

Supporting Information

Synthesis and biological evaluation of novel 4,5-disubstituted 2*H*-1,2,3-triazoles as *cis*-constrained analogues of combretastatin A-4

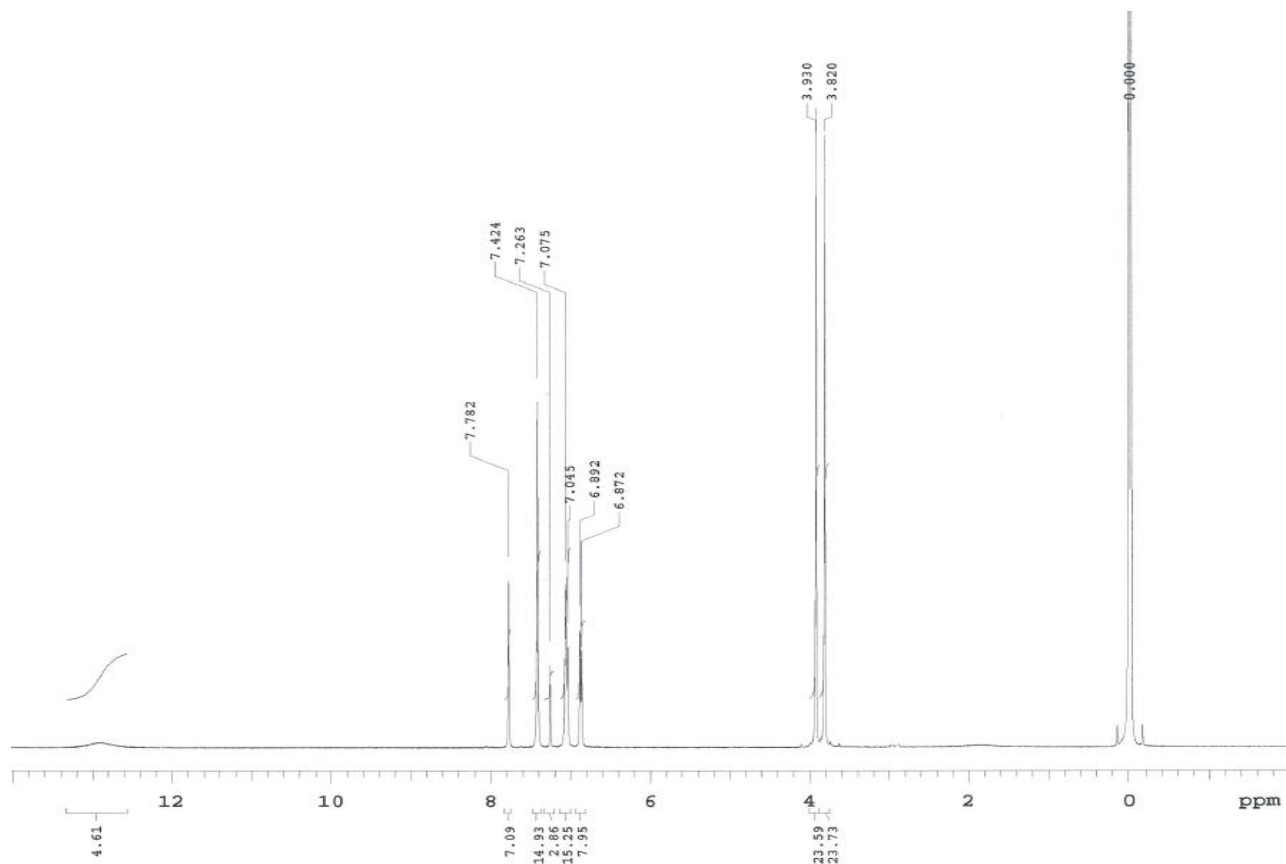
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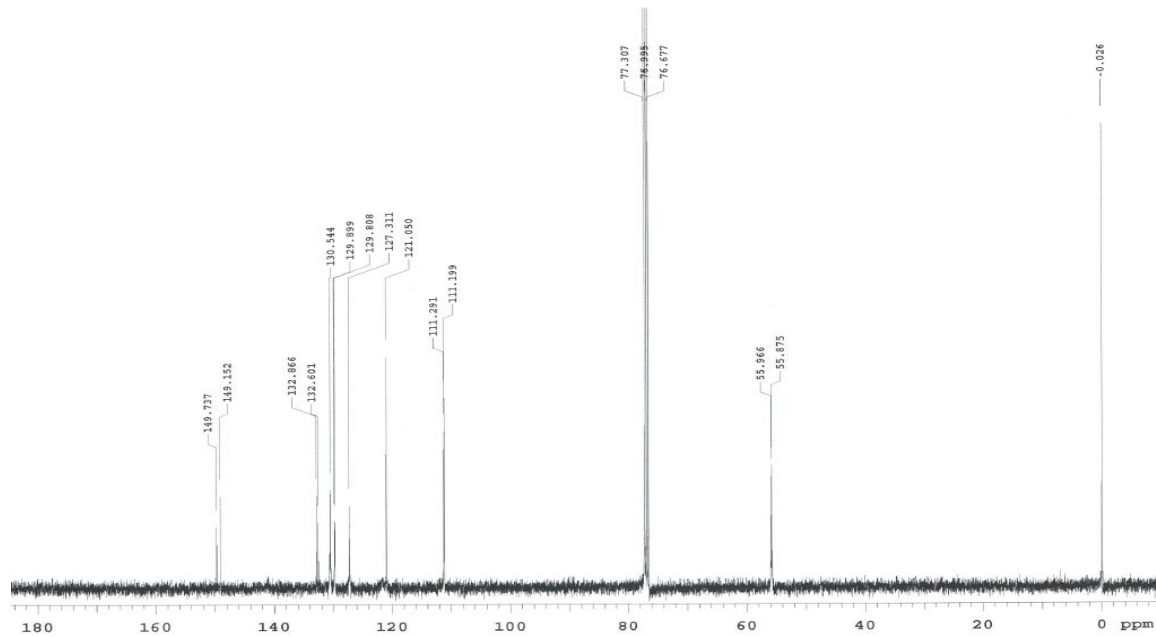
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^c Department of Biochemistry and Molecular Biology, University of Arkansas for Medical Sciences, Little Rock, AR 72205-7199, U.S.A.

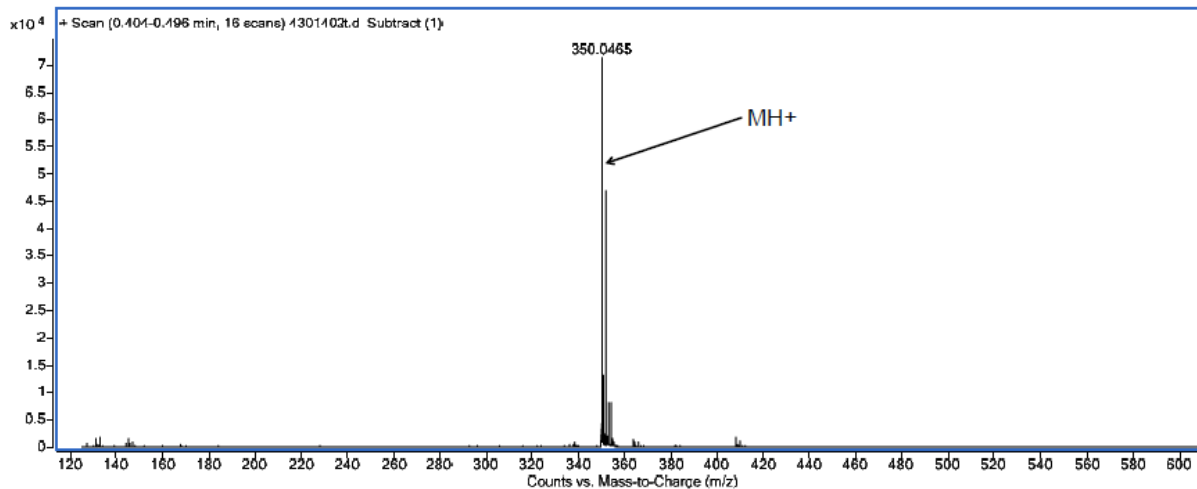
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Representative ¹H NMR spectra of compound 4-(3,4-dichlorophenyl)-5-(3,4-dimethoxyphenyl)-2H-1,2,3-triazole (2a)



Representative ¹³C NMR spectra of compound 4-(3,4-dichlorophenyl)-5-(3,4-dimethoxyphenyl)-2H-1,2,3-triazole (2a)

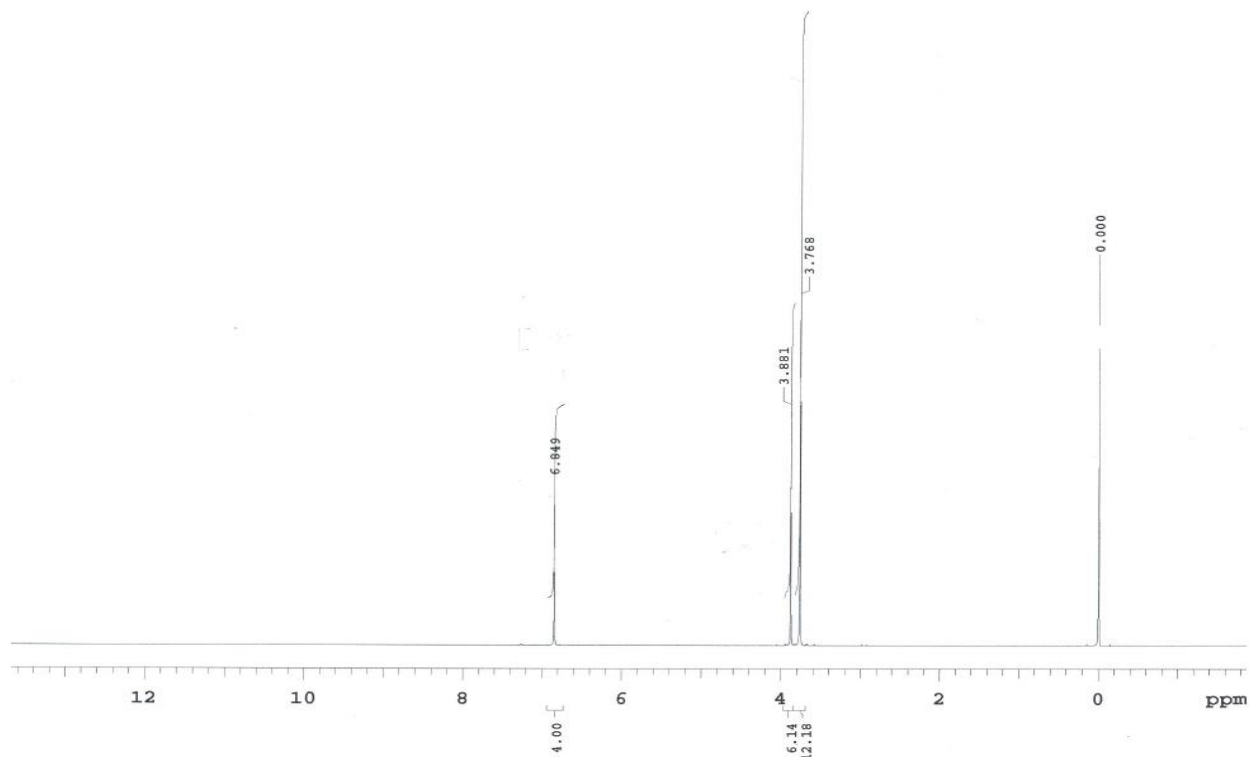


Measured Mass 350.0465

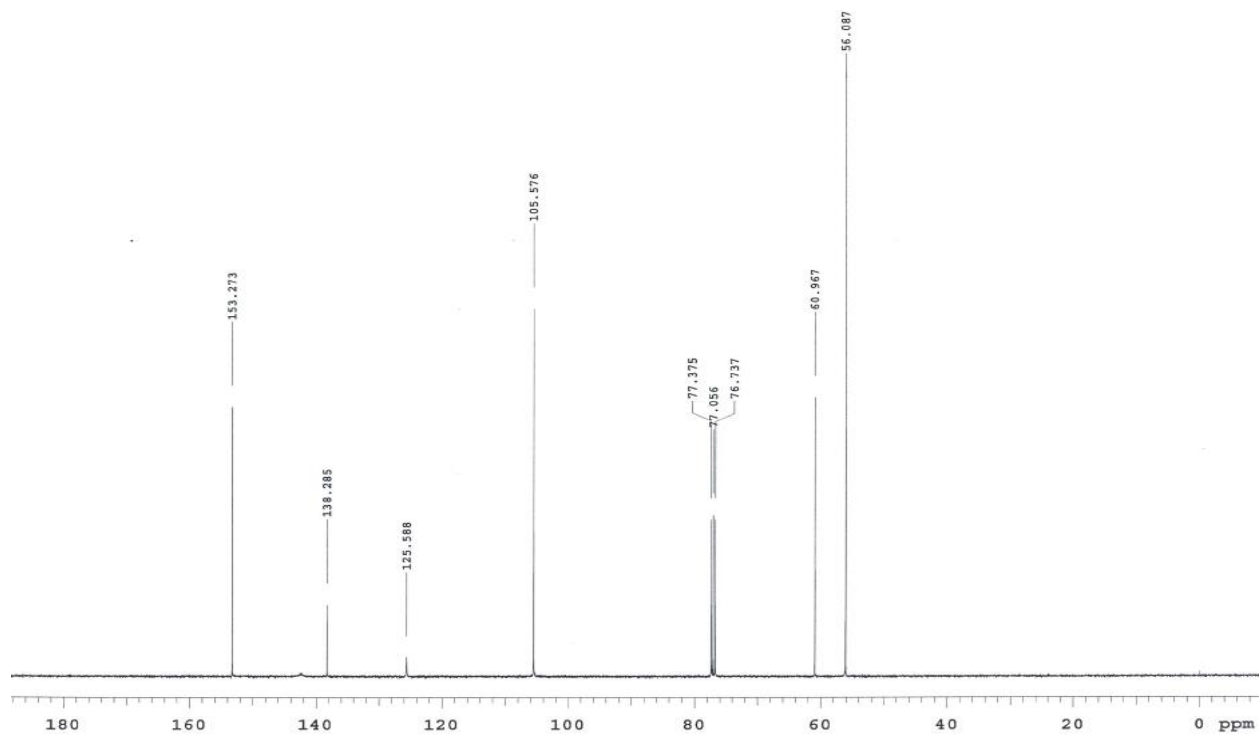
<u>Element</u>	<u>Low Limit</u>	<u>High Limit</u>
C	5	25
H	5	25
N	0	5
O	0	7
Cl	0	2

<u>Formula</u>	<u>Calculated Mass</u>	<u>mDaError</u>	<u>ppmError</u>	<u>RDB</u>
C ₁₈ H ₁₆ O ₃ Cl ₂	350.0471	-0.6	-1.7	10
C ₁₆ H ₁₄ N ₃ O ₂ Cl ₂	350.0458	0.7	2.1	10.5
C ₂₅ H ₆ N ₂ O	350.0475	-1.0	-2.8	24
C ₁₉ H ₁₁ N ₂ O ₃ Cl	350.0453	1.2	3.5	15
C ₂₂ H ₉ N ₃ Cl	350.0480	-1.5	-4.1	19.5
C ₂₂ H ₈ N ₄ O	350.0448	1.7	4.9	19.5

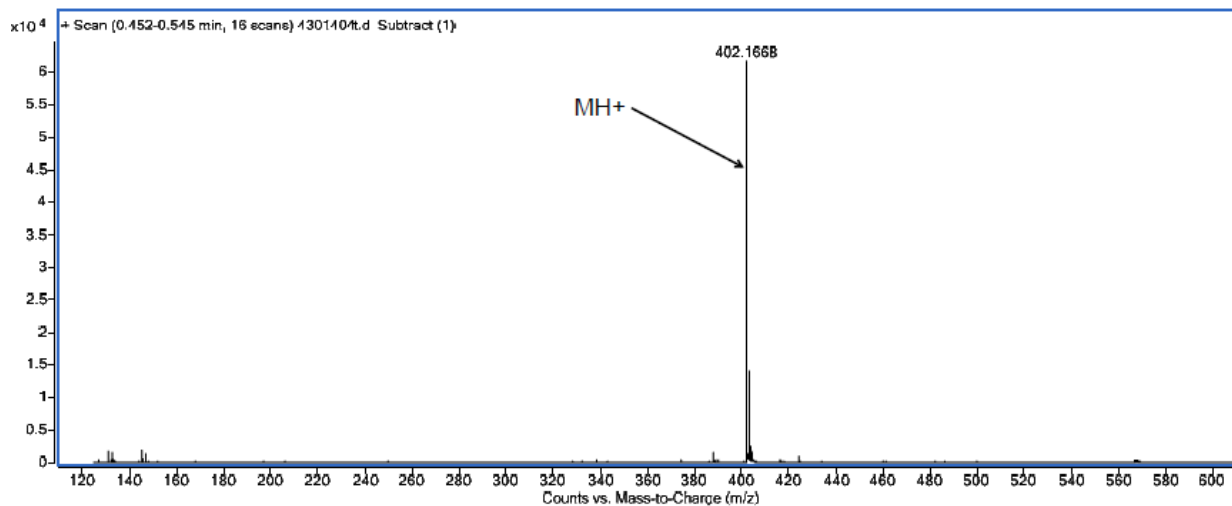
Representative HRMS spectra of compound 4-(3,4-dichlorophenyl)-5-(3,4-dimethoxy phenyl)-2H-1,2,3-triazole (2a)



Representative ¹H NMR spectra of compound 4,5-bis(3,4,5-trimethoxyphenyl)-2H-1,2,3-triazole (2b)



Representative ¹³C NMR spectra of compound 4,5-bis(3,4,5-trimethoxyphenyl)-2H-1,2,3-triazole (2b)



