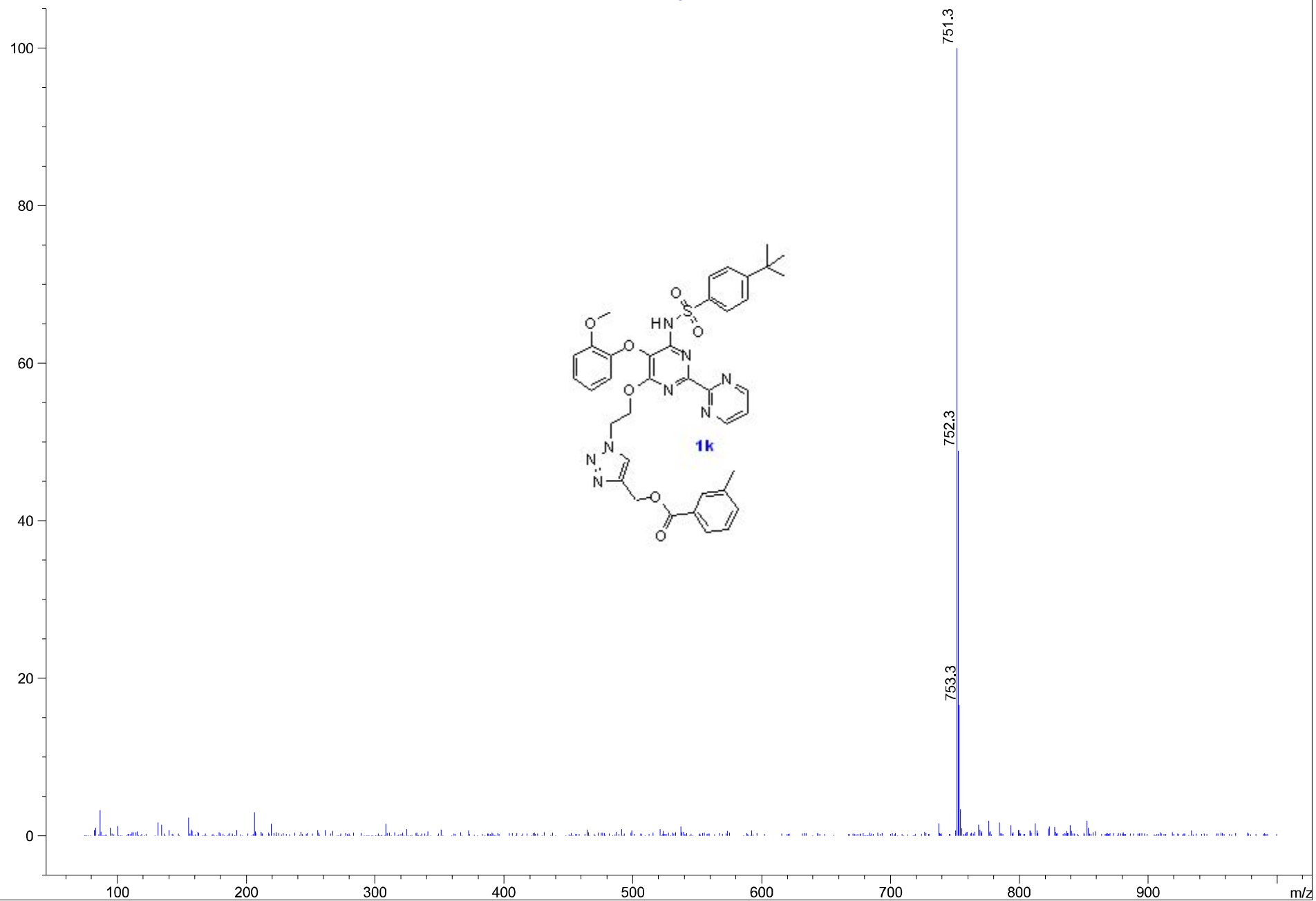


Figure 47: Mass Spectrum of (1-(2-(6-(4-tert-Butylphenyl)sulfonamido)-5-(2-methoxyphenoxy)-2,2'-bipyrimidin-4-yl-oxy)ethyl)-1H-1,2,3-triazol-4-yl)methyl 3-methylbenzoate (**1k**)

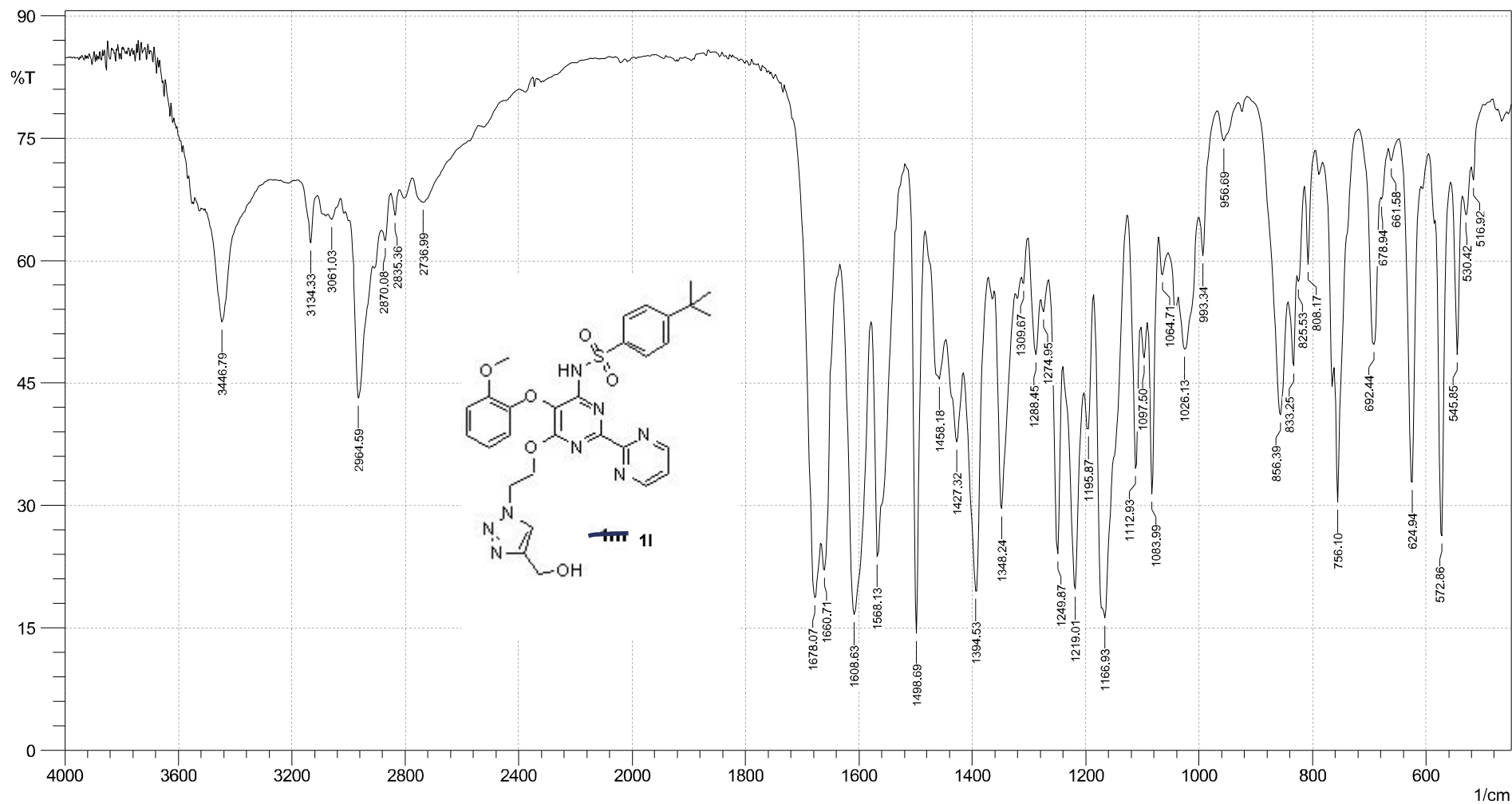


Figure 48: IR Spectrum of 4-tert-Butyl-N-(6-(2-(4-(hydroxymethyl)-1H-1,2,3-triazol-1-yl)ethoxy)-5-(2-methoxyphenoxy)-2,2'-bipyrimidin-4-yl)benzenesulfonamide (**11**)