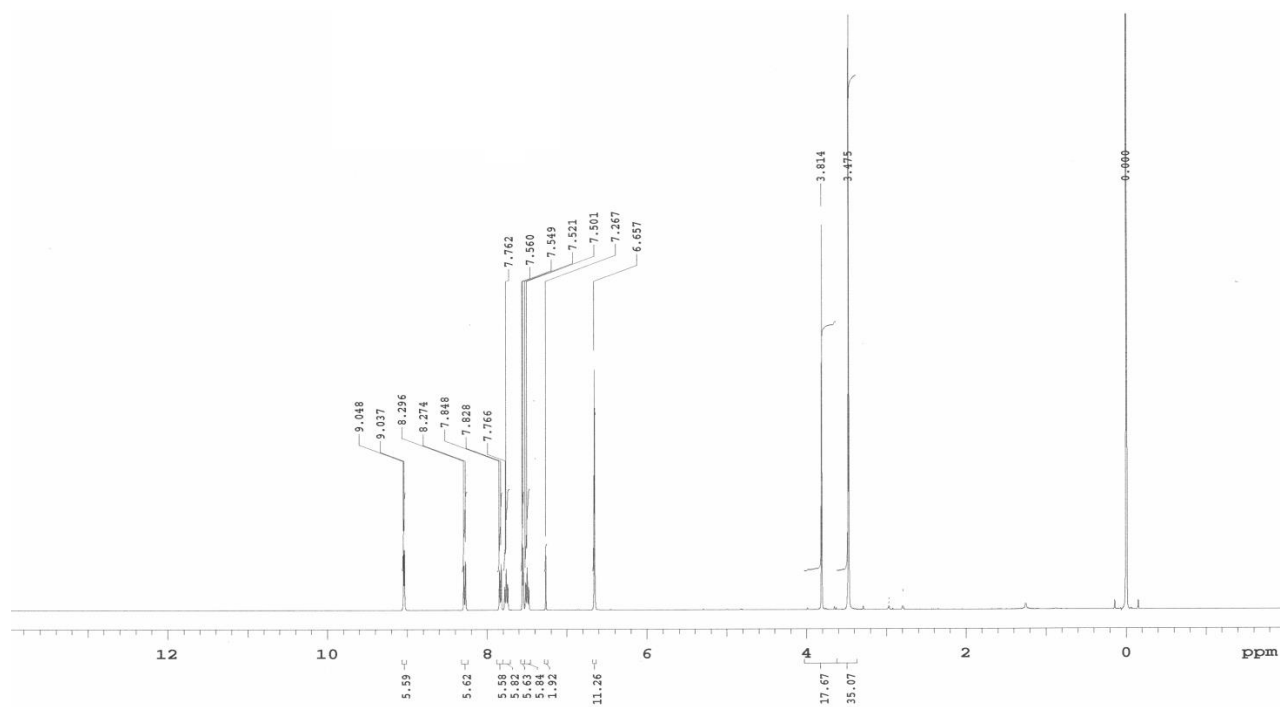
Measured Mass

402.1668

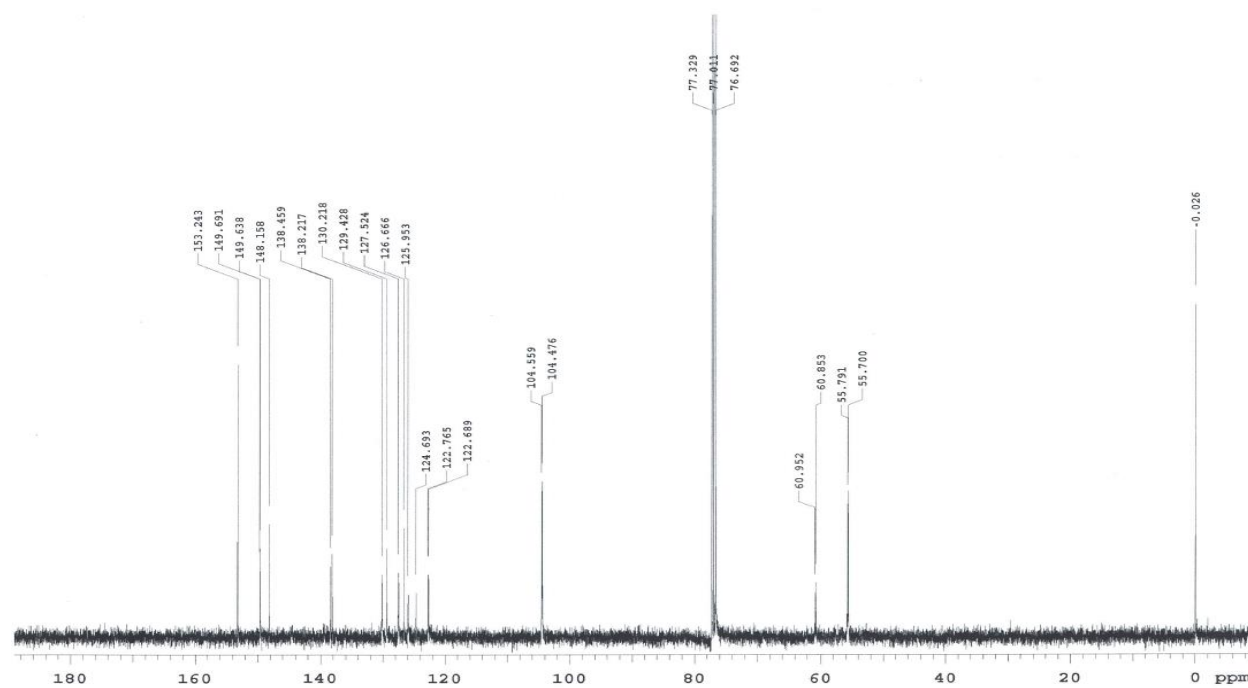
<u>Element</u>	<u>Low Limit</u>	<u>High Limit</u>
C	5	25
H	5	25
N	0	5
O	0	7
Cl	0	2

<u>Formula</u>	<u>Calculated Mass</u>	<u>mDaError</u>	<u>ppmError</u>	<u>RDB</u>
C ₂₀ H ₂₄ N ₃ O ₆	402.1660	0.8	2.1	10.5
C ₂₃ H ₂₂ N ₄ O ₃	402.1686	-1.8	-4.6	15

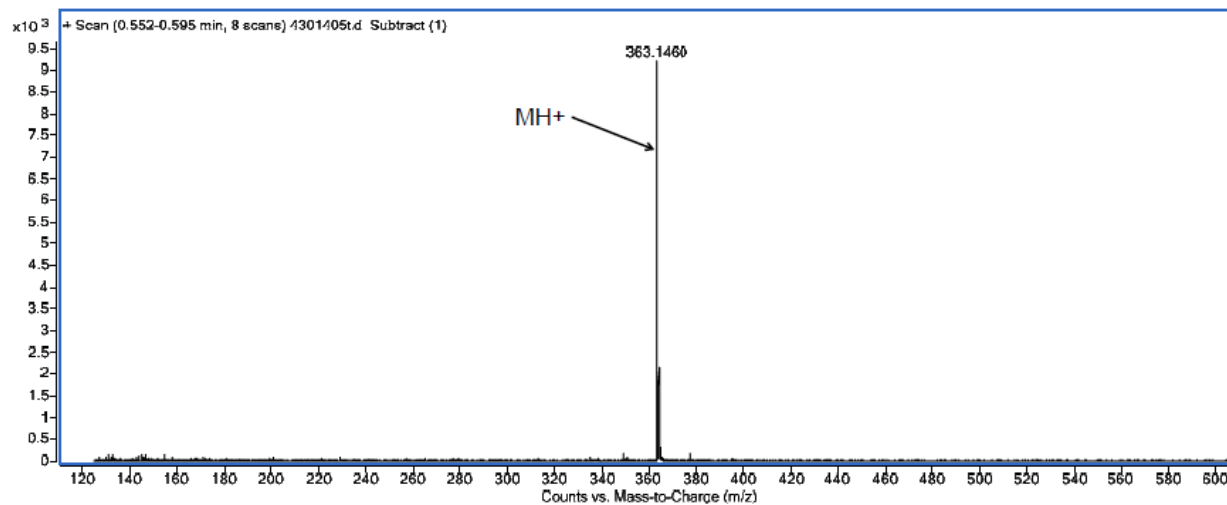
Representative HRMS spectra of compound 4,5-bis(3,4,5-trimethoxyphenyl)-2H-1,2,3-triazole (2b)



Representative ^1H NMR spectra of compound 4-(5-(3,4,5-trimethoxyphenyl)-2H-1,2,3-triazol-4-yl)quinolone (2c)



Representative ^{13}C NMR spectra of compound 4-(5-(3,4,5-trimethoxyphenyl)-2H-1,2,3-triazol-4-yl)quinolone (2c)



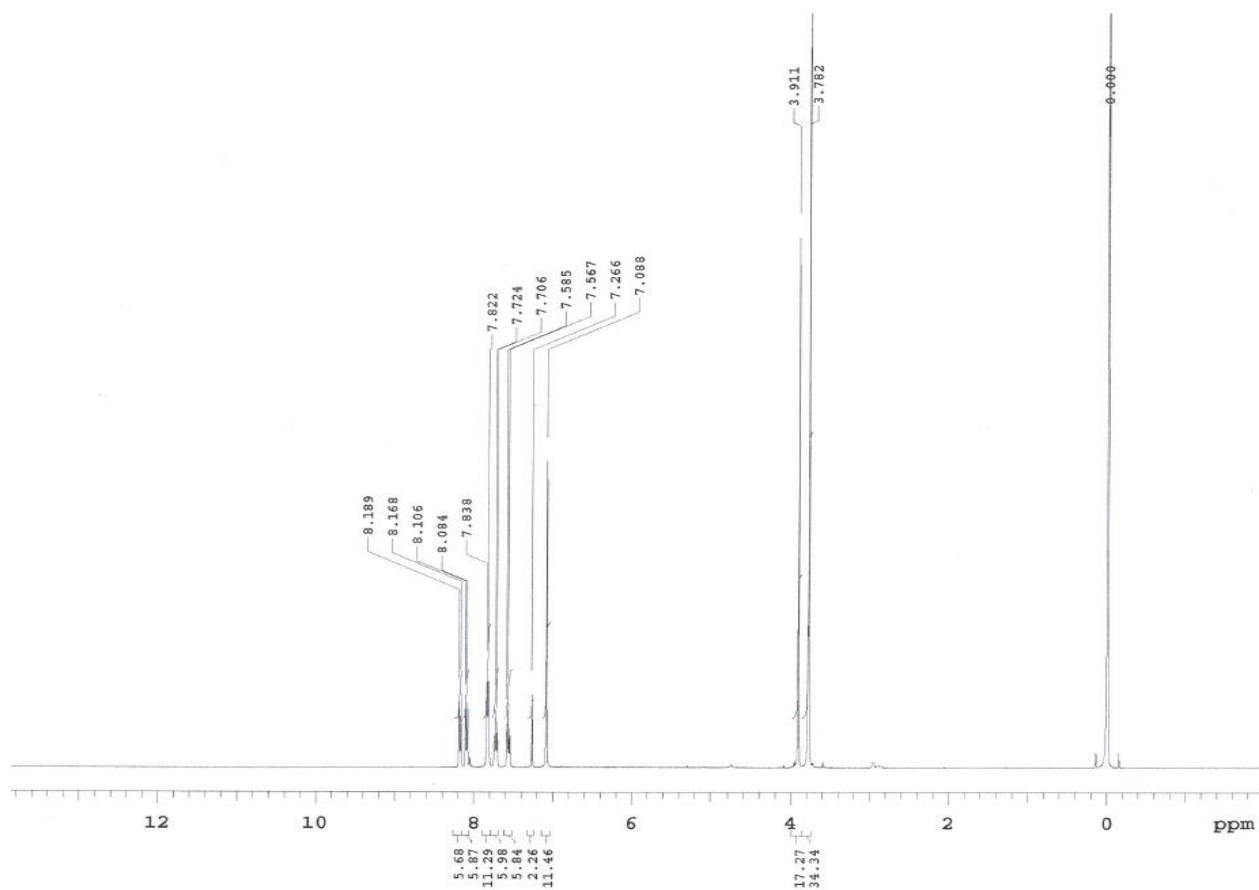
Measured Mass

363.146

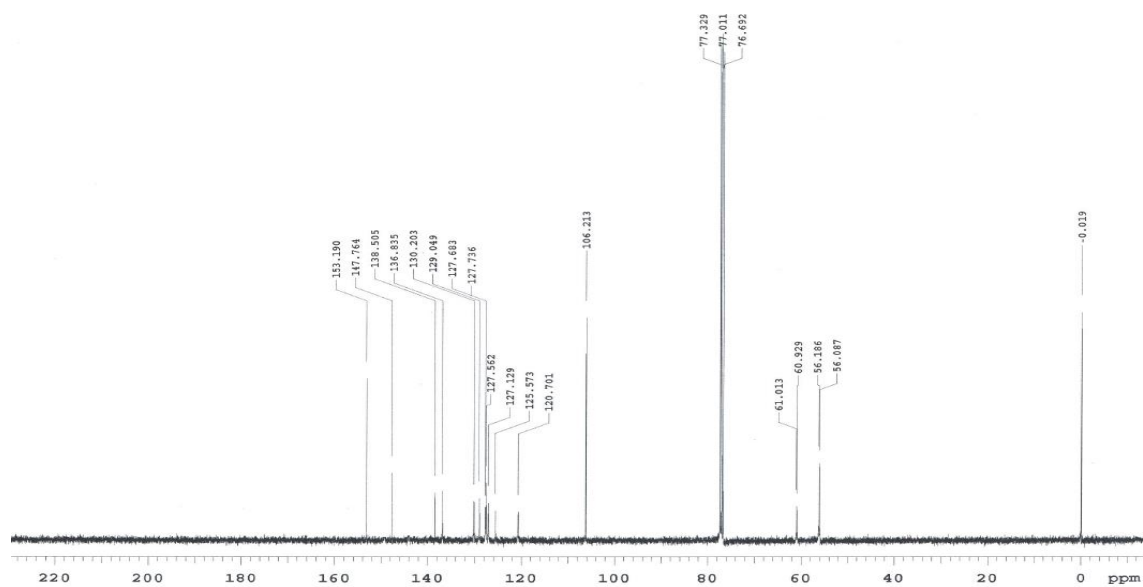
<u>Element</u>	<u>Low Limit</u>	<u>High Limit</u>
C	5	25
H	5	25
N	0	5
O	0	7

<u>Formula</u>	<u>Calculated Mass</u>	<u>mDaError</u>	<u>ppmError</u>	<u>RDB</u>
C22 H21 N O4	363.1465	-0.5	-1.4	13
C20 H19 N4 O3	363.1452	0.8	2.3	13.5

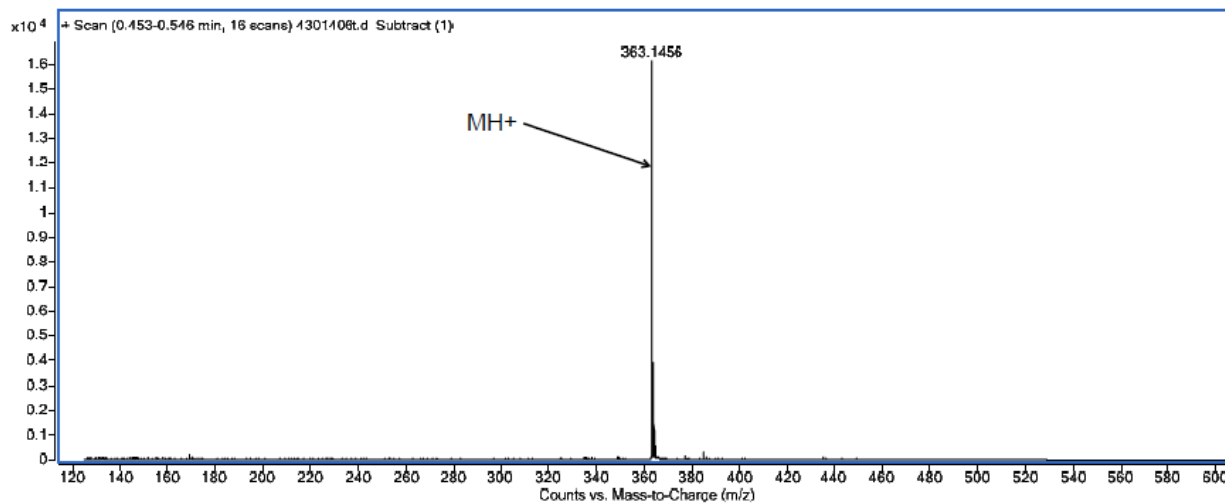
Representative HRMS spectra of compound 4-(5-(3,4,5-trimethoxyphenyl)-2H-1,2,3-triazol-4-yl)quinolone (2c)



Representative ^1H NMR spectra of compound 2-(5-(3,4,5-trimethoxyphenyl)-2H-1,2,3-triazol-4-yl)quinolone (2d)



Representative ^{13}C NMR spectra of compound 2-(5-(3,4,5-trimethoxyphenyl)-2H-1,2,3-triazol-4-yl)quinolone (2d)



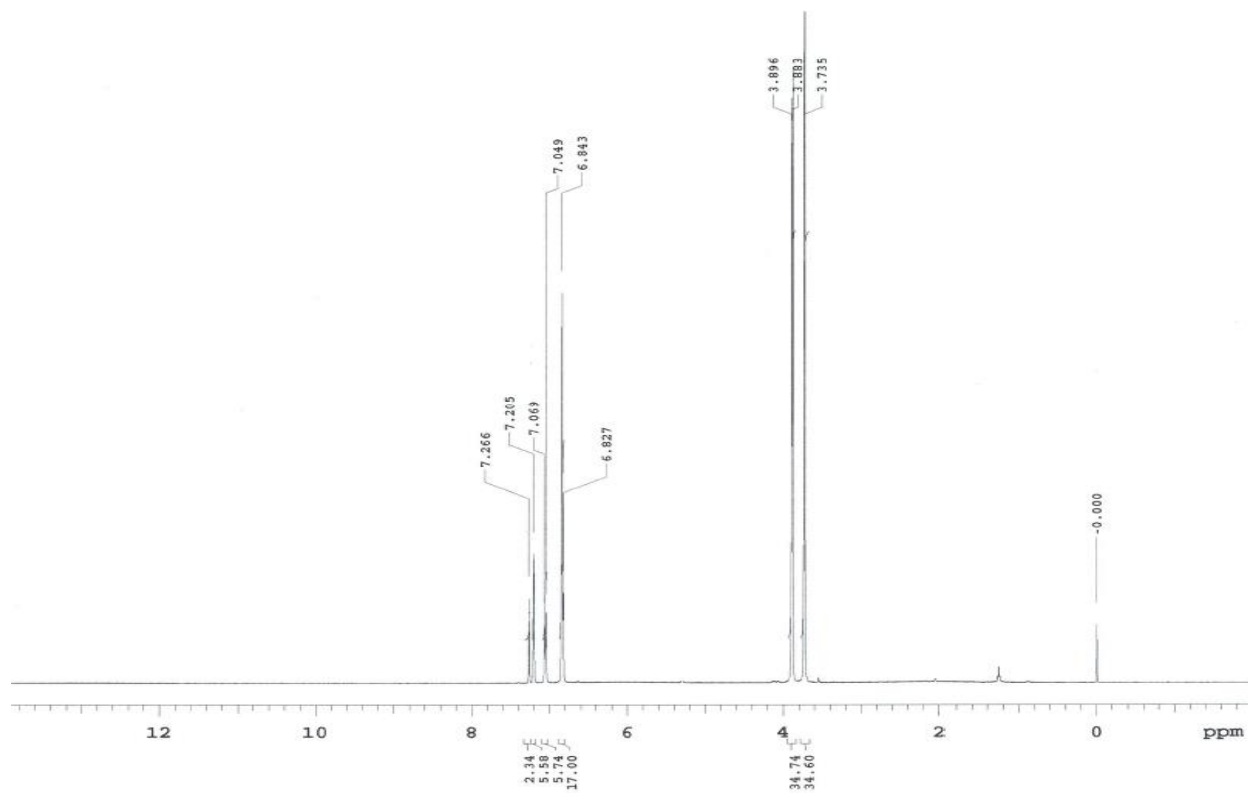
Measured Mass

363.1456

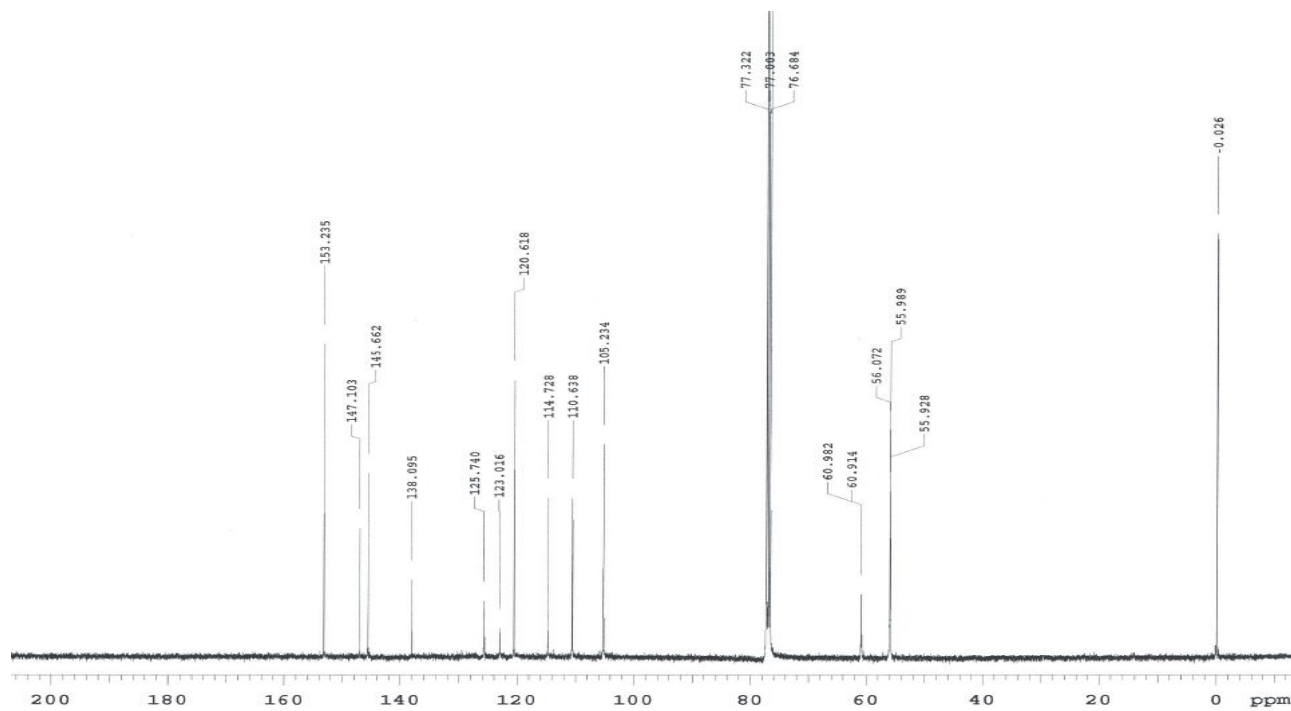
<u>Element</u>	<u>Low Limit</u>	<u>High Limit</u>
C	5	25
H	5	25
N	0	5
O	0	7

<u>Formula</u>	<u>Calculated Mass</u>	<u>mDaError</u>	<u>ppmError</u>	<u>RDB</u>
C ₂₀ H ₁₉ N ₄ O ₃	363.1452	0.4	1.2	13.5
C ₂₂ H ₂₁ N O ₄	363.1465	-0.9	-2.5	13
C ₁₉ H ₂₃ O ₇	363.1438	1.8	4.9	8.5

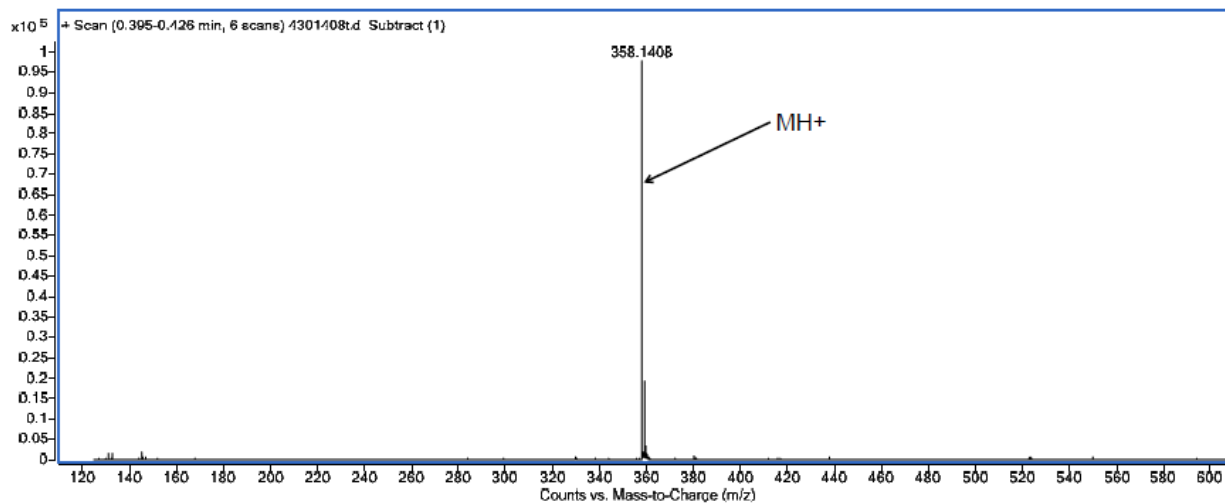
Representative HRMS spectra of compound 2-(5-(3,4,5-trimethoxyphenyl)-2H-1,2,3-triazol-4-yl)quinolone (2d)



Representative ¹H NMR spectra of compound 2-methoxy-5-(5-(3,4,5-trimethoxyphenyl)-2H-1,2,3-triazol-4-yl)phenol (2e)



Representative ¹³C NMR spectra of compound 2-methoxy-5-(5-(3,4,5-trimethoxyphenyl)-2H-1,2,3-triazol-4-yl)phenol (2e)



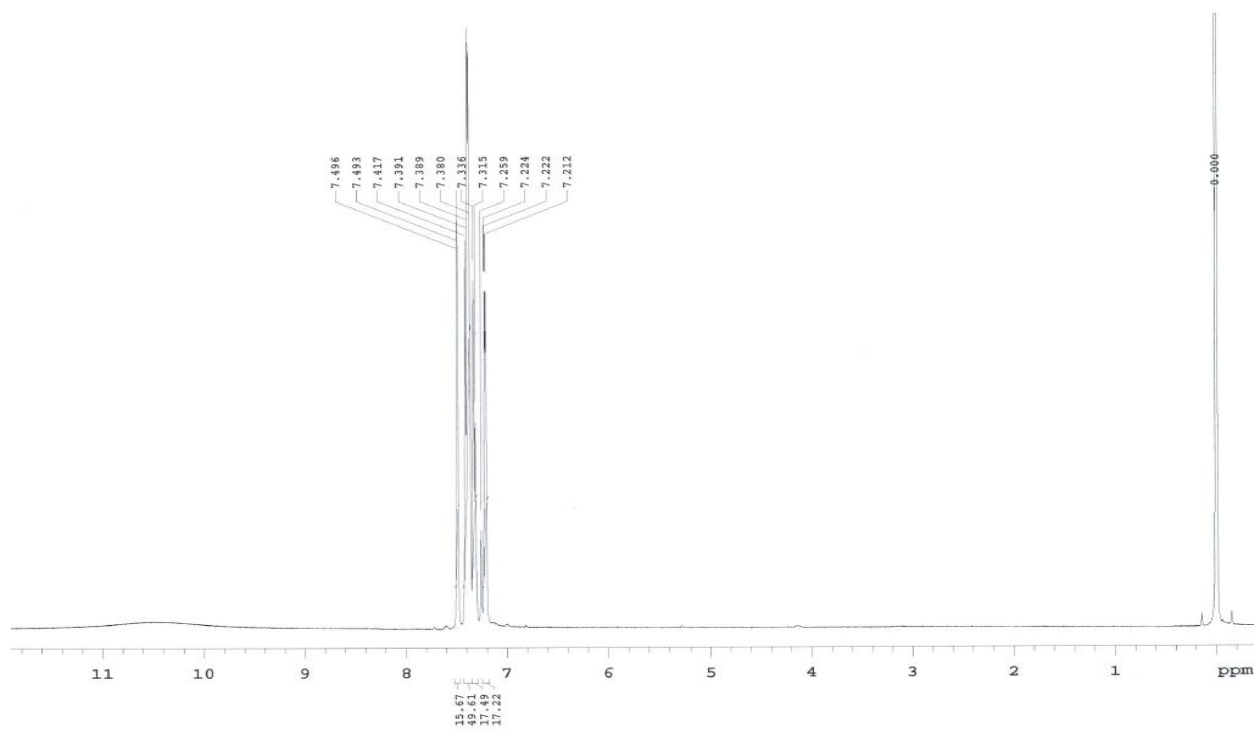
Measured Mass

358.1408

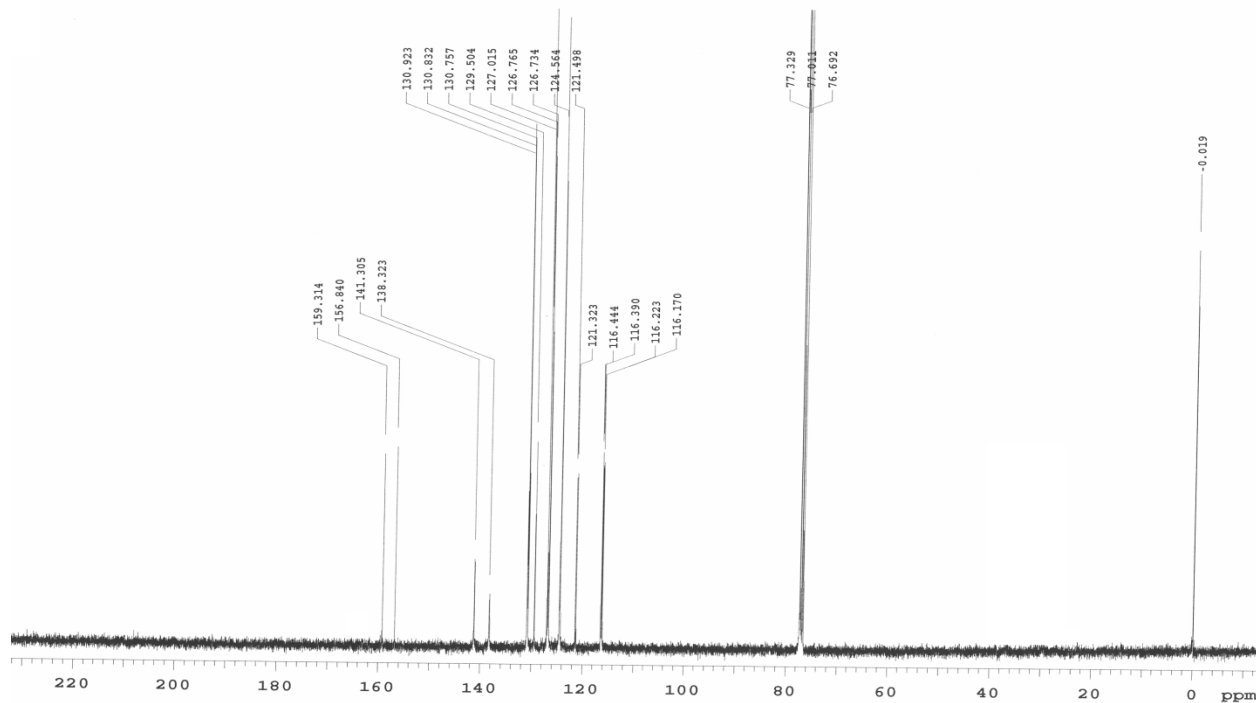
<u>Element</u>	<u>Low Limit</u>	<u>High Limit</u>
C	5	25
H	5	25
N	0	5
O	0	7

<u>Formula</u>	<u>Calculated Mass</u>	<u>mDaError</u>	<u>ppmError</u>	<u>RDB</u>
C ₂₀ H ₂₂ O ₆	358.1411	-0.3	-0.8	10
C ₁₈ H ₂₀ N ₃ O ₅	358.1397	1.1	2.9	10.5
C ₂₁ H ₁₈ N ₄ O ₂	358.1424	-1.6	-4.5	15

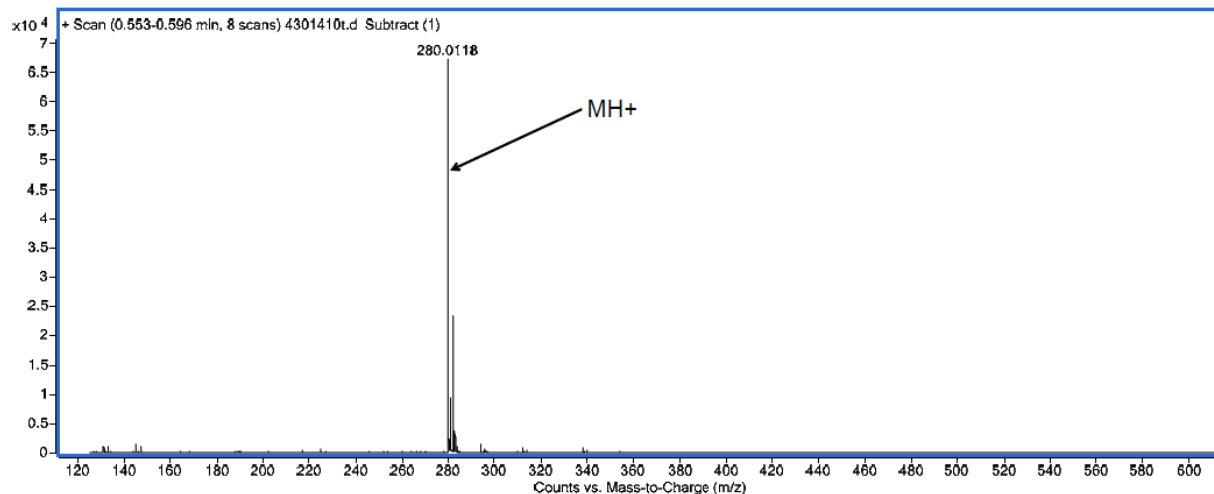
Representative HRMS spectra of compound 2-methoxy-5-(5-(3,4,5-trimethoxyphenyl)-2H-1,2,3-triazol-4-yl)phenol (2e)



Representative ^1H NMR spectra of compound 4-(4-chloro-3-fluorophenyl)-5-(thiophen-3-yl)-2H-1,2,3-triazole (2f)



Representative ^{13}C NMR spectra of compound 4-(4-chloro-3-fluorophenyl)-5-(thiophen-3-yl)-2H-1,2,3-triazole (2f)



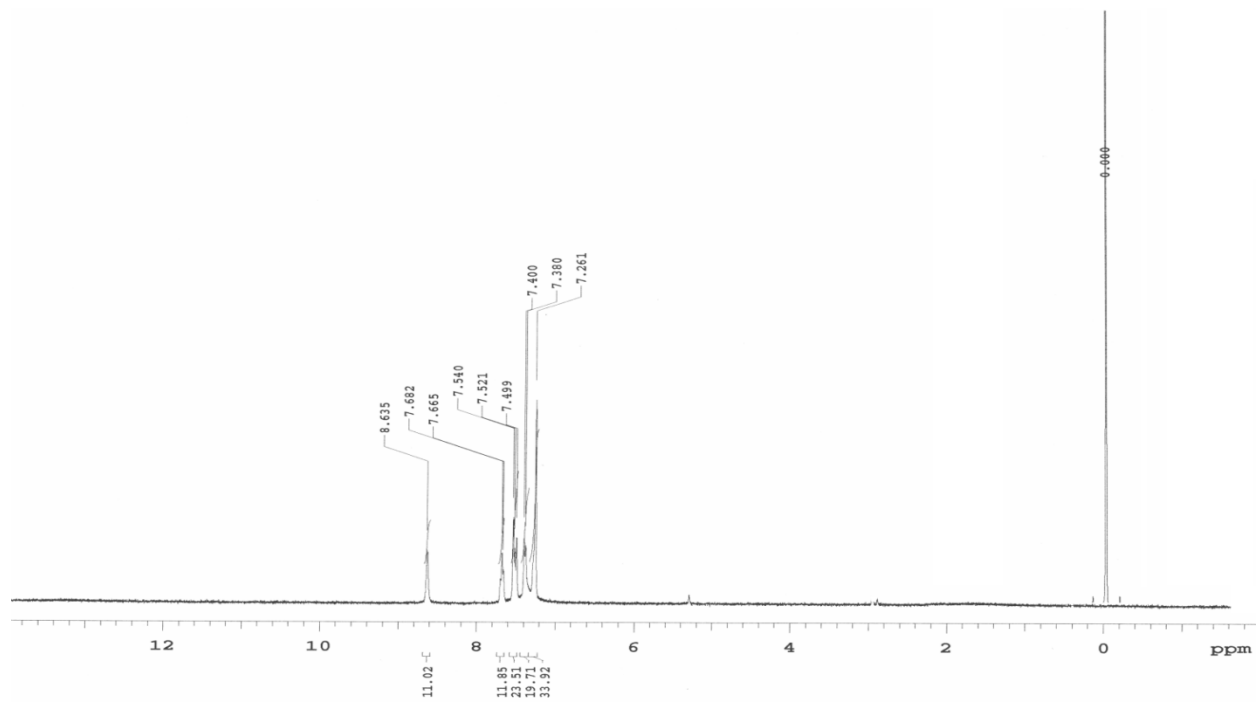
Measured Mass

280.0118

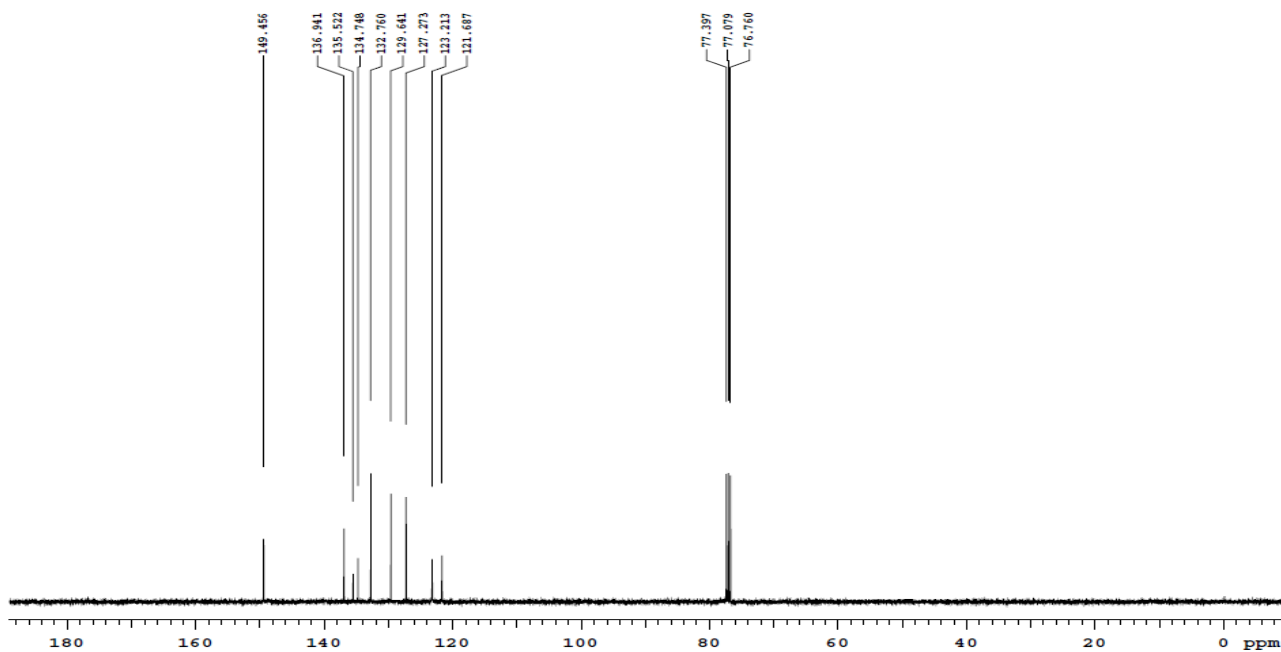
<u>Element</u>	<u>Low Limit</u>	<u>High Limit</u>
C	5	25
H	5	25
S	0	2
N	0	5
Cl	0	1
F	0	1

<u>Formula</u>	<u>Calculated Mass</u>	<u>mDaError</u>	<u>ppmError</u>	<u>RDB</u>
C10 H7 N5 F S2	280.0121	-0.3	-1.2	9.5
C15 H8 N2 S2	280.0123	-0.5	-1.9	13
C17 H9 S Cl	280.0108	1.0	3.6	13
C12 H8 N3 F S Cl	280.0106	1.2	4.3	9.5