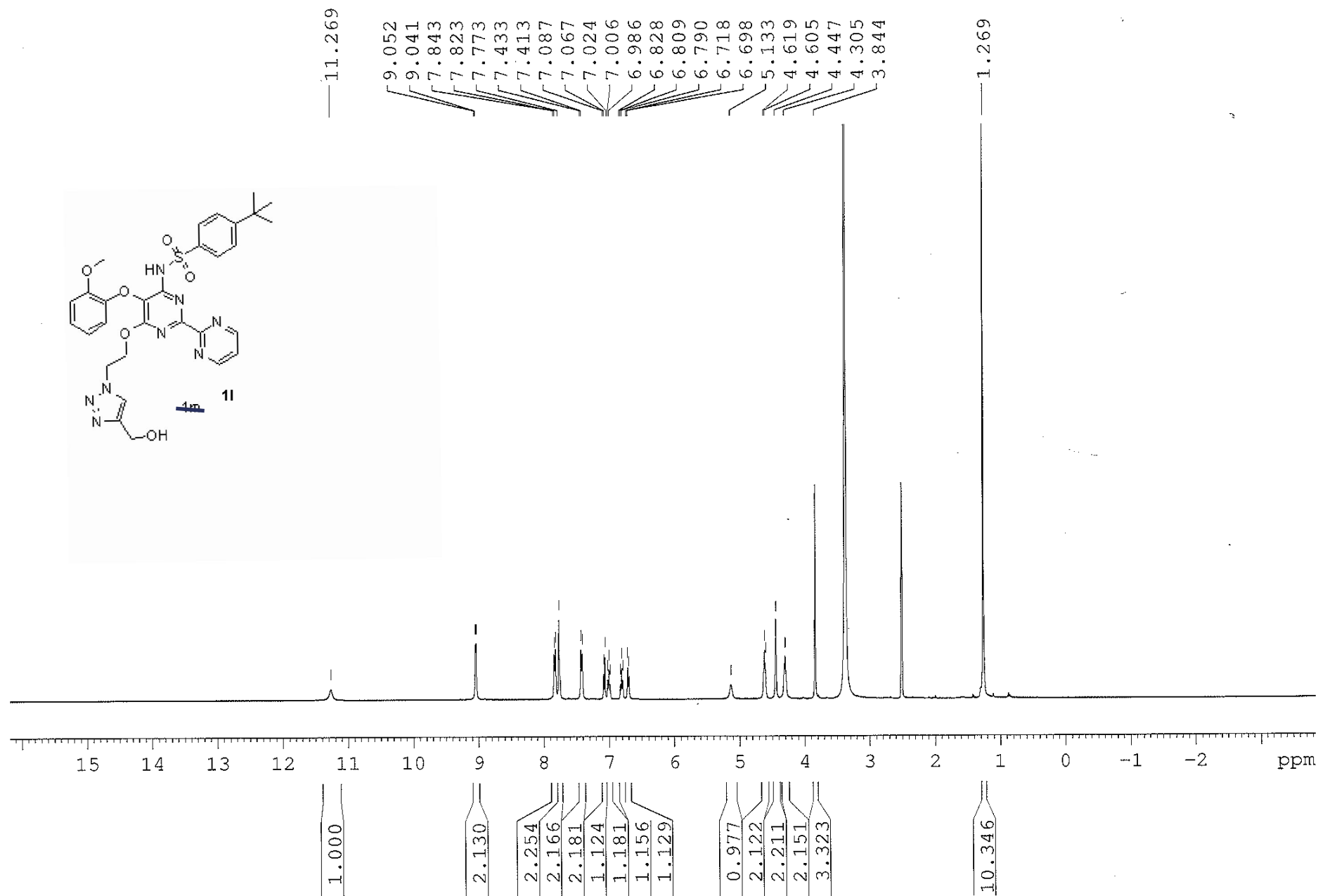


Figure 49: ¹H-NMR Spectrum of 4-tert-Butyl-N-(6-(2-(4-(hydroxymethyl)-1H-1,2,3-triazol-1-yl)ethoxy)-5-(2-methoxyphenoxy)-2,2'-bipyrimidin-4-yl)benzenesulfonamide (**11**)

1m CMR

161.20
157.66
150.75
148.41
147.00
143.91
143.13
136.43
134.68
129.04
128.68
128.54
126.56
123.45
118.88
115.24
113.65
111.40

71.11
69.75

-55.46
-47.77

-28.69
-22.41

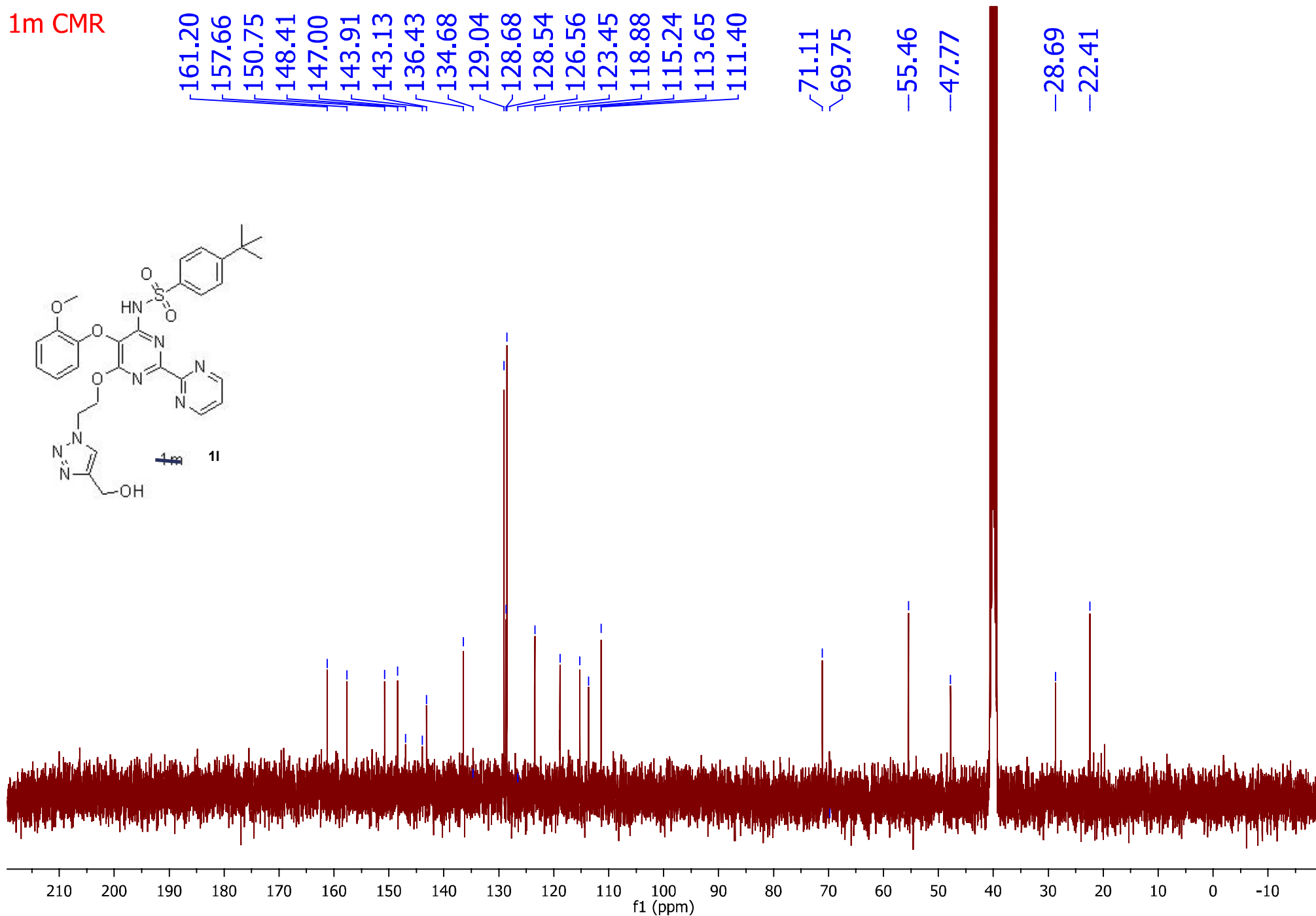
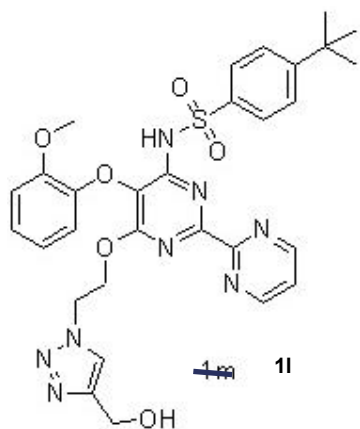


Figure 50: ^{13}C -NMR Spectrum of 4-tert-Butyl-N-(6-(2-(4-(hydroxymethyl)-1H-1,2,3-triazol-1-yl)ethoxy)-5-(2-methoxyphenoxy)-2,2'-bipyrimidin-4-yl)benzenesulfonamide (**1I**)

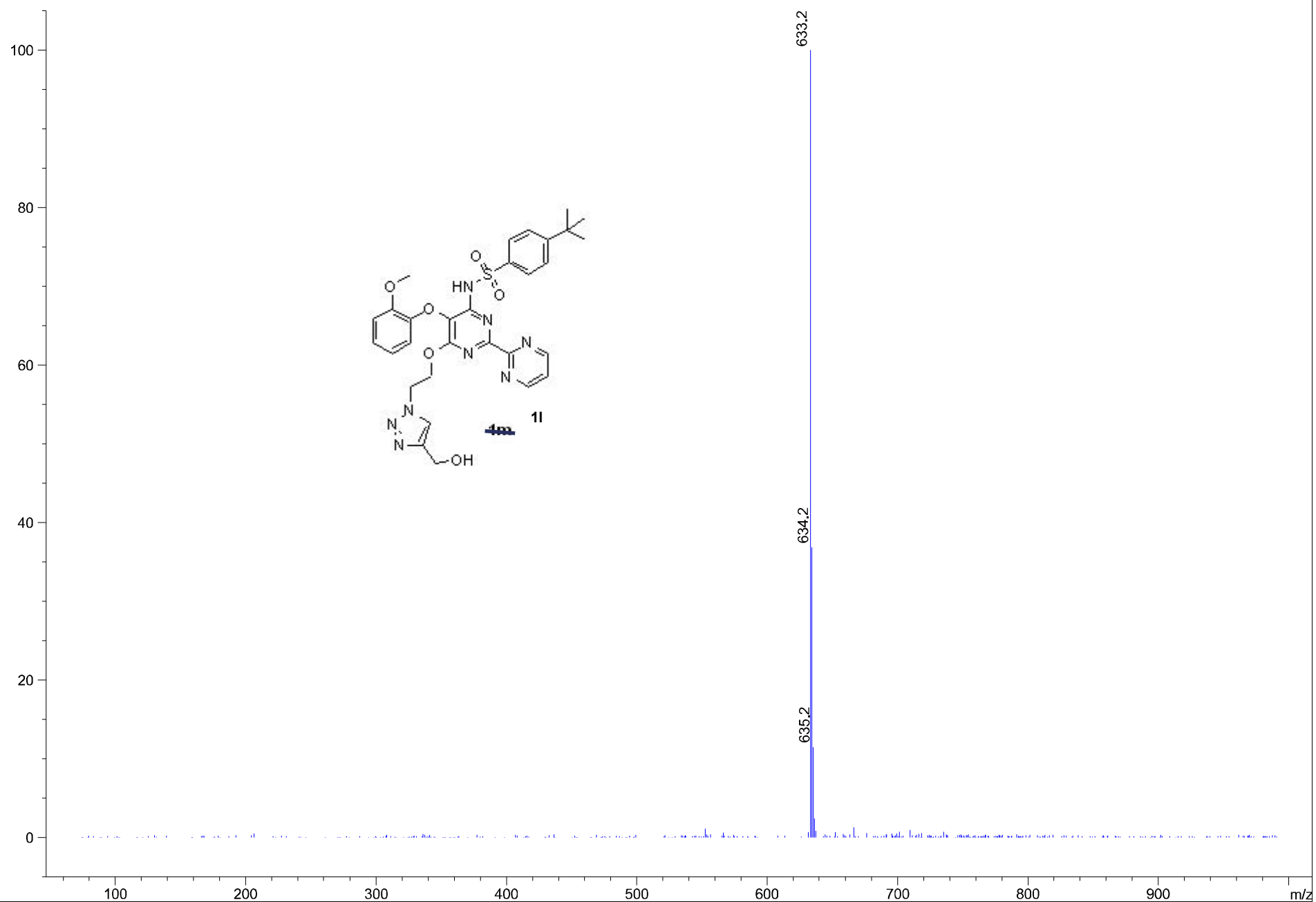


Figure 51: Mass Spectrum of 4-tert-Butyl-N-(6-(2-(4-(hydroxymethyl)-1H-1,2,3-triazol-1-yl)ethoxy)-5-(2-methoxy- phenoxy)-2,2'-bipyrimidin-4-yl)benzenesulfonamide (**1I**)