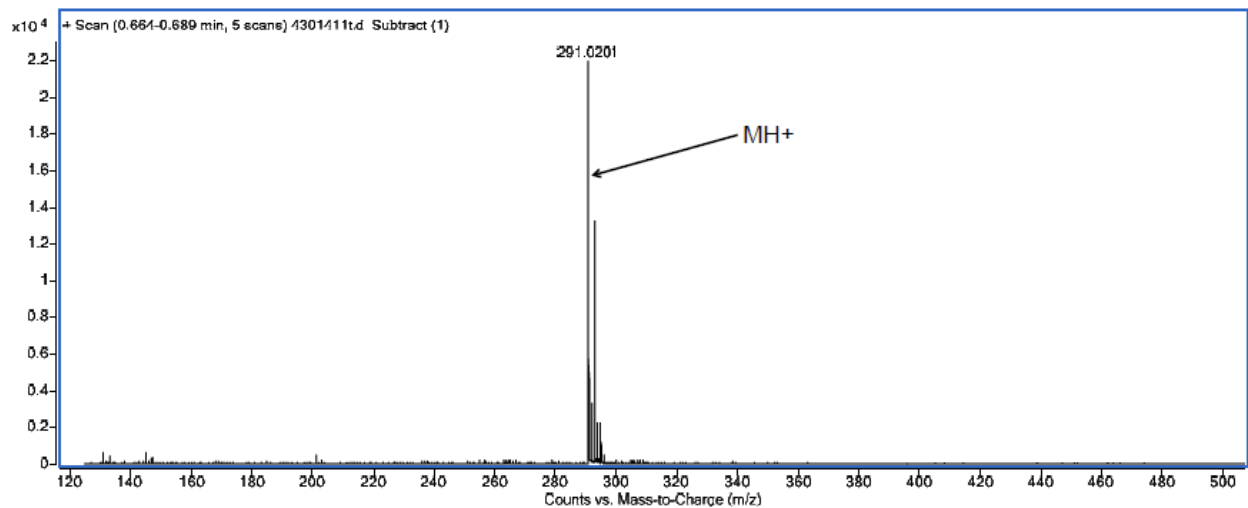
Representative HRMS spectra of compound 4-(4-chloro-3-fluorophenyl)-5-(thiophen-3-yl)-2H-1,2,3-triazole (2f)



Representative ^1H NMR spectra of compound 2-(5-(2,4-dichlorophenyl)-2H-1,2,3-triazol-4-yl)pyridine (2g)



Representative ^{13}C NMR spectra of compound 2-(5-(2,4-dichlorophenyl)-2H-1,2,3-triazol-4-yl)pyridine (2g)

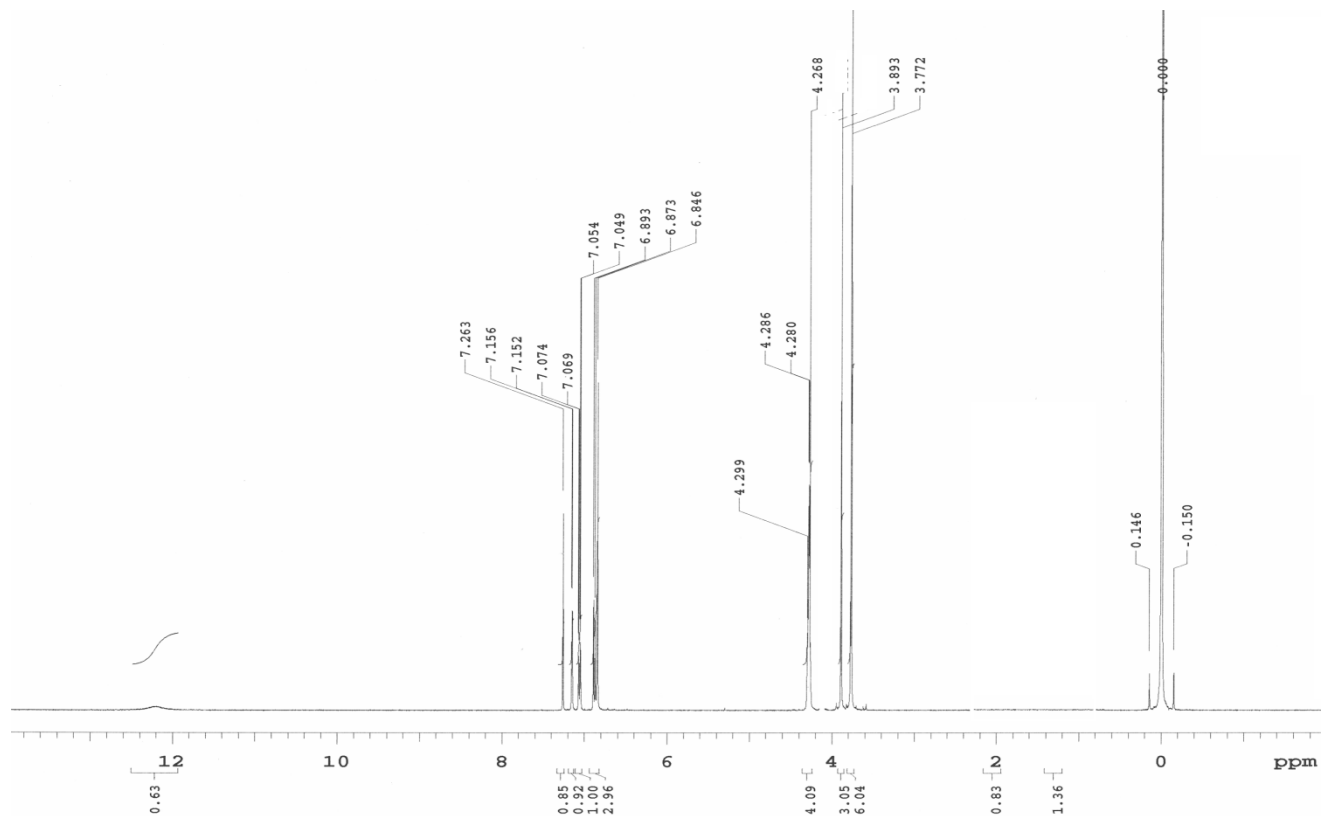


Measured Mass 291.0201

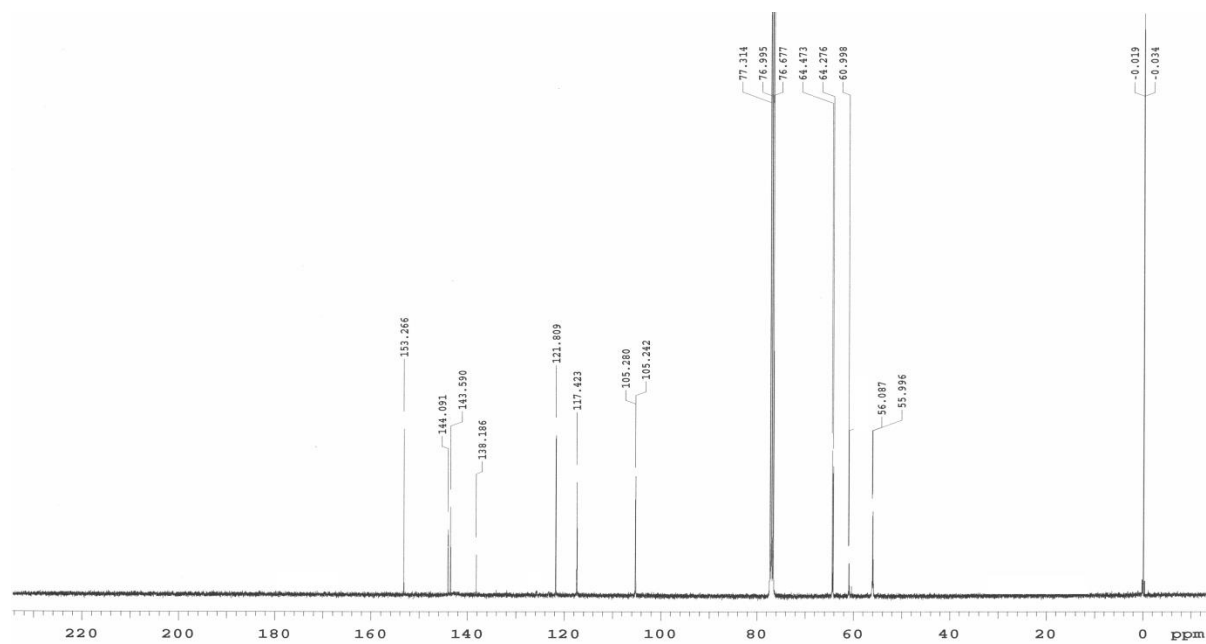
<u>Element</u>	<u>Low Limit</u>	<u>High Limit</u>
C	5	25
H	5	25
N	0	5
Cl	0	2

<u>Formula</u>	<u>Calculated Mass</u>	<u>mDaError</u>	<u>ppmError</u>	<u>RDB</u>
C13 H9 N4 Cl2	291.0199	0.2	0.8	10.5

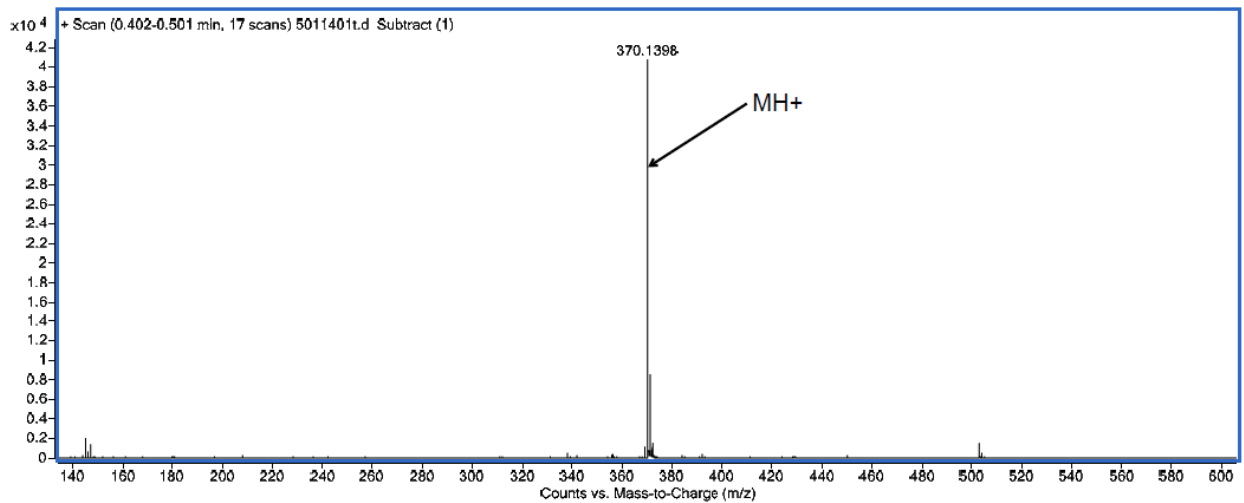
Representative HRMS spectra of compound 2-(5-(2,4-dichlorophenyl)-2H-1,2,3-triazol-4-yl)pyridine (2g)



Representative ^1H NMR spectra of compound 4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-5-(3,4,5-trimethoxy phenyl)-2H-1,2,3-triazole (2h):



Representative ^{13}C NMR spectra of compound 4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-5-(3,4,5-trimethoxy phenyl)-2H-1,2,3-triazole (2h):



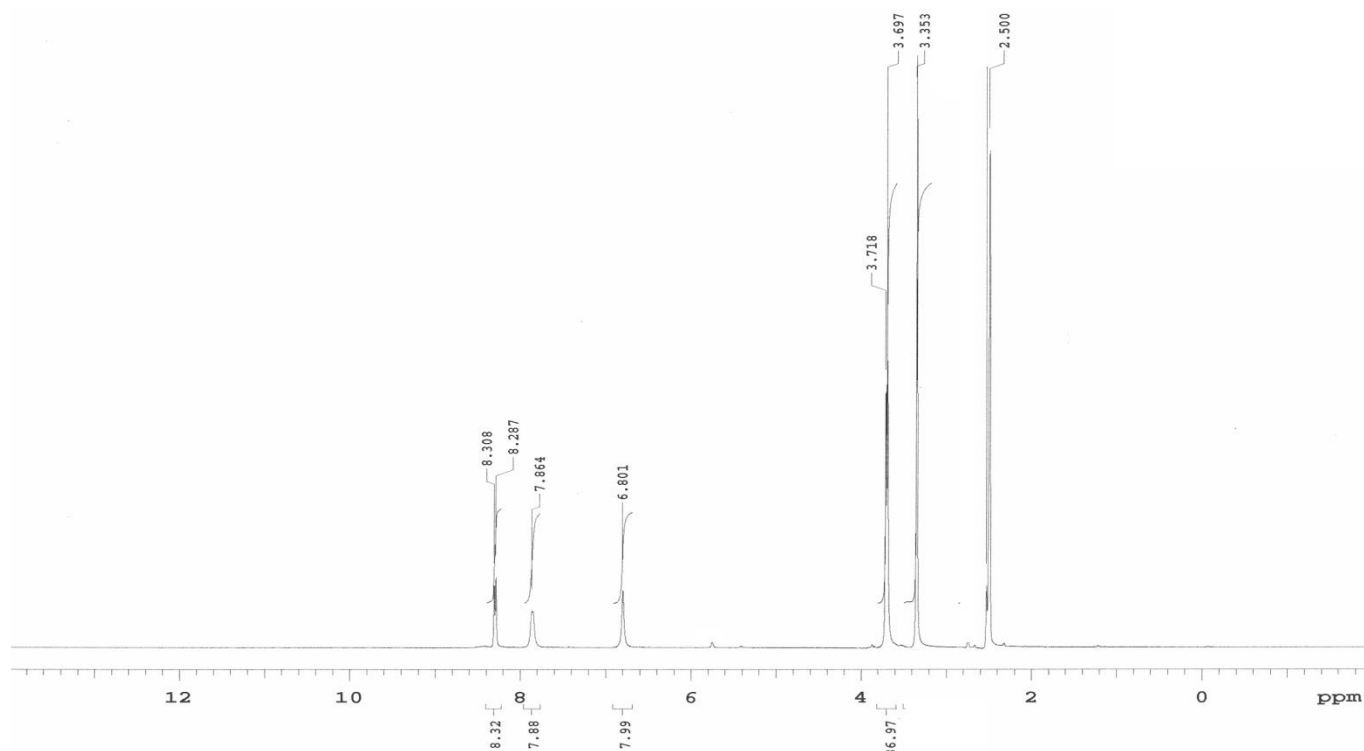
Measured Mass

370.1398

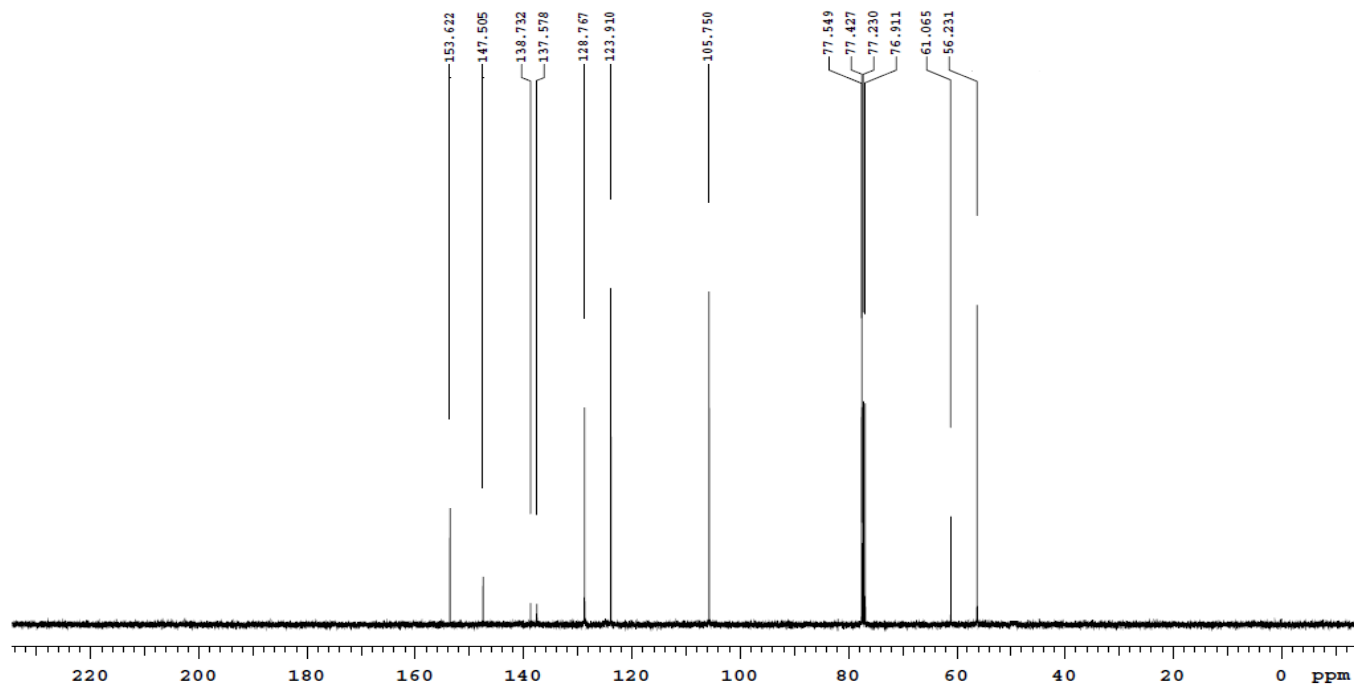
<u>Element</u>	<u>Low Limit</u>	<u>High Limit</u>
C	10	25
H	5	25
N	0	5
O	0	6

<u>Formula</u>	<u>Calculated Mass</u>	<u>mDaError</u>	<u>ppmError</u>	<u>RDB</u>
C ₁₉ H ₂₀ N ₃ O ₅	370.1397	0.1	0.1	11.5
C ₂₁ H ₂₂ O ₆	370.1411	-1.3	-3.5	11

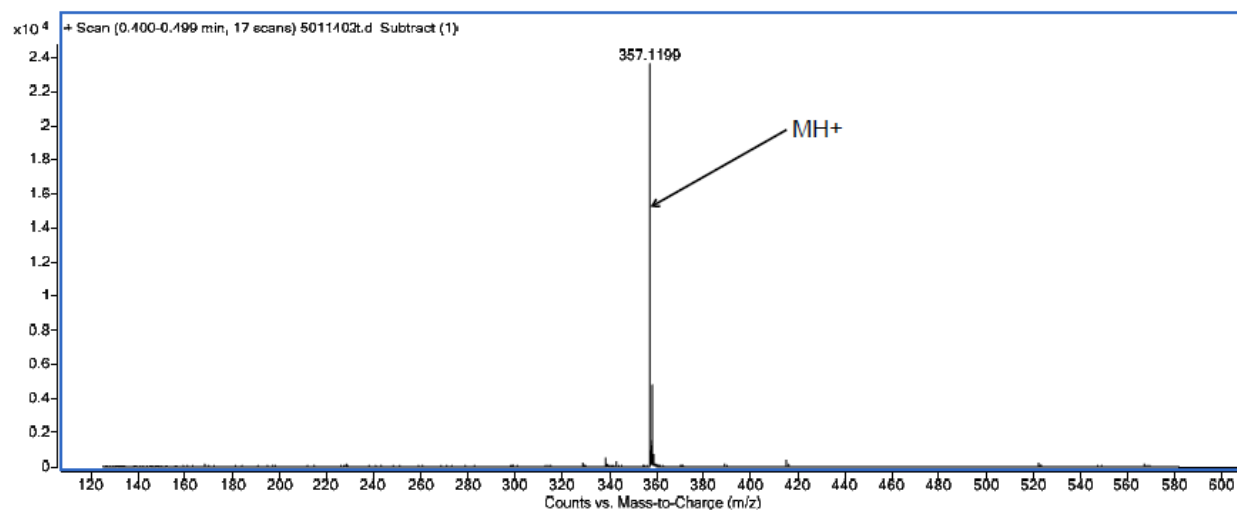
Representative HRMS spectra of compound 4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-5-(3,4,5-trimethoxy phenyl)-2H-1,2,3-triazole (2h):



Representative ^1H NMR spectra of compound 4-(4-nitrophenyl)-5-(3,4,5-trimethoxyphenyl)-2H-1,2,3-triazole (2i)



Representative ^{13}C NMR spectra of compound 4-(4-nitrophenyl)-5-(3,4,5-trimethoxyphenyl)-2H-1,2,3-triazole (2i)



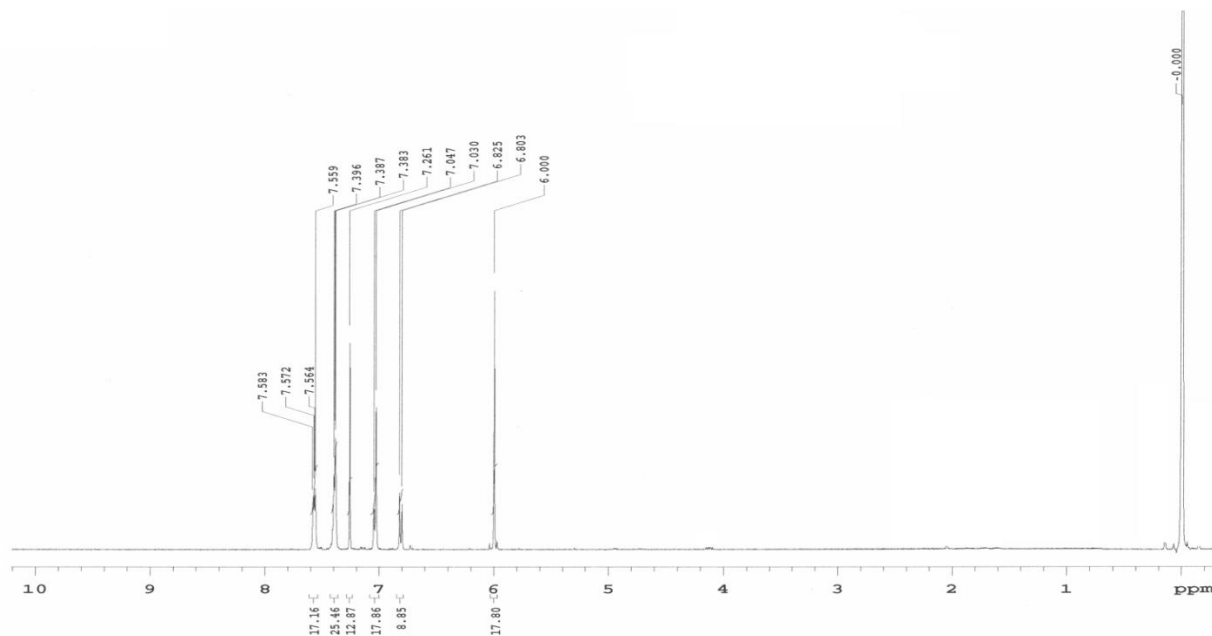
Measured Mass

357.1199

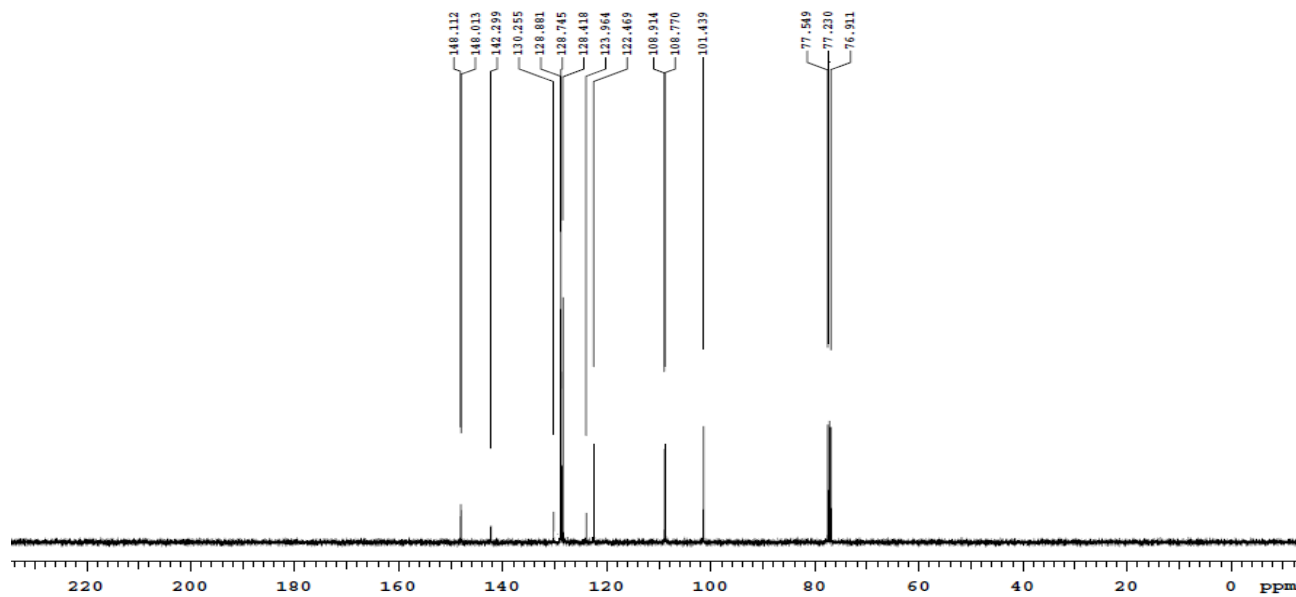
<u>Element</u>	<u>Low Limit</u>	<u>High Limit</u>
C	10	25
H	5	25
N	0	5
O	0	6

<u>Formula</u>	<u>Calculated Mass</u>	<u>mDaError</u>	<u>ppmError</u>	<u>RDB</u>
C ₁₇ H ₁₇ N ₄ O ₅	357.1193	0.6	1.6	11.5
C ₁₉ H ₁₉ N O ₆	357.1207	-0.8	-2.2	11

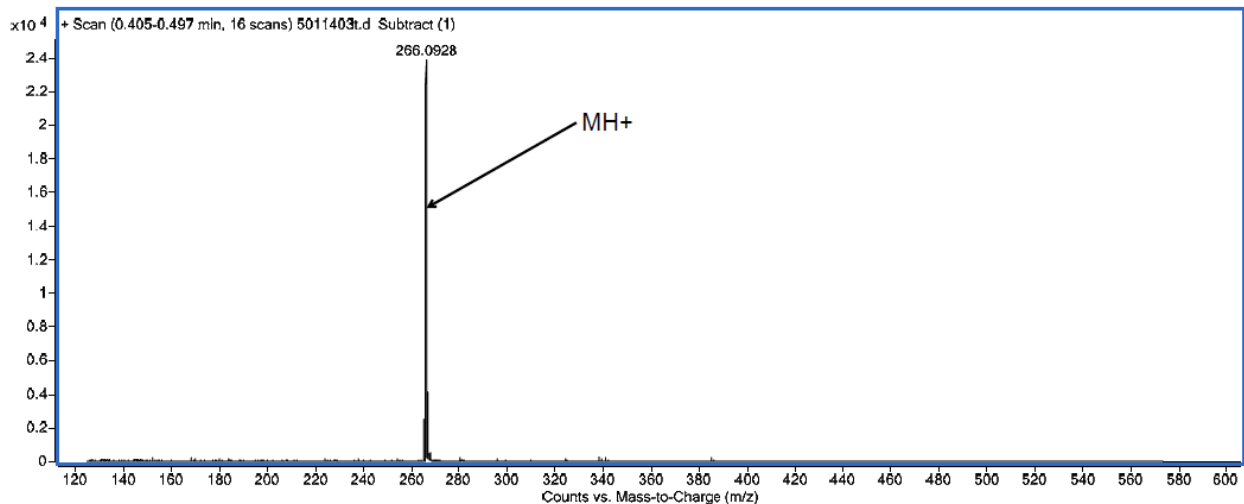
Representative HRMS spectra of compound 4-(4-nitrophenyl)-5-(3,4,5-trimethoxyphenyl)-2H-1,2,3-triazole (2i)



Representative ^1H NMR spectra of compound 4-(benzo[d][1,3]dioxol-5-yl)-5-phenyl-2H-1,2,3-triazole (2j)



Representative ^{13}C NMR spectra of compound 4-(benzo[d][1,3]dioxol-5-yl)-5-phenyl-2H-1,2,3-triazole (2j)



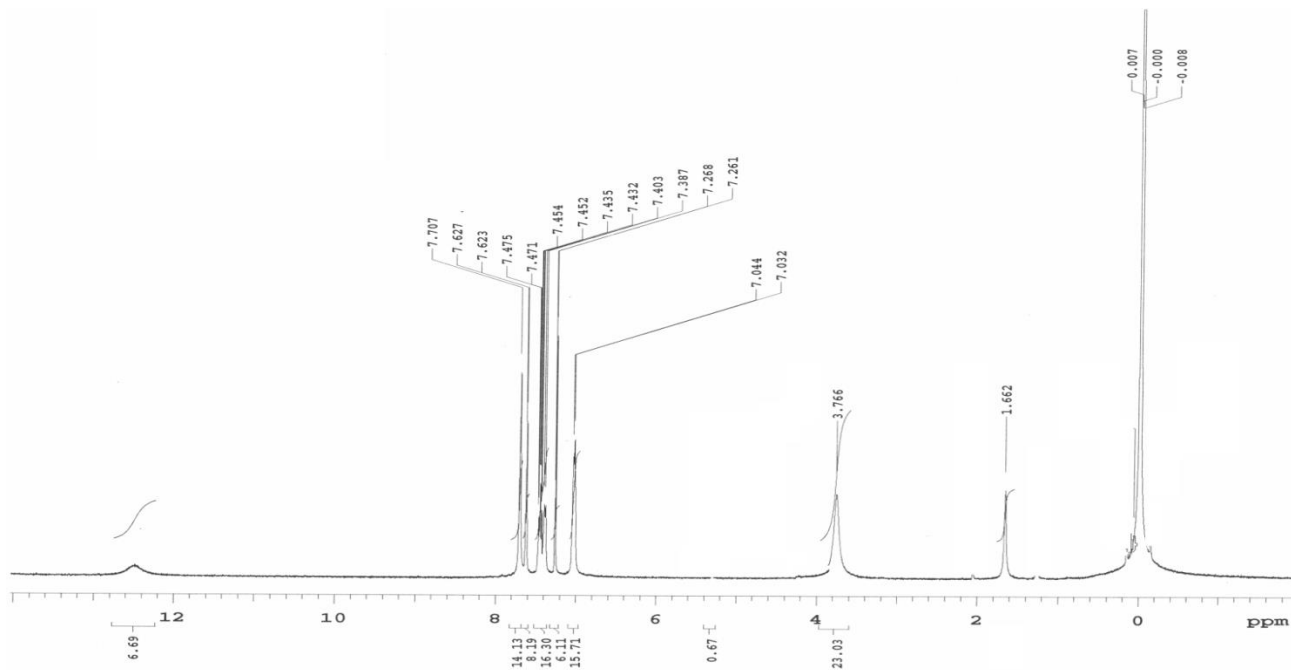
Measured Mass

266.0928

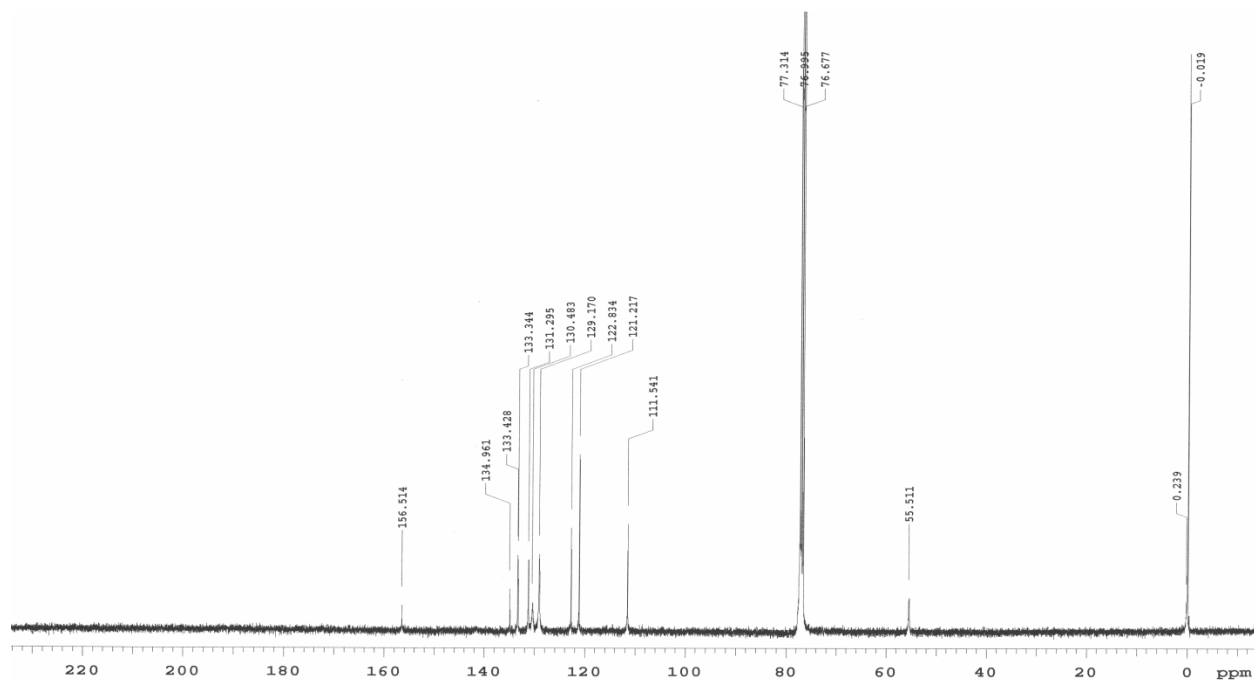
<u>Element</u>	<u>Low Limit</u>	<u>High Limit</u>
C	10	25
H	5	25
N	0	5
O	0	6

<u>Formula</u>	<u>Calculated Mass</u>	<u>mDaError</u>	<u>ppmError</u>	<u>RDB</u>
C ₁₅ H ₁₂ N ₃ O ₂	266.0924	0.4	1.5	11.5
C ₁₇ H ₁₄ O ₃	266.0937	-0.9	-3.6	11

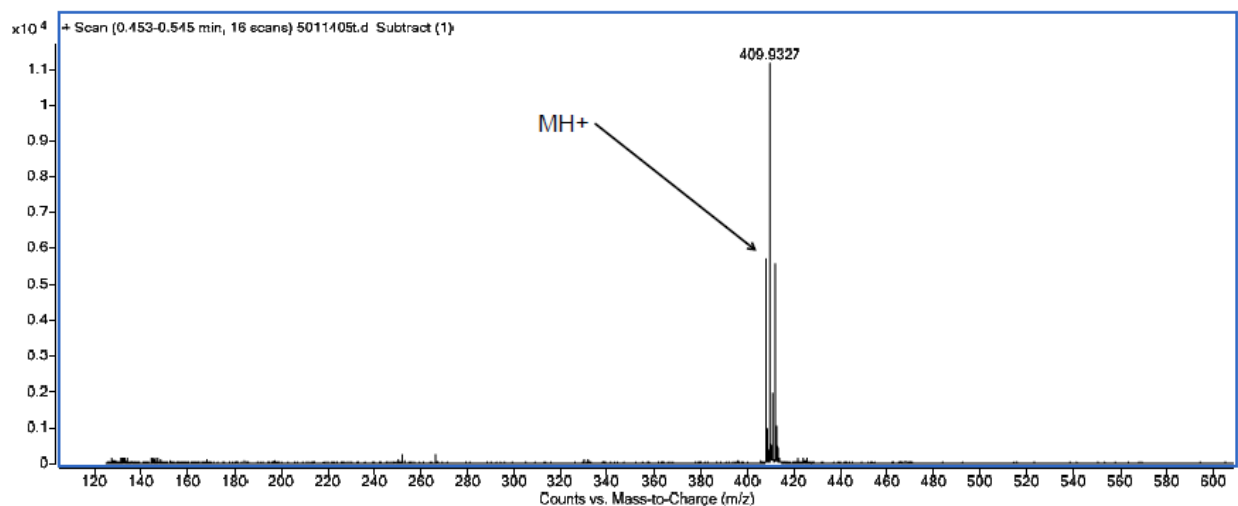
Representative HRMS spectra of compound 4-(benzo[d][1,3]dioxol-5-yl)-5-phenyl-2H-1,2,3-triazole (2j)



Representative ¹H NMR spectra of compound 4-(3,5-dibromophenyl)-5-(2-methoxyphenyl)-2H-1,2,3-triazole (2k)



Representative ¹³C NMR spectra of compound 4-(3,5-dibromophenyl)-5-(2-methoxyphenyl)-2H-1,2,3-triazole (2k)