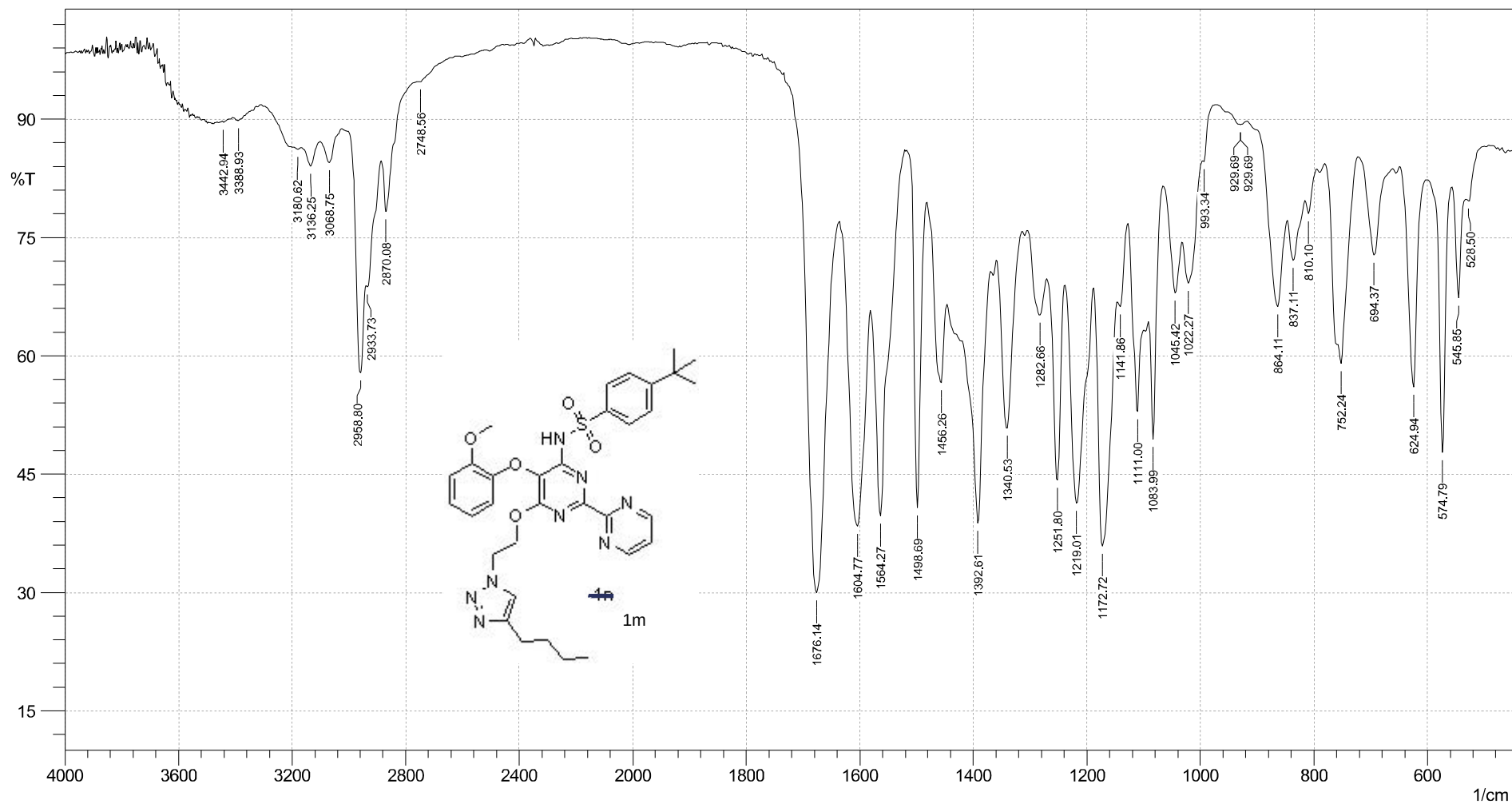


Figure 52: IR Spectrum of 4-tert-Butyl-N-(6-(2-(4-butyl-1H-1,2,3-triazol-1-yl)ethoxy)-5-(2-methoxyphenoxy)-2,2'-bipyrimidin-4-yl)benzenesulfonamide (**1m**)

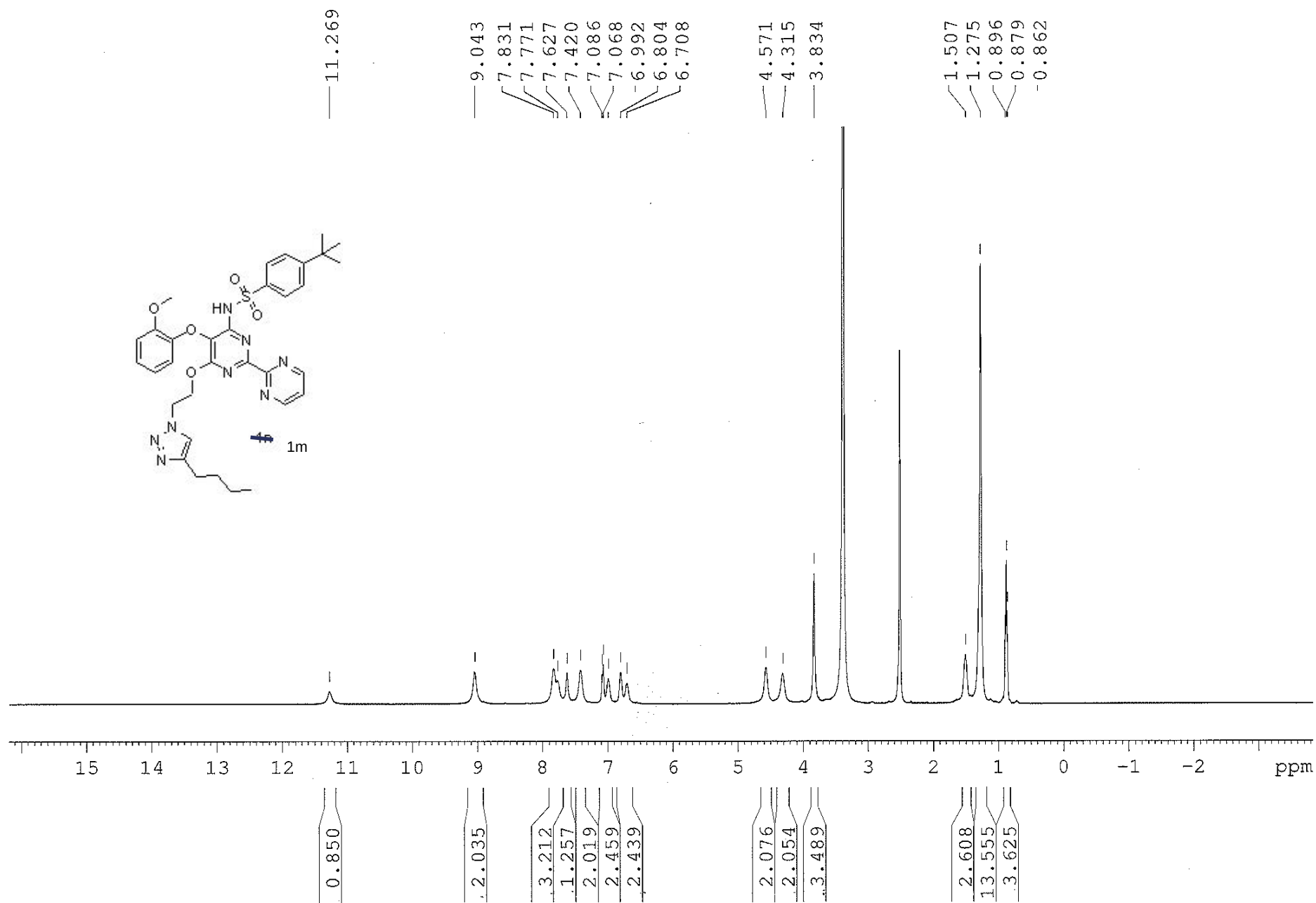


Figure 53: ¹H-NMR Spectrum of 4-tert-Butyl-N-(6-(2-(4-butyl-1H-1,2,3-triazol-1-yl)ethoxy)-5-(2-methoxyphenoxy)-2,2'-bipyrimidin-4-yl)benzenesulfonamide (**1m**)

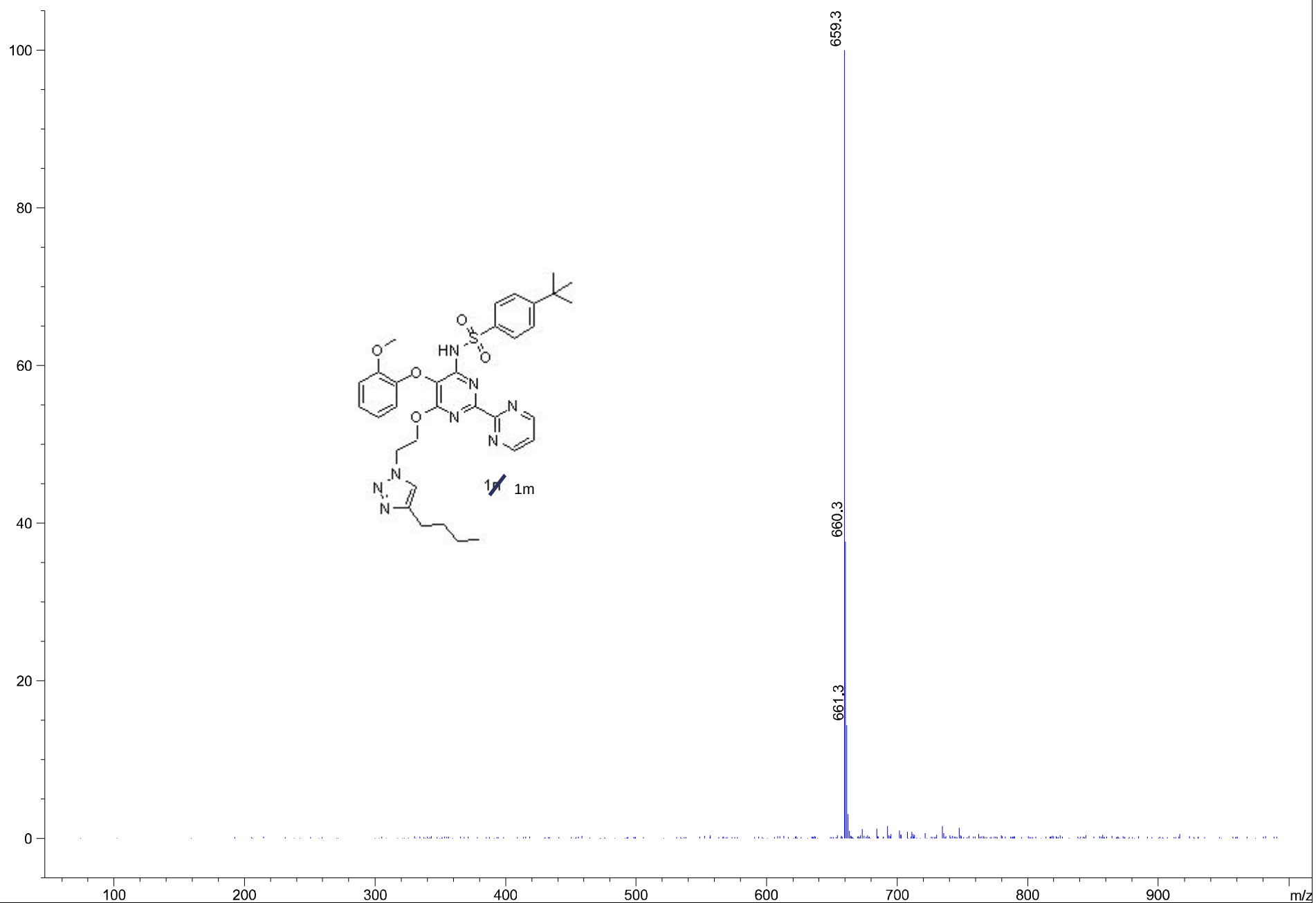


Figure 54: ^1H -NMR Spectrum of 4-tert-Butyl-N-(6-(2-(4-butyl-1H-1,2,3-triazol-1-yl)ethoxy)-5-(2-methoxyphenoxy)-2,2'-bipyrimidin-4-yl)benzenesulfonamide (**1m**)

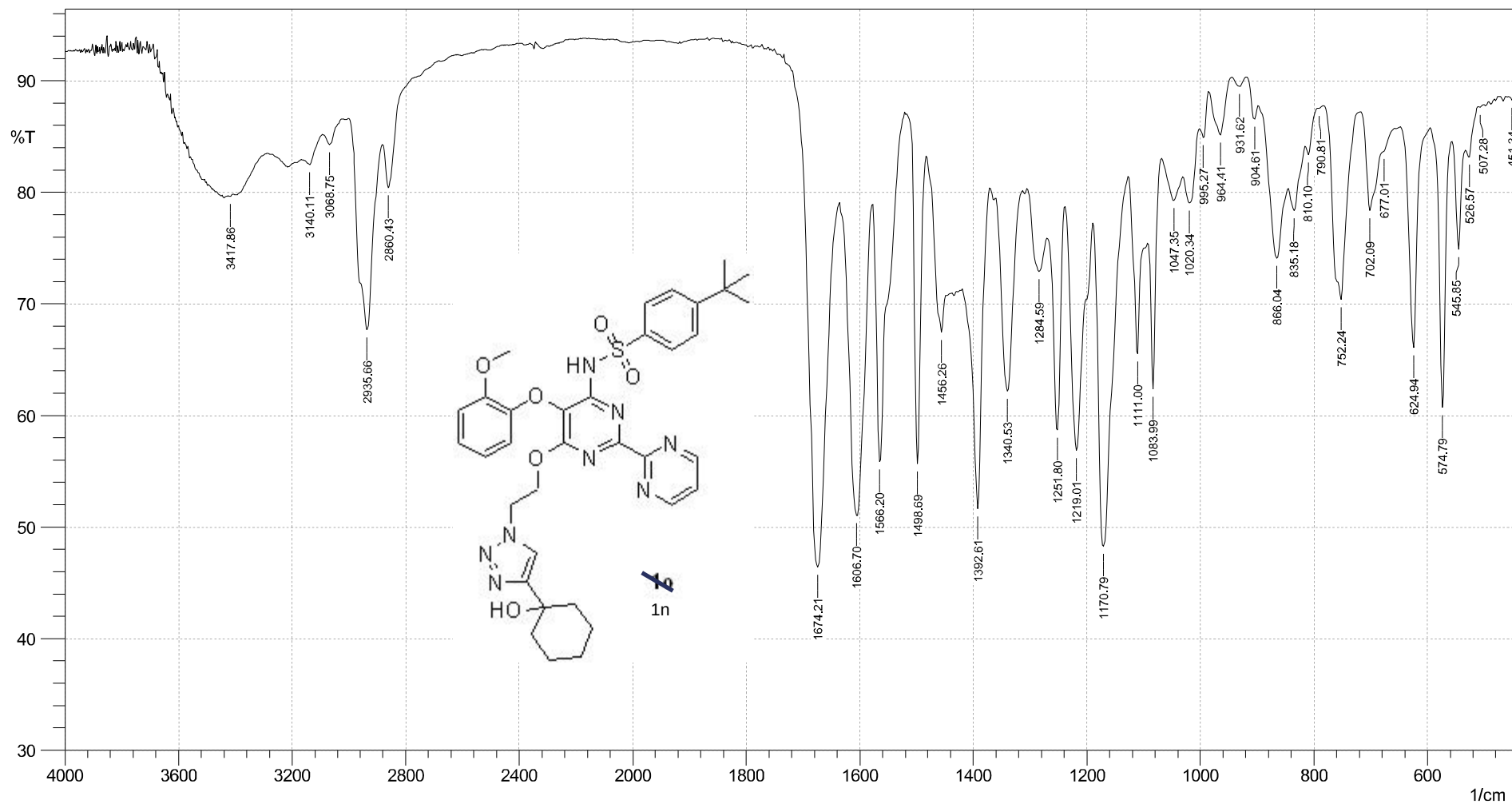


Figure 55: IR Spectrum of 4-tert-Butyl-N-(6-(2-(4-(1-hydroxycyclohexyl)-1H-1,2,3-triazol-1-yl)ethoxy)-5-(2-methoxyphenoxy)-2,2'-bipyrimidin-4-yl)benzenesulfonamide (**1n**)