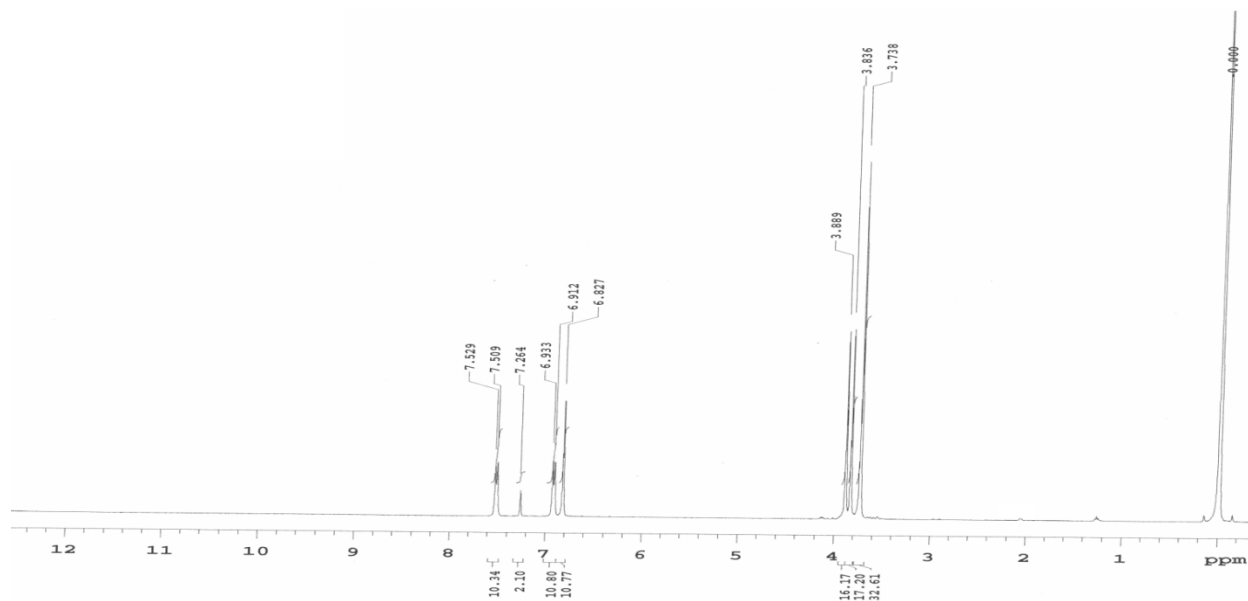
Measured Mass

407.9342

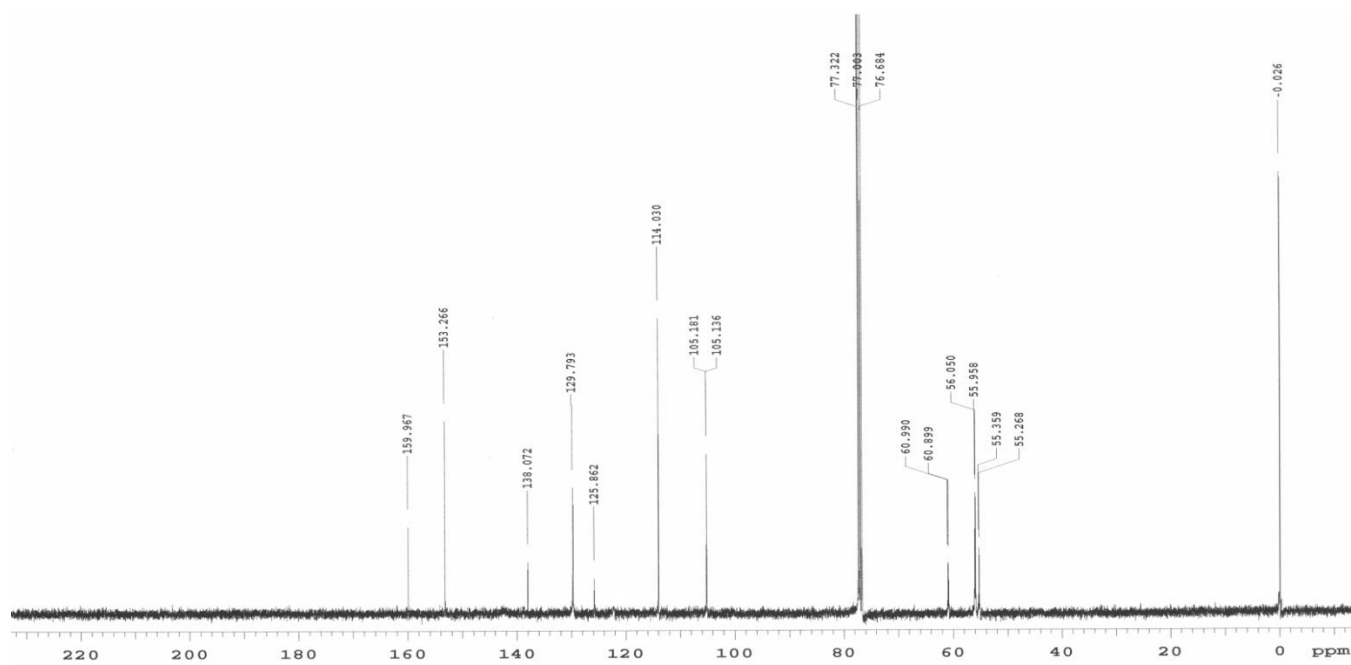
<u>Element</u>	<u>Low Limit</u>	<u>High Limit</u>
Br	0	2
C	10	25
H	5	25
N	0	5
O	0	6

<u>Formula</u>	<u>Calculated Mass</u>	<u>mDaError</u>	<u>ppmError</u>	<u>RDB</u>
C ₁₅ H ₁₂ N ₃ O Br ₂	407.9342	0.0	0.1	10.5
C ₁₇ H ₁₄ O ₂ Br ₂	407.9355	-1.3	-3.2	10

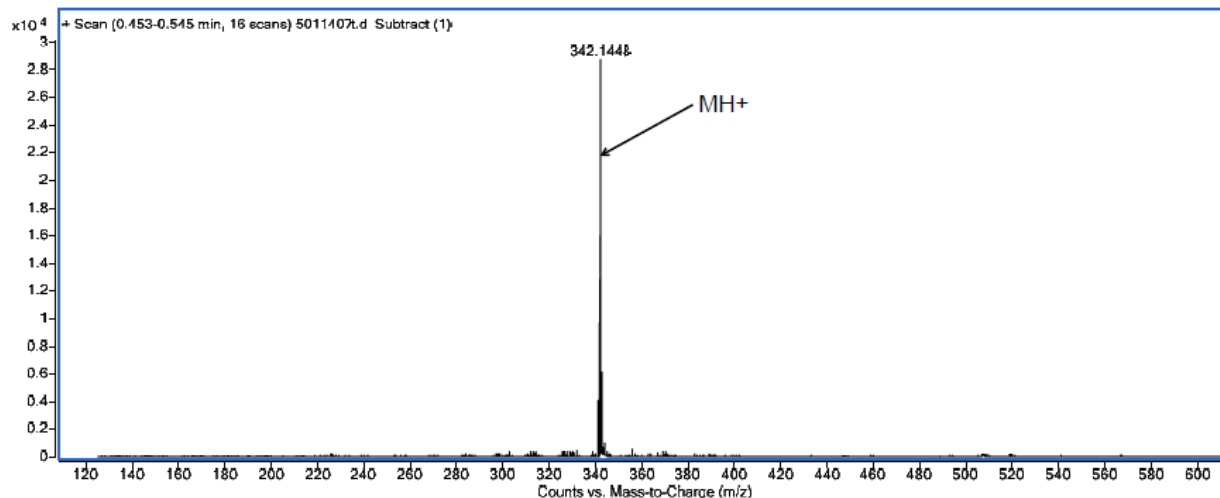
Representative HRMS spectra of compound 4-(3,5-dibromophenyl)-5-(2-methoxyphenyl)-2H-1,2,3-triazole (2k)



Representative ¹H NMR spectra of compound 4-(4-methoxyphenyl)-5-(3,4,5-trimethoxyphenyl)-2H-1,2,3-triazole (2l)



Representative ¹³C NMR spectra of compound 4-(4-methoxyphenyl)-5-(3,4,5-trimethoxyphenyl)-2H-1,2,3-triazole (2l)



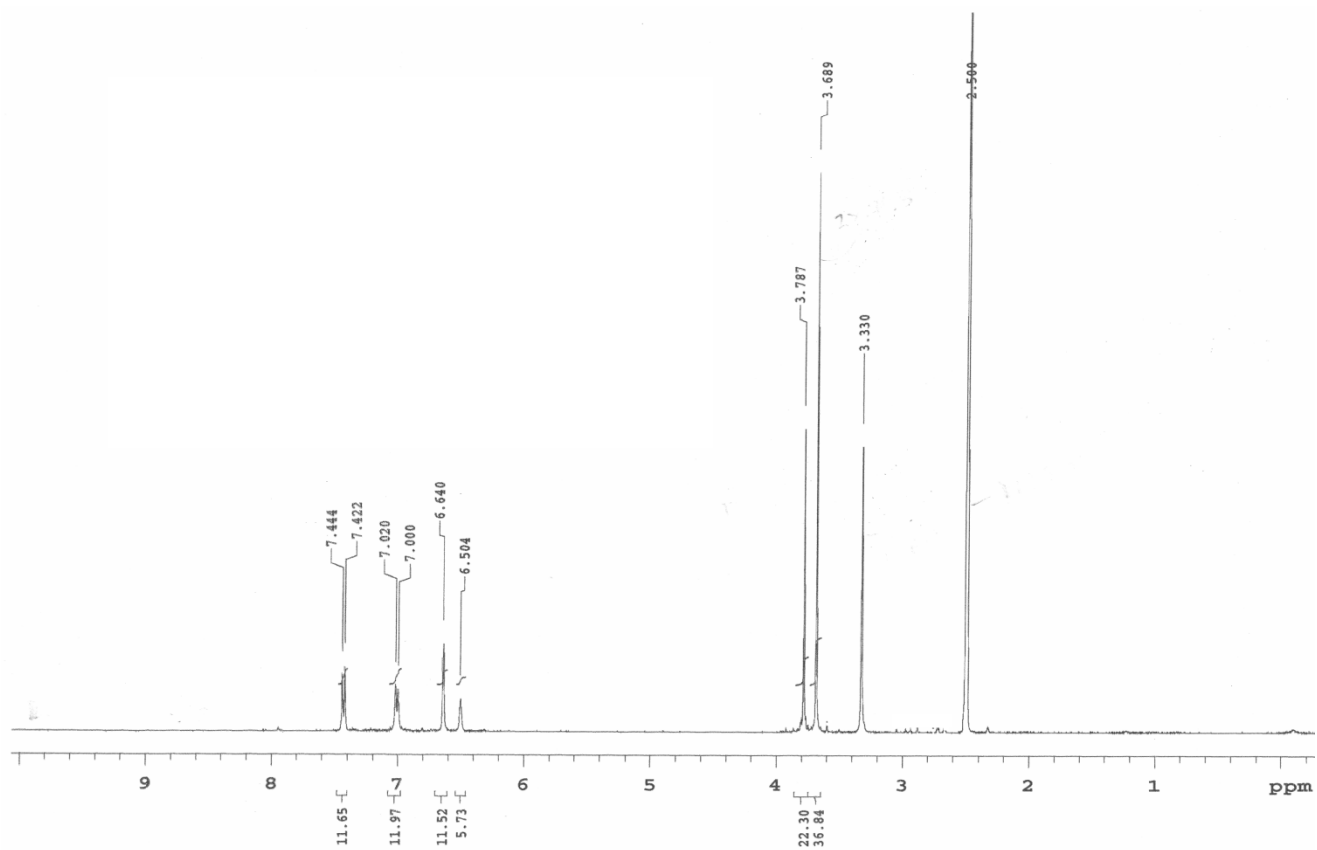
Measured Mass

342.1448

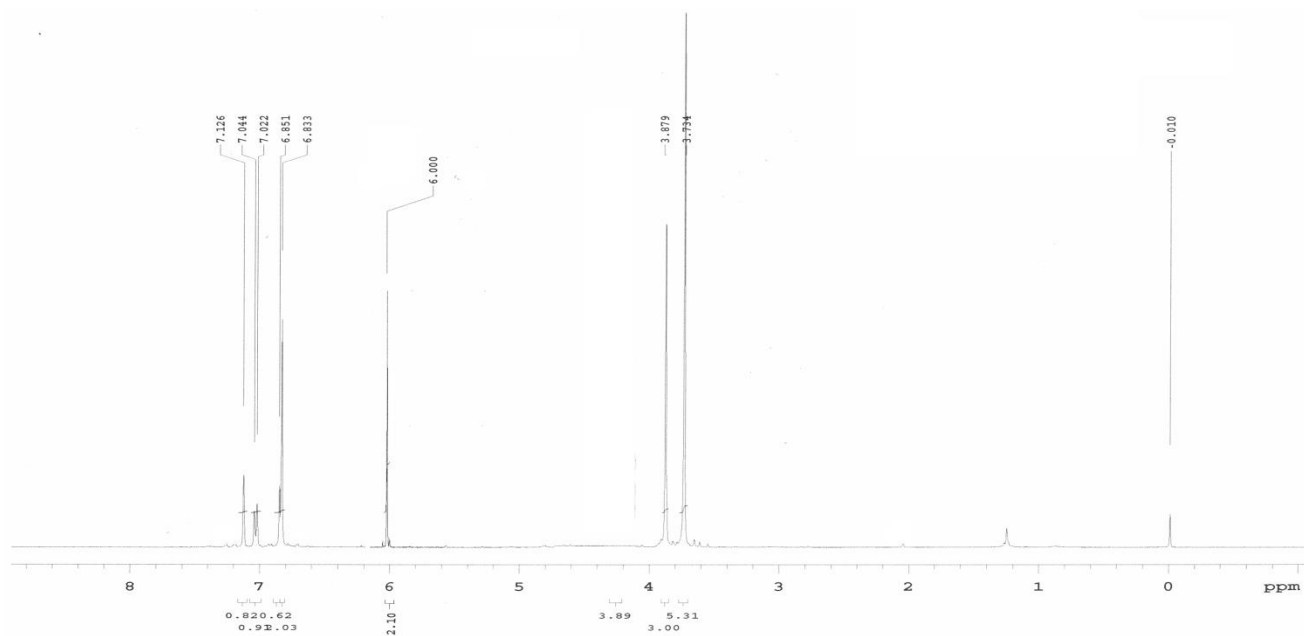
<u>Element</u>	<u>Low Limit</u>	<u>High Limit</u>
C	10	25
H	5	25
N	0	5
O	0	6

<u>Formula</u>	<u>Calculated Mass</u>	<u>mDaError</u>	<u>ppmError</u>	<u>RDB</u>
C ₁₈ H ₂₀ N ₃ O ₄	342.1448	0.0	-0.1	10.5
C ₂₀ H ₂₂ O ₅	342.1462	-1.4	-4.0	10

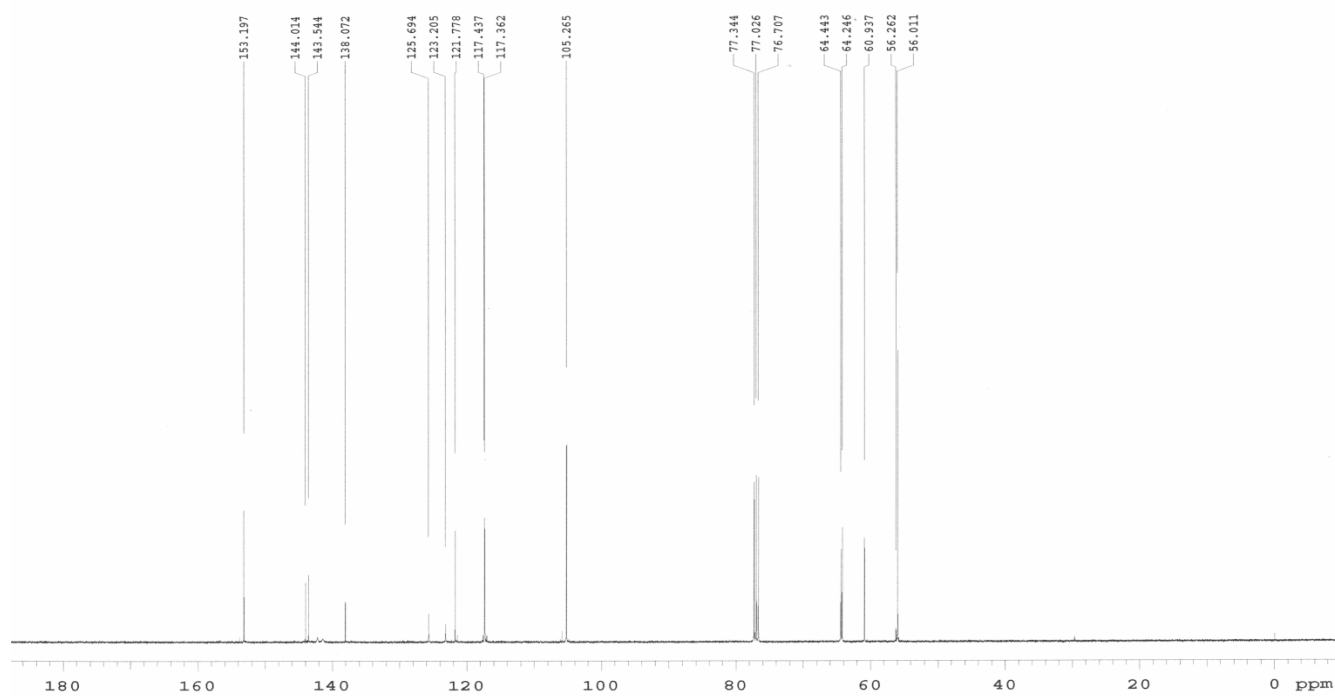
Representative HRMS spectra of compound 4-(4-methoxyphenyl)-5-(3,4,5-trimethoxyphenyl)-2H-1,2,3-triazole (2l)



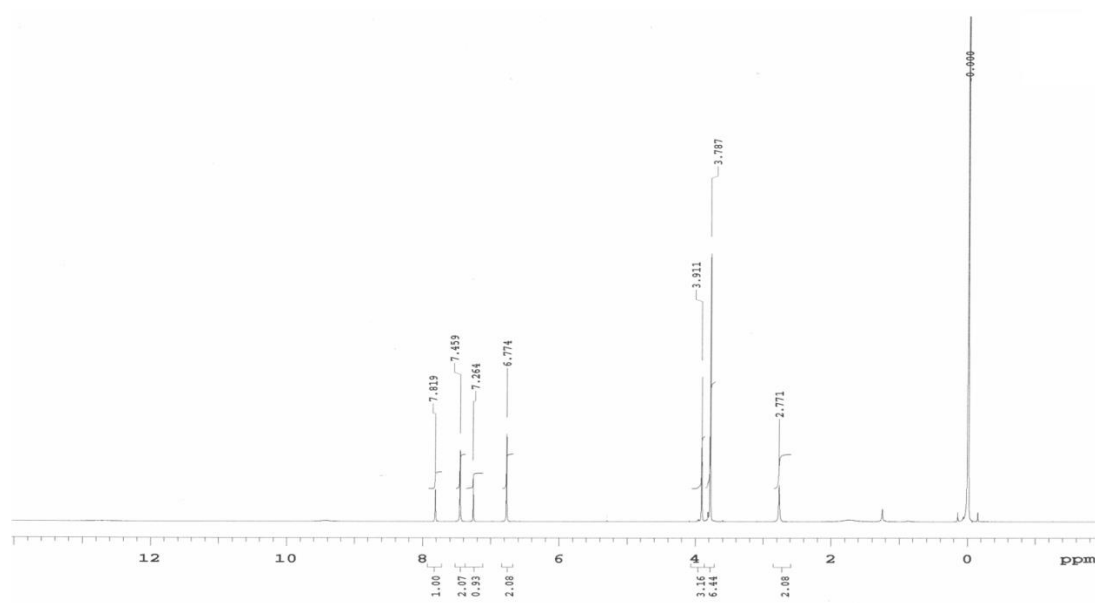
Representative ¹H NMR spectra of compound 4-(3,5-dimethoxyphenyl)-5-(4-methoxyphenyl)-2H-1,2,3-triazole (2m):



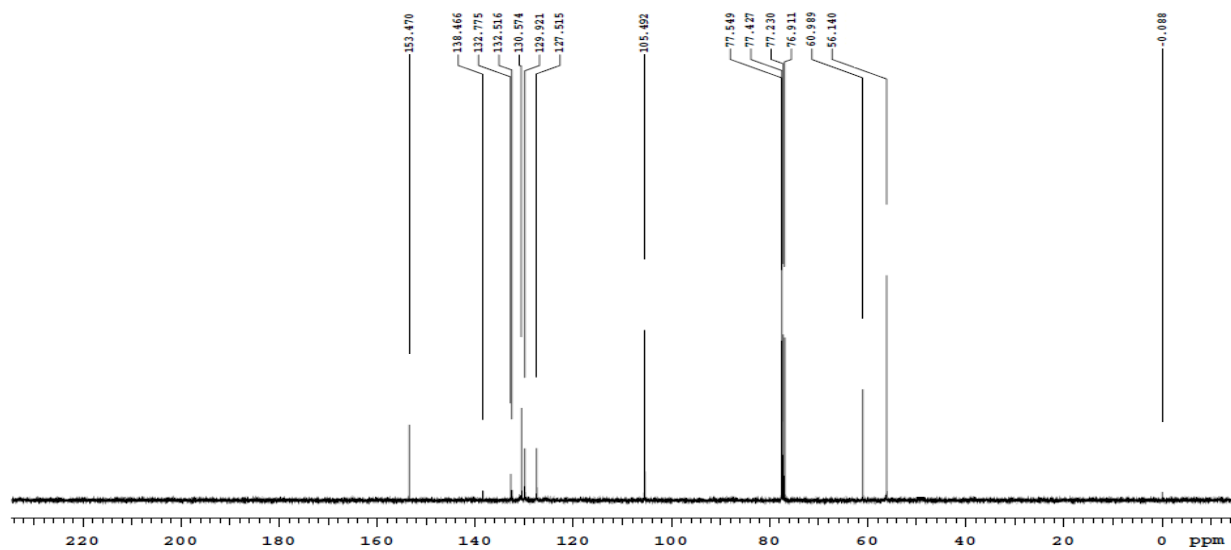
Representative ^1H NMR spectra of 4-(benzo[d][1,3]dioxol-5-yl)-5-(3,4,5-trimethoxyphenyl)-2H-1,2,3-triazole (2n)