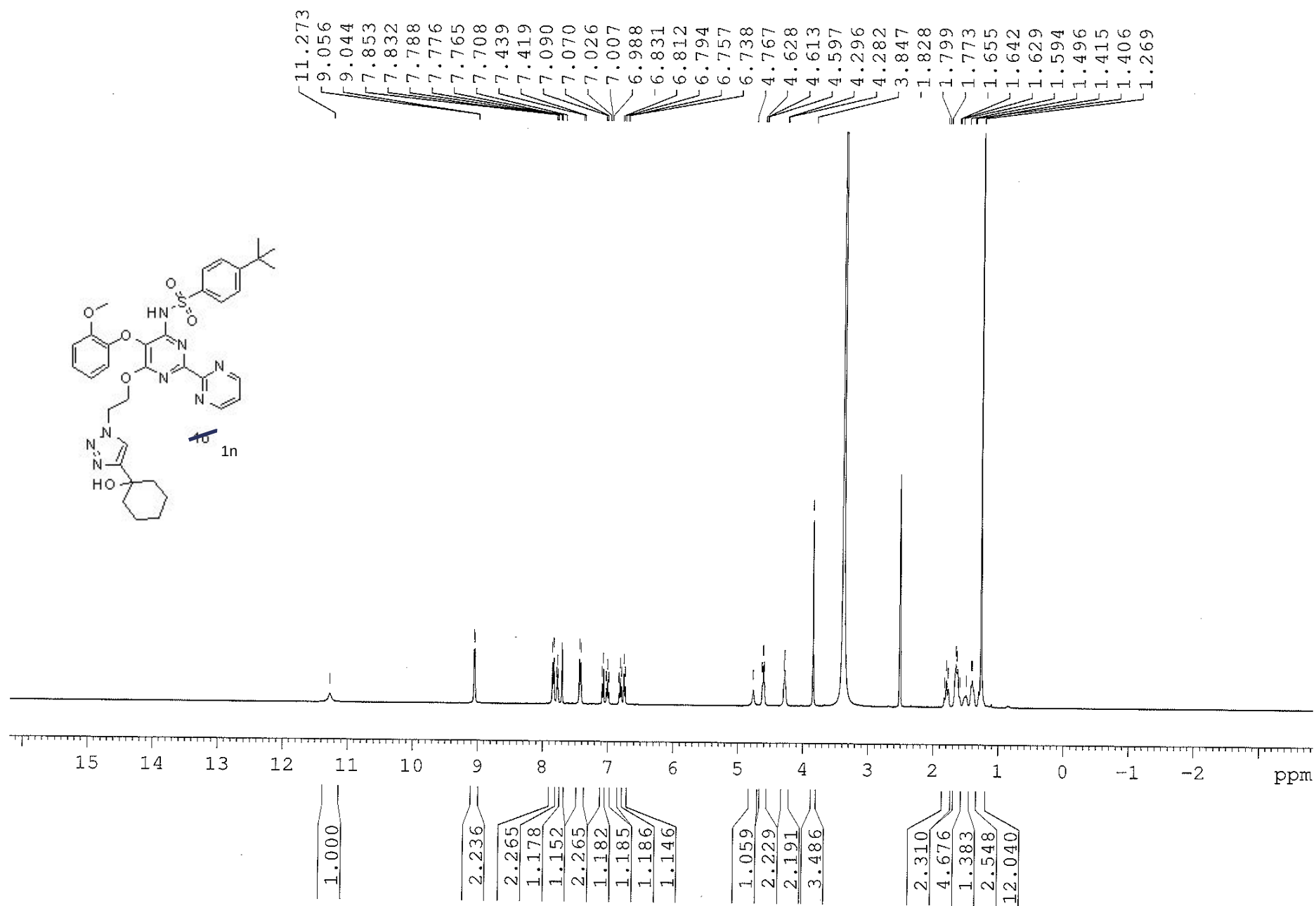
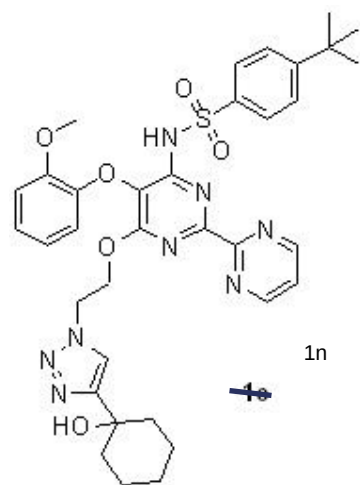


Figure 56: ¹H-NMR Spectrum of 4-tert-Butyl-N-(6-(2-(4-(1-hydroxycyclohexyl)-1H-1,2,3-triazol-1-yl)ethoxy)-5-(2-methoxyphenoxy)-2,2'-bipyrimidin-4-yl)benzenesulfonamide (**1n**)

1o CMR



159.15
158.32
157.41
156.25
151.25
149.29
146.80
146.13
138.43
128.55
125.64
124.42
123.25
122.84
121.89
120.90
115.49
113.30