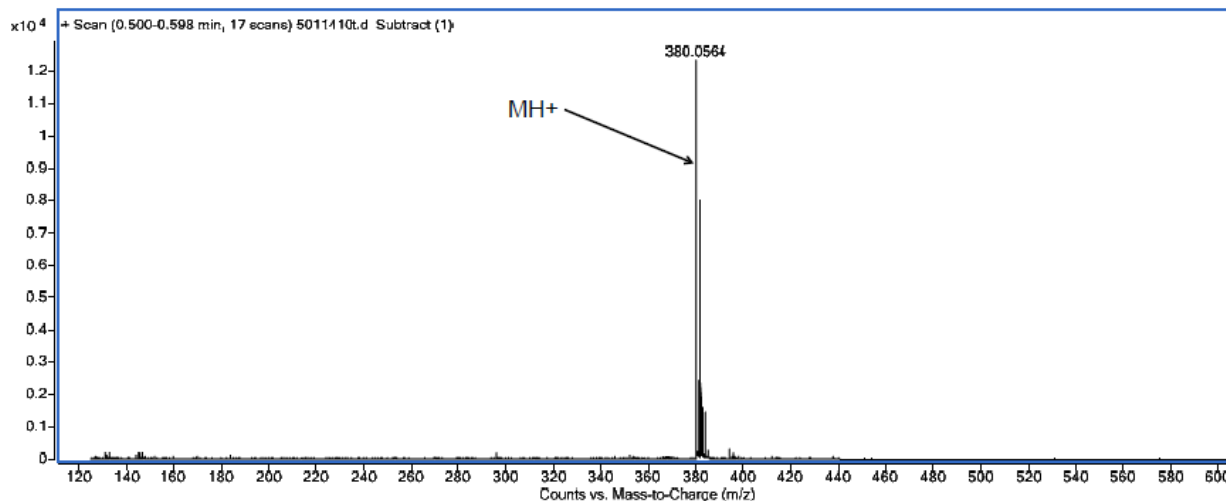
Representative ^{13}C NMR spectra of compound 4-(benzo[d][1,3]dioxol-5-yl)-5-(3,4,5-trimethoxyphenyl)-2H-1,2,3-triazole (2n)



Representative ^1H NMR spectra of compound 4-(3,4-dichlorophenyl)-5-(3,4,5-trimethoxyphenyl)-2H-1,2,3-triazole (2o)



Representative ^{13}C NMR spectra of compound 4-(3,4-dichlorophenyl)-5-(3,4,5-trimethoxyphenyl)-2H-1,2,3-triazole (2o)



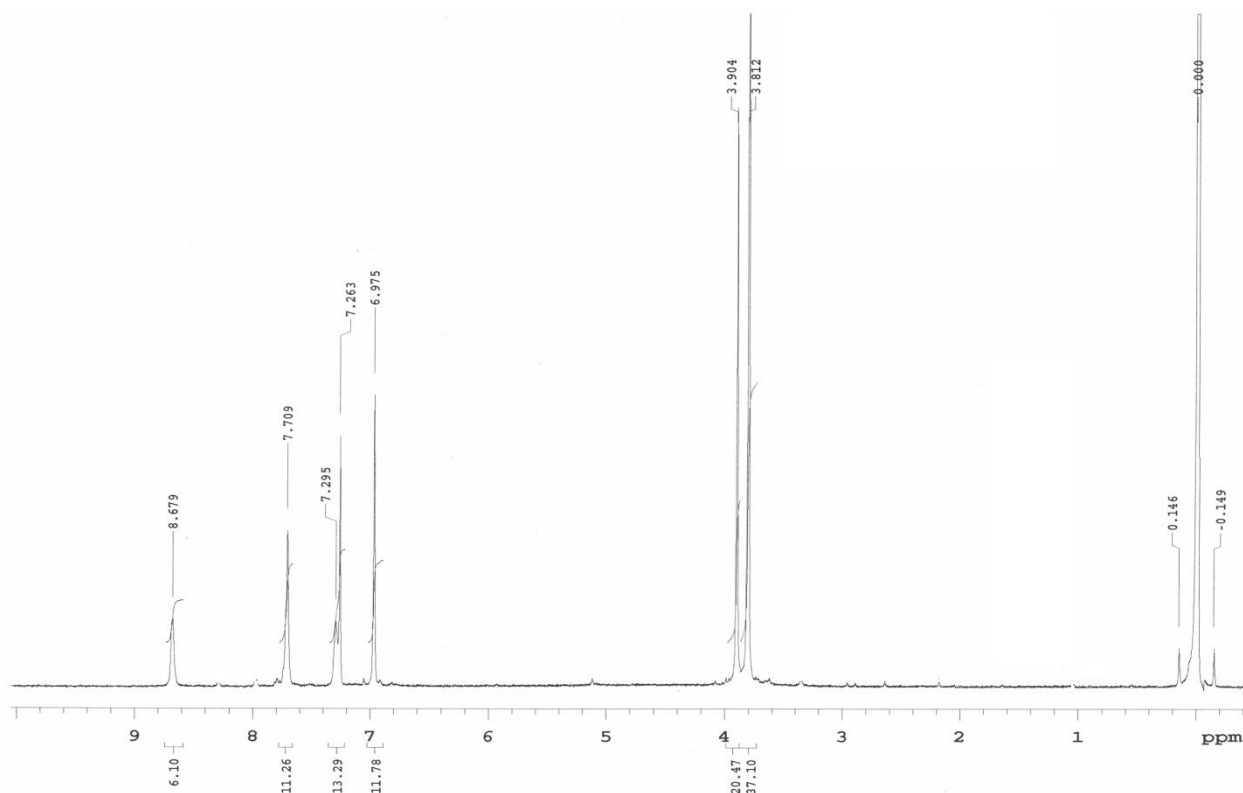
Measured Mass

380.0564

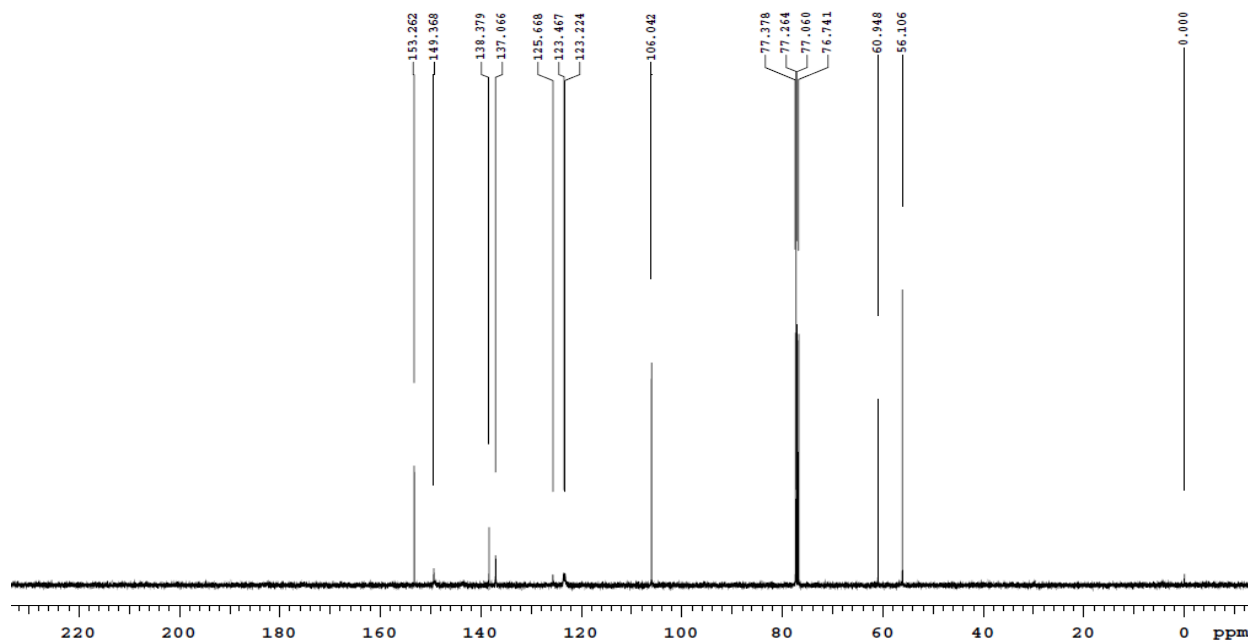
<u>Element</u>	<u>Low Limit</u>	<u>High Limit</u>
C	10	25
H	5	25
N	0	5
O	0	6
Cl	0	2

<u>Formula</u>	<u>Calculated Mass</u>	<u>mDaError</u>	<u>ppmError</u>	<u>RDB</u>
C ₁₇ H ₁₆ N ₃ O ₃ Cl ₂	380.0563	0.1	0.2	10.5
C ₂₄ H ₆ N ₅ O	380.0567	-0.3	-0.8	24.5
C ₂₀ H ₁₃ N ₂ O ₄ Cl	380.0558	0.6	1.5	15
C ₂₃ H ₁₀ N ₅ O	380.0553	1.1	2.8	19.5
C ₁₉ H ₁₈ O ₄ Cl ₂	380.0577	-1.3	-3.3	10

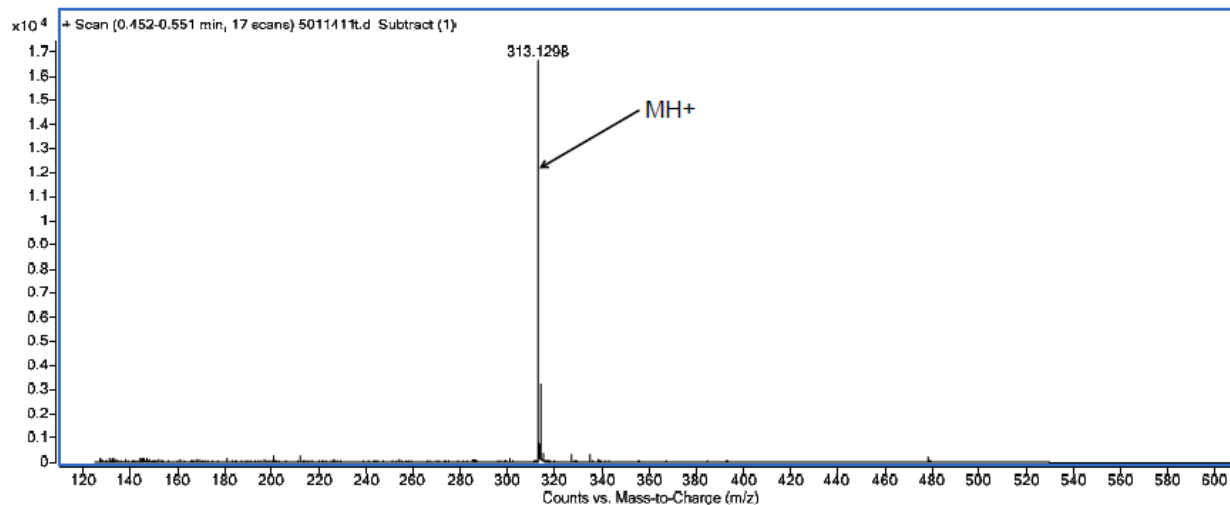
Representative HRMS spectra of compound 4-(3,4-dichlorophenyl)-5-(3,4,5-trimethoxyphenyl)-2H-1,2,3-triazole (2o)



Representative ^1H NMR spectra of compound 2-(5-(3,4,5-trimethoxyphenyl)-2H-1,2,3-triazol-4-yl)pyridine (2p)



Representative ^{13}C NMR spectra of compound 2-(5-(3,4,5-trimethoxyphenyl)-2H-1,2,3-triazol-4-yl)pyridine (2p)



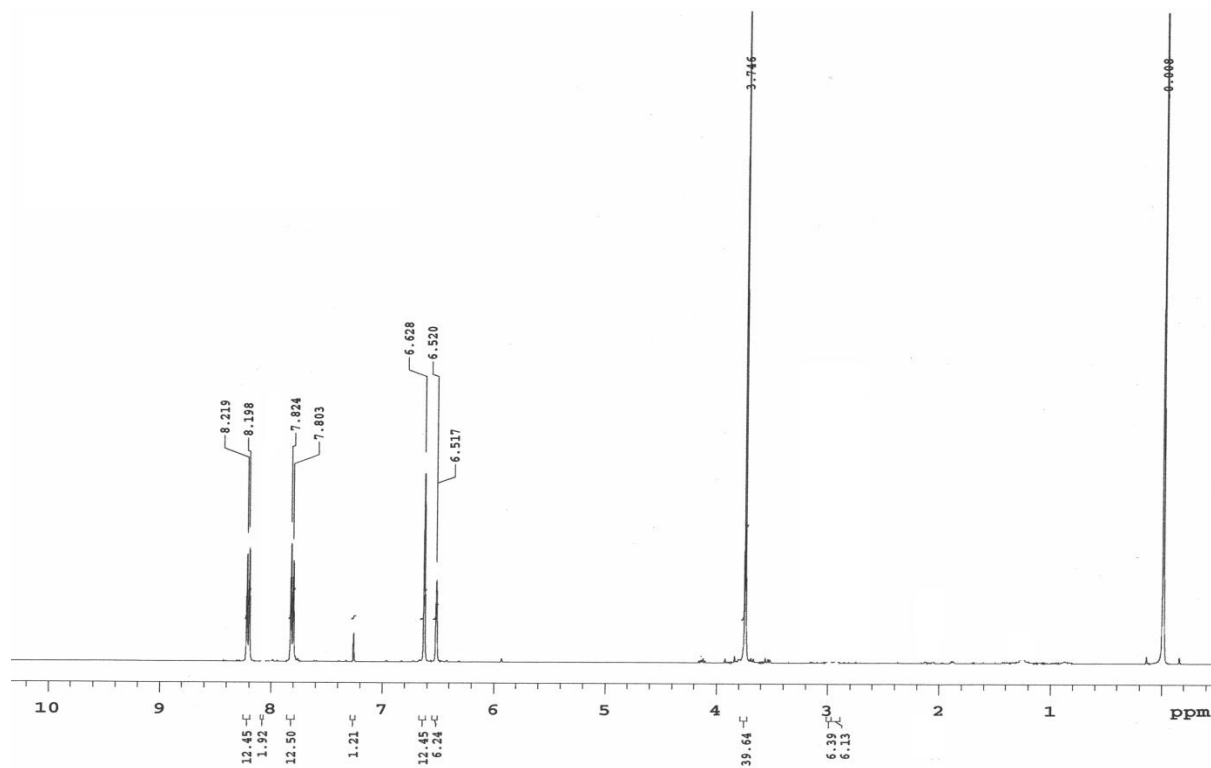
Measured Mass

313.1298

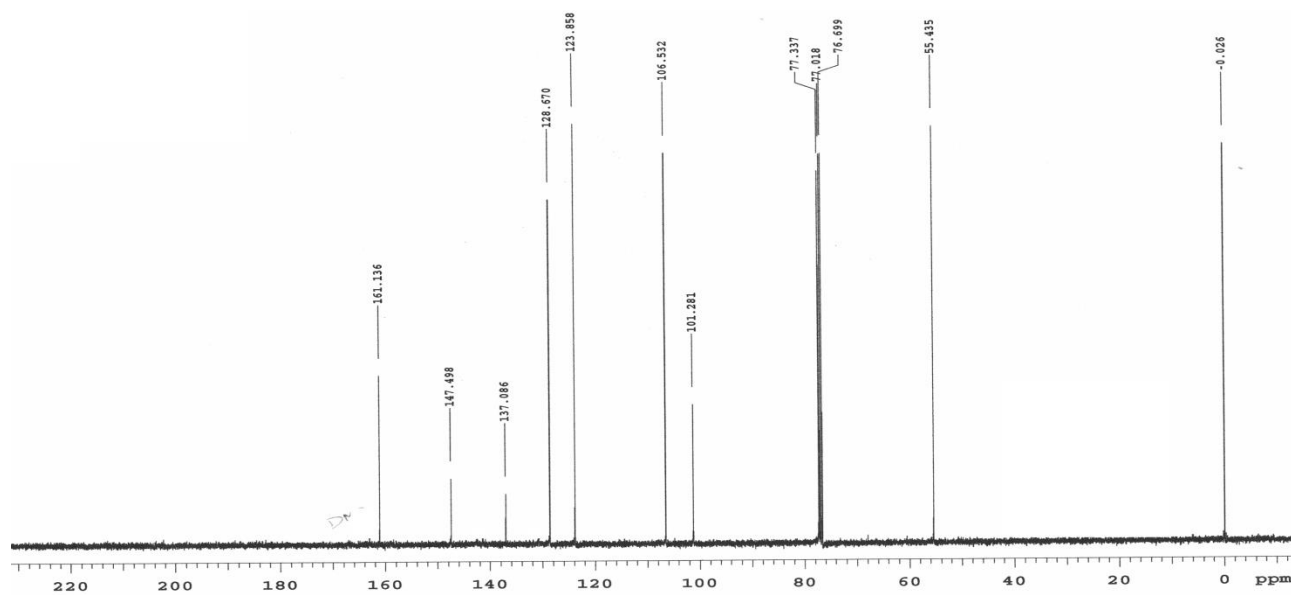
<u>Element</u>	<u>Low Limit</u>	<u>High Limit</u>
C	10	25
H	5	25
N	0	5
O	0	6

<u>Formula</u>	<u>Calculated Mass</u>	<u>mDaError</u>	<u>ppmError</u>	<u>RDB</u>
C ₁₆ H ₁₇ N ₄ O ₃	313.1295	0.3	0.9	10.5
C ₁₈ H ₁₉ N ₄ O ₄	313.1309	-1.1	-3.4	10

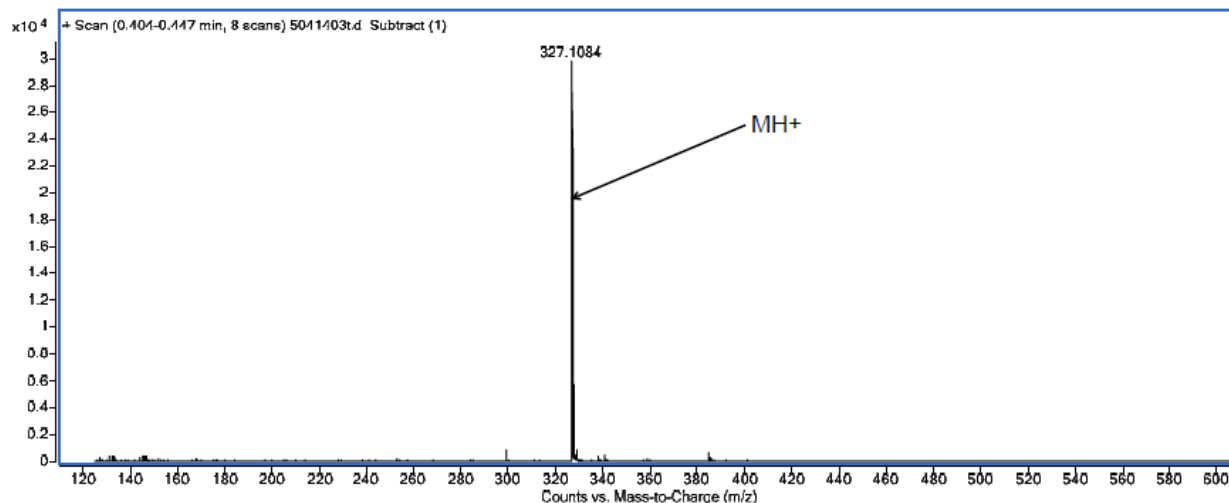
Representative HRMS spectra of compound 2-(5-(3,4,5-trimethoxyphenyl)-2H-1,2,3-triazol-4-yl)pyridine (2p)