-68.41
56.21
47.42
45.89
38.19
35.24
31.24
25.72
22.06

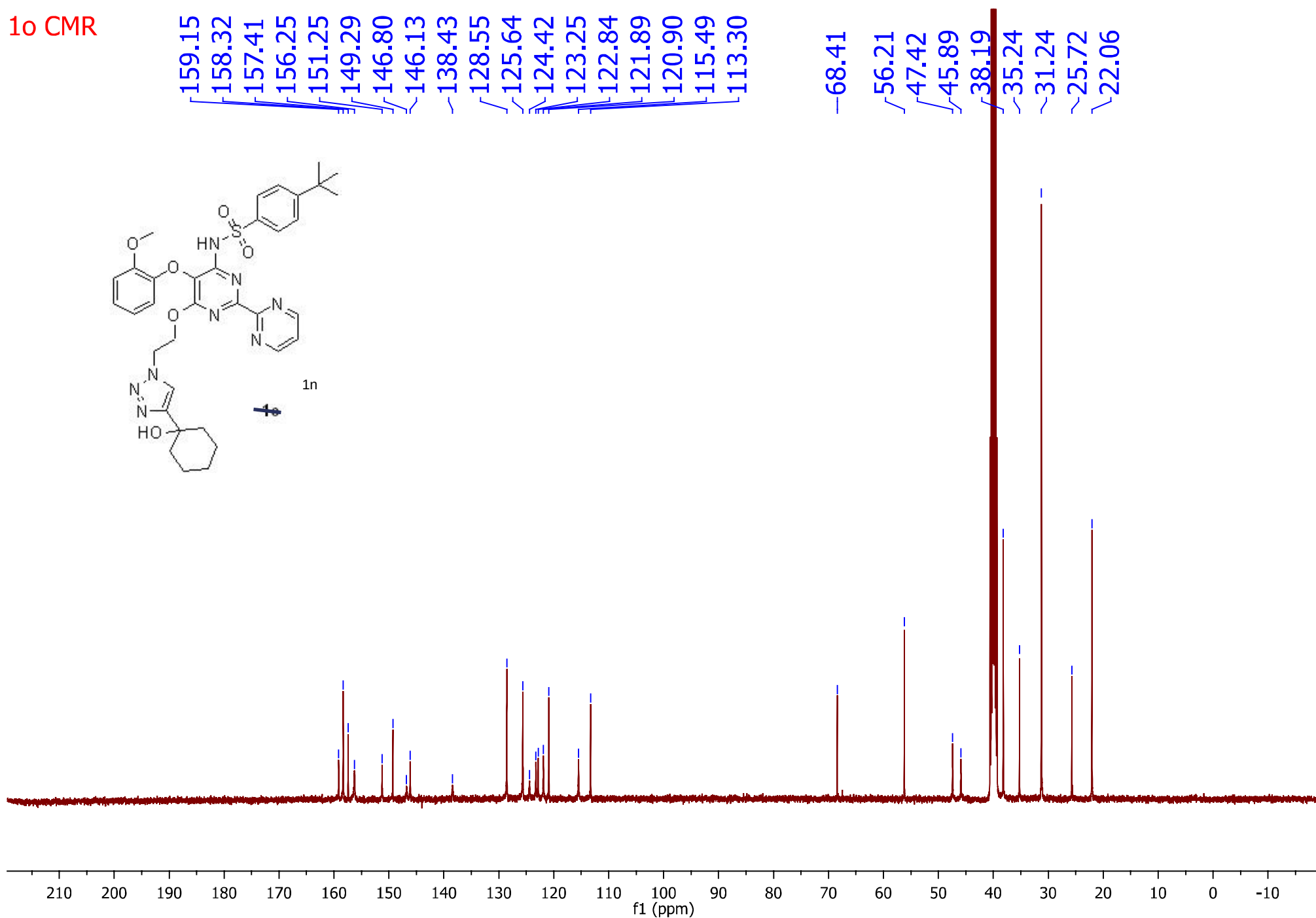


Figure 57: ^{13}C -NMR Spectrum of 4-tert-Butyl-N-(6-(2-(4-(1-hydroxycyclohexyl)-1H-1,2,3-triazol-1-yl)ethoxy)-5-(2-methoxyphenoxy)-2,2'-bipyrimidin-4-yl)benzenesulfonamide (**1n**)

*MSD1 SPC, time=0.420 of D:\DATA\2014\JUNE\250614\2506201411.D ES-API, Pos, Scan, Frag: 70



Figure 58: Mass NMR Spectrum of 4-tert-Butyl-N-(6-(2-(4-(1-hydroxycyclohexyl)-1H-1,2,3-triazol-1-yl)ethoxy)-5-(2-methoxyphenoxy)-2,2'-bipyrimidin-4-yl)benzenesulfonamide (**1n**)

Docking with 2XP2 receptor

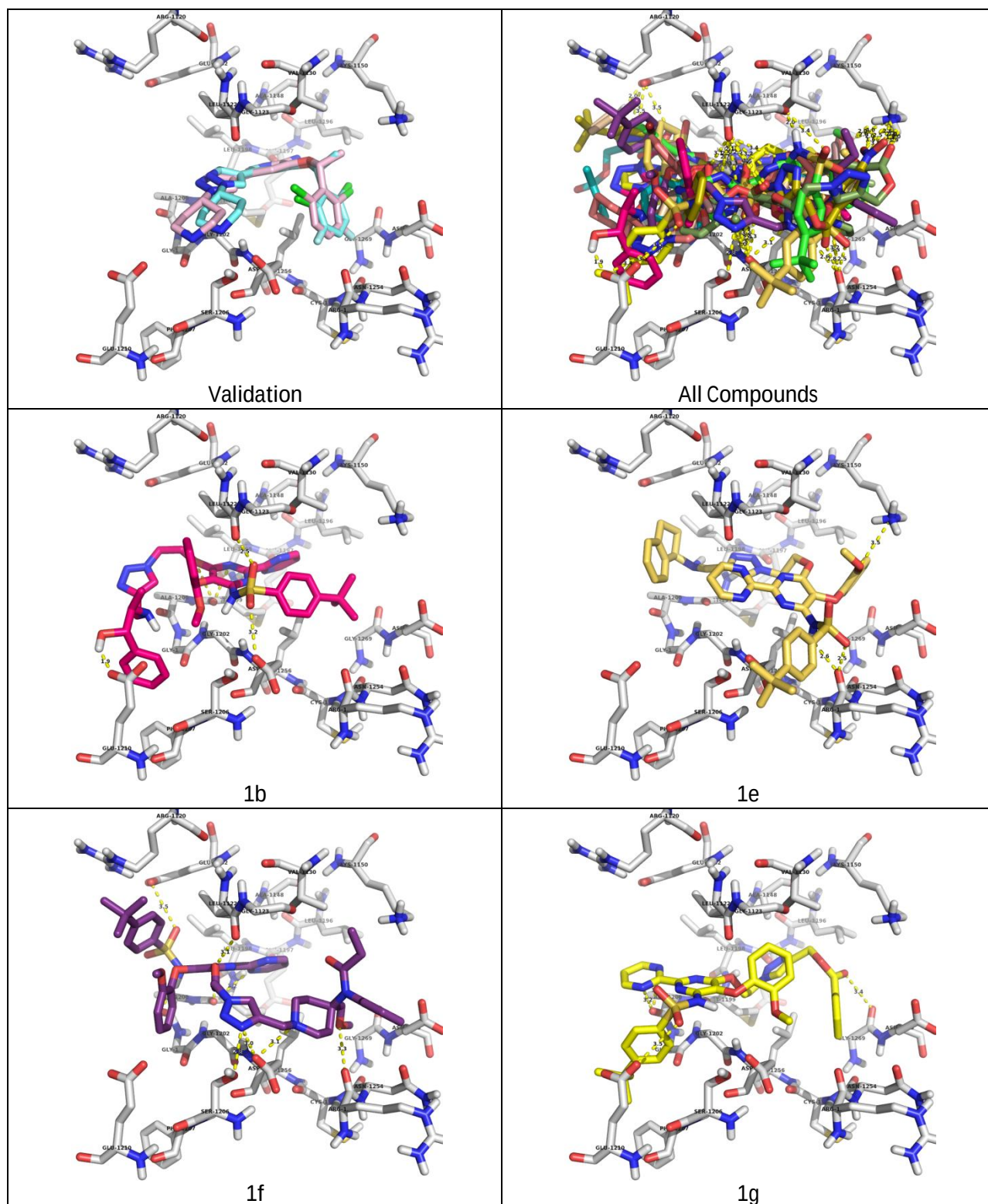


Figure 59:

Validation, docking mode of all synthesized compounds, 1b, 1e, 1f and 1g with 2XP2 receptor

Docking with 2XP2 receptor

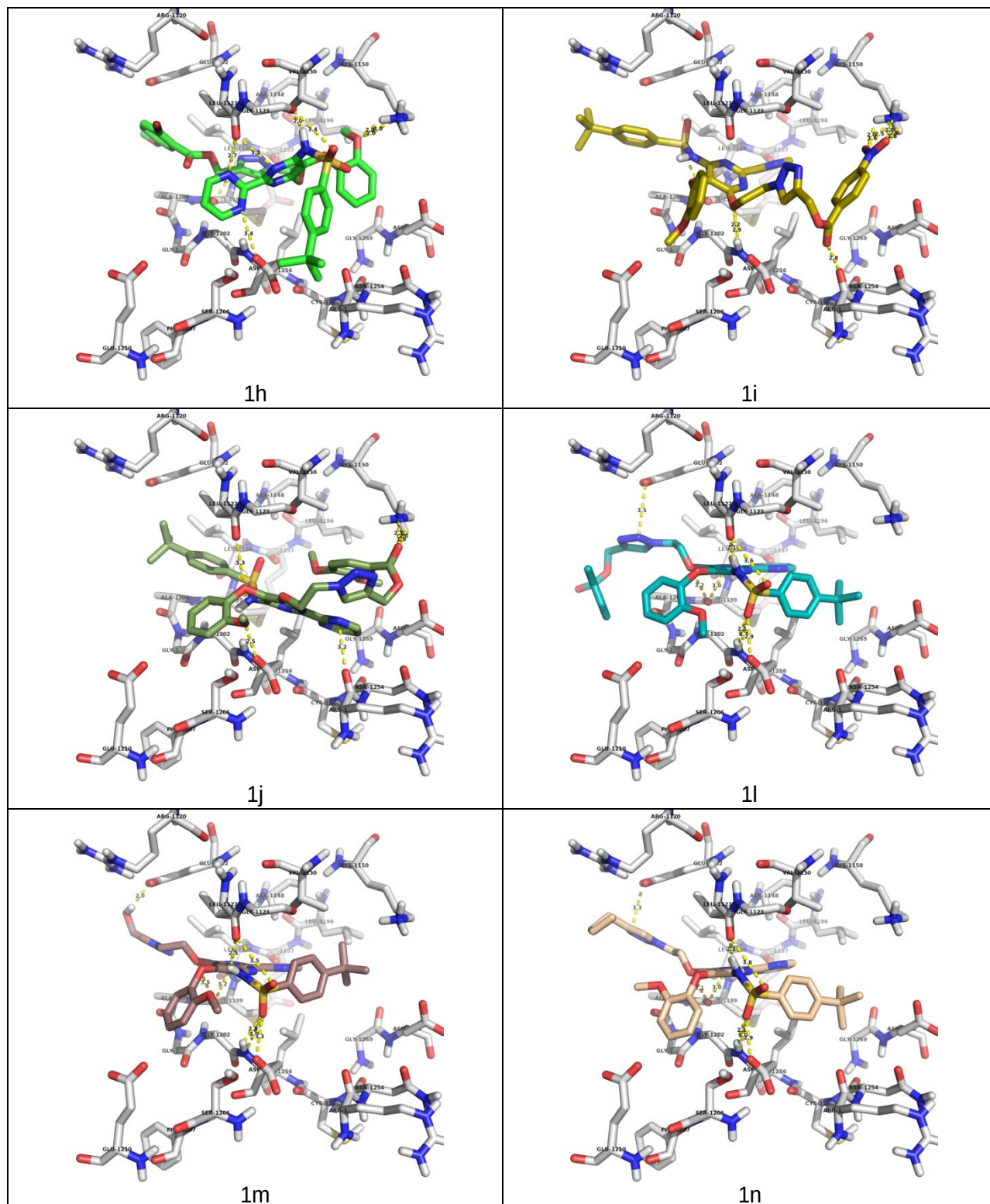


Figure 60: Docking mode of synthesized compounds 1h-j, 1l-n with 2XP2 receptor

Docking with 4EMV receptor

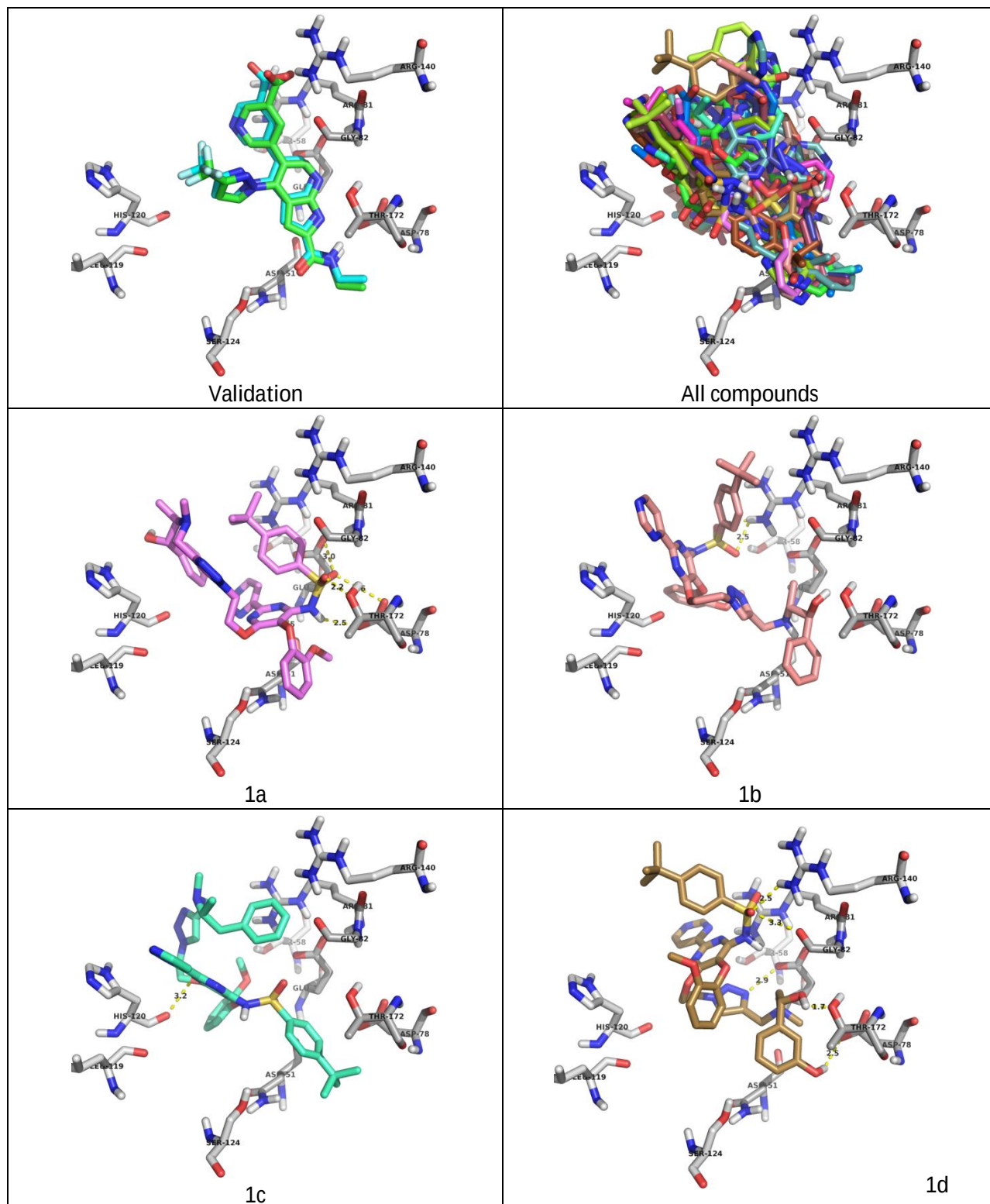


Figure 61: Validation, docking mode of all synthesized compounds, 1a-d with 4EMV receptor