Representative ^1H NMR spectra of compound 4-(3,5-dimethoxyphenyl)-5-(4-nitrophenyl)-2H-1,2,3-triazole (2q)



Representative ^{13}C NMR spectra of compound 4-(3,5-dimethoxyphenyl)-5-(4-nitrophenyl)-2H-1,2,3-triazole (2q)



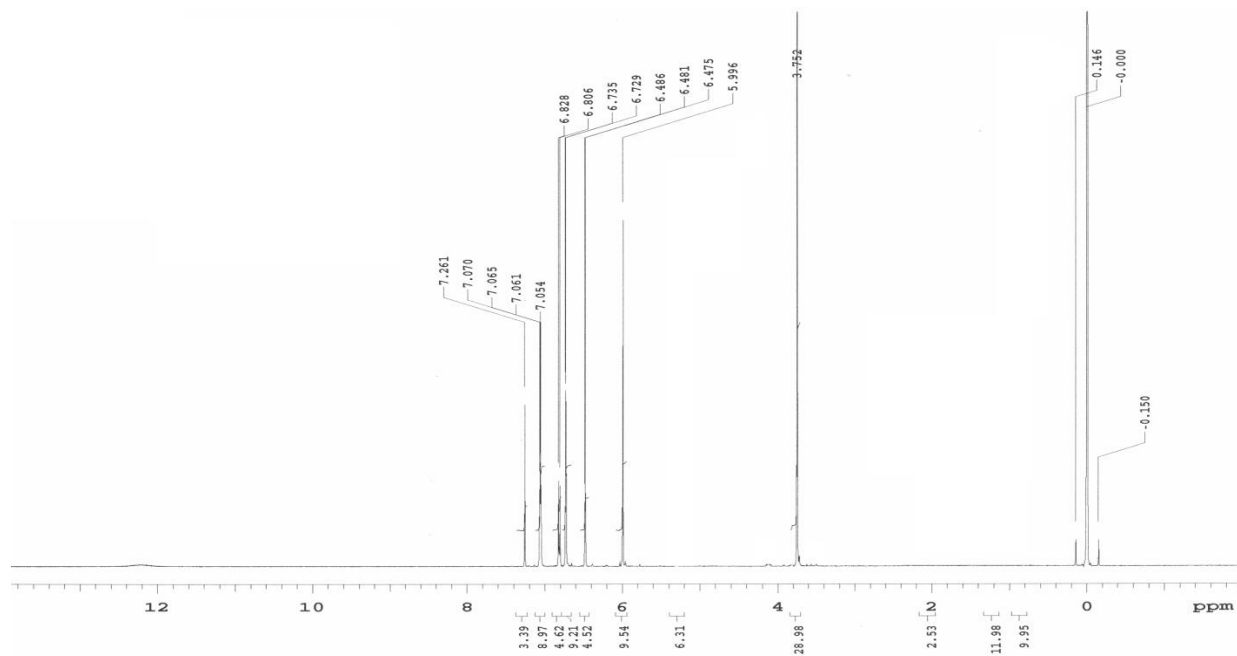
Measured Mass

327.1084

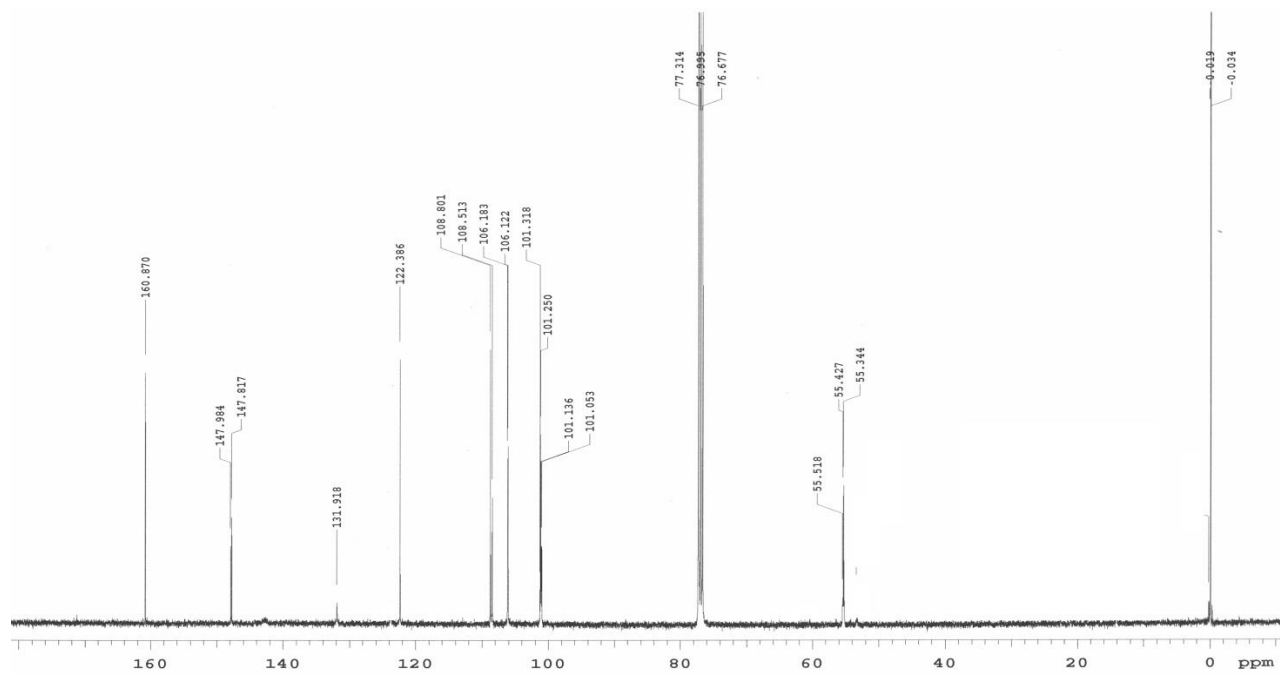
<u>Element</u>	<u>Low Limit</u>	<u>High Limit</u>
C	10	25
H	5	25
N	0	5
O	0	6

<u>Formula</u>	<u>Calculated Mass</u>	<u>mDaError</u>	<u>ppmError</u>	<u>RDB</u>
C ₁₆ H ₁₅ N ₄ O ₄	327.1088	-0.4	-1.2	11.5

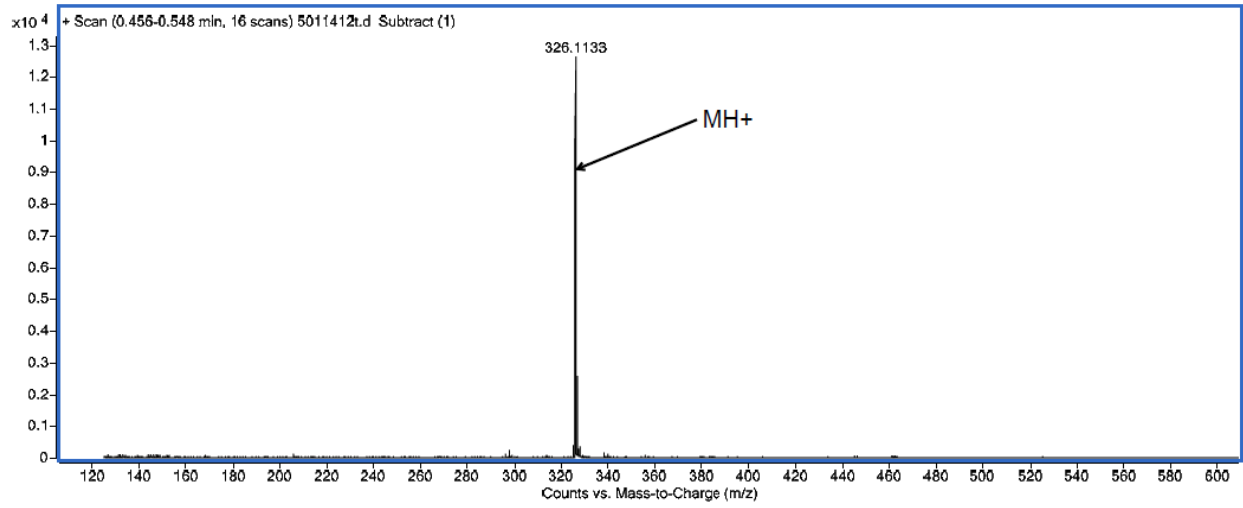
Representative HRMS spectra of compound 4-(3,5-dimethoxyphenyl)-5-(4-nitrophenyl)-2H-1,2,3-triazole (2q)



Representative ^1H NMR spectra of compound 4-(benzo[d][1,3]dioxol-5-yl)-5-(3,5-dimethoxyphenyl)-2H-1,2,3-triazole (2r)



Representative ^{13}C NMR spectra of compound 4-(benzo[d][1,3]dioxol-5-yl)-5-(3,5-dimethoxyphenyl)-2H-1,2,3-triazole (2r)

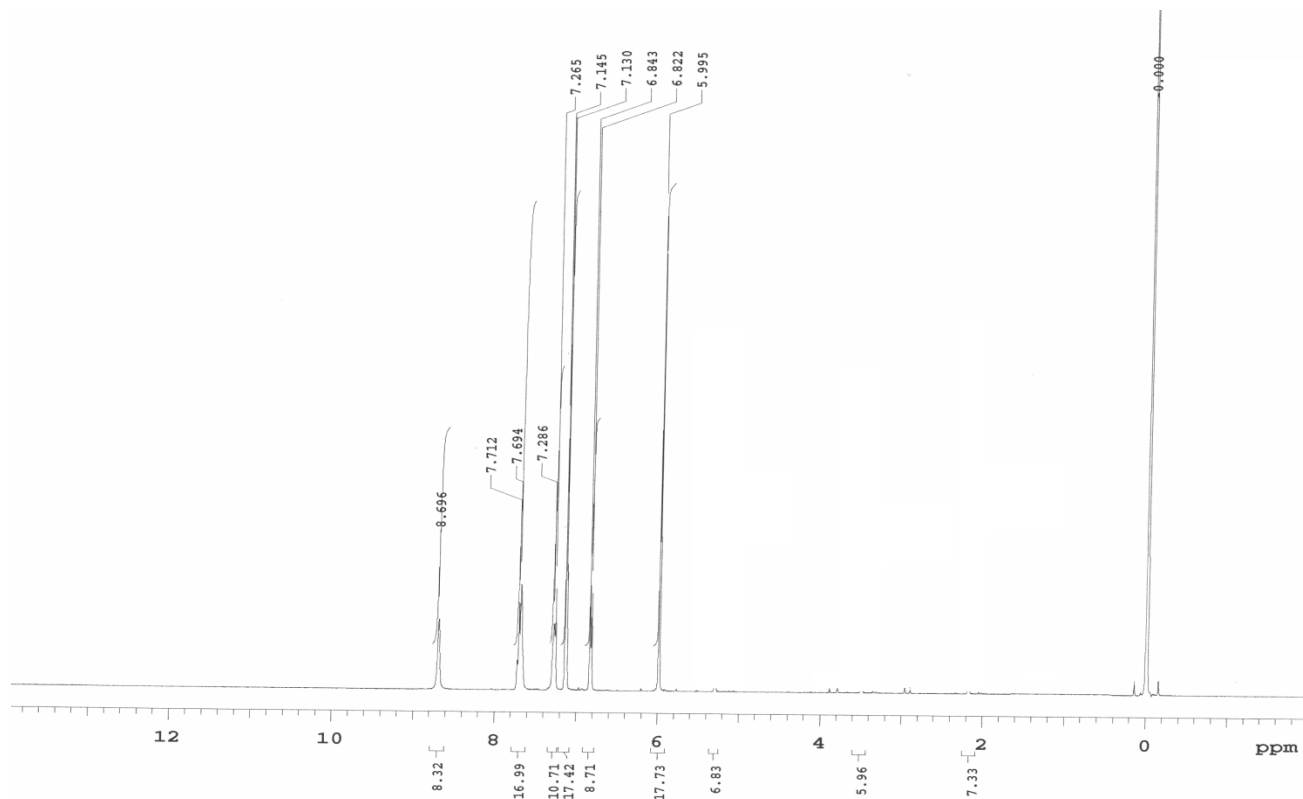


Measured Mass 326.1133

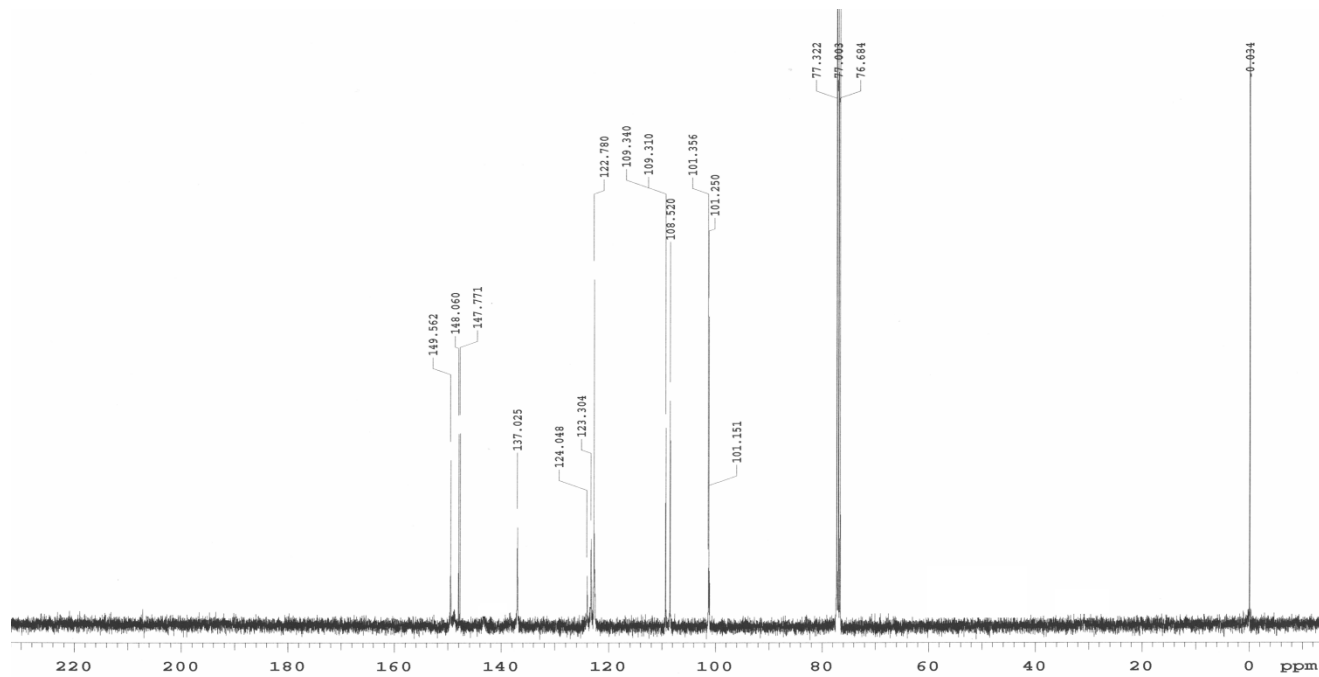
<u>Element</u>	<u>Low Limit</u>	<u>High Limit</u>
C	10	25
H	5	25
N	0	5
O	0	6

<u>Formula</u>	<u>Calculated Mass</u>	<u>mDaError</u>	<u>ppmError</u>	<u>RDB</u>
C ₁₇ H ₁₆ N ₃ O ₄	326.1135	-0.2	-0.7	11.5
C ₁₉ H ₁₈ O ₅	326.1149	-1.6	-4.8	11

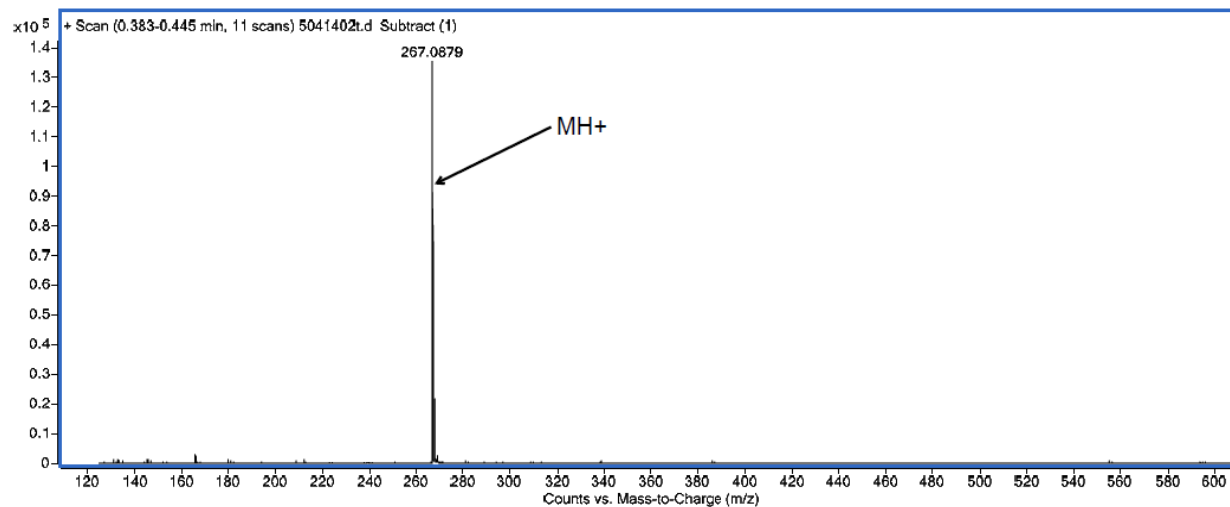
Representative HRMS spectra of compound 4-(benzo[d][1,3]dioxol-5-yl)-5-(3,5-dimethoxyphenyl)-2H-1,2,3-triazole (2r)



Representative ^1H NMR spectra of compound 2-(5-(benzo[d][1,3]dioxol-5-yl)-2H-1,2,3-triazol-4-yl)pyridine (2s)



Representative ^{13}C NMR spectra of compound 2-(5-(benzo[d][1,3]dioxol-5-yl)-2H-1,2,3-triazol-4-yl)pyridine (2s)



Measured Mass

267.0879

<u>Element</u>	<u>Low Limit</u>	<u>High Limit</u>
C	10	25
H	5	25
N	0	5
O	0	6

<u>Formula</u>	<u>Calculated Mass</u>	<u>mDaError</u>	<u>ppmError</u>	<u>RDB</u>
C ₁₄ H ₁₁ N ₄ O ₂	267.0877	0.2	0.9	11.5
C ₁₆ H ₁₃ N O ₃	267.0890	-1.1	-4.1	11

Representative HRMS spectra of compound 2-(5-(benzo[d][1,3]dioxol-5-yl)-2H-1,2,3-triazol-4-yl)pyridine (2s)