# Efficient Synthesis of a Novel Resorcyclide as Anticancer Agent Based on Hsp90 Inhibition

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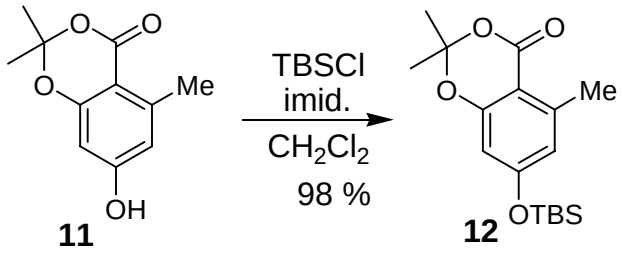
## Supporting information

## General Methods

All non-aqueous reactions were carried out in oven-dried glassware under a slight positive pressure of argon unless otherwise noted. All reagents were commercially available and used without further purification from Sigma-Aldrich and TCI America, unless indicated otherwise. Solvents were reagent grade and purified by standard techniques: THF was distilled from Na-benzophenone or filtered through a dry-solvent system; $CH_2Cl_2$ was distilled from $CaH_2$ or filtered through a dry-solvent system; all other solvents were Aldrich "anhydrous" grade solvents, unless indicated otherwise. Reactions were magnetically stirred and monitored by thin layer chromatography on Merck silica gel 60-$F_{254}$ coated 0.25 mm plates. Preparative thin layer chromatography was performed with Merck silica gel 60-$F_{254}$ coated 0.50 mm plates. Flash chromatography was performed with Sorbent Technology silica gel 60 (particle size 32-63 μm), unless indicated otherwise. Yields reported are for isolated, spectroscopically pure compounds. Melting points are uncorrected. $CDCl_3$ was allowed to stand over $K_2CO_3$ and 4 A MS to neutralize and dry prior to NMR sample preparation. NMR spectra were recorded on Bruker DRX 300

or 400 MHz and DMX 500MHz spectrometers. Proton and Carbon chemical shifts were referenced to residual solvent peaks. Abbreviations for $^1$H NMR: s = singlet, d = doublet, t = triplet, q = quartlet, m = multiplet, or br = broad. IR spectra were recorded on a Perkin-Elmer Paragon 1000 FTIR spectrometer. High resolution mass spectra were acquired in the Columbia University Mass Spectral Core facility on a JEOL HX110 spectrometer. Optical rotations were measured on a JASCO DIP-1000 spectrometer.

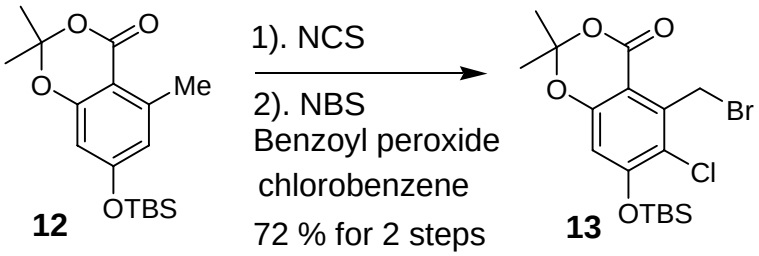
## Experimental and Spectra data:




**11** **12**

**Procedure:** To 3.63 g compound **11** (17.5 mmol, 1.0 eq.) in 60 ml of anhydrous $CH_2Cl_2$ was added TBSCl (2.90 g, 19.2 mmol, 1.1 eq.) and imidazole (1.43 g, 21.0 mmol, 1.2 eq.) at rt. After stirring for 6h, pH=7 buffer solution was added to the reaction mixture, the organic layer was separated and the aqueous layer was extracted with $CH_2Cl_2$ (3 x 10 ml). The combined organic layers were washed with brine and dried over $MgSO_4$, concentrated and purified via flash chromatography (Hexane / EA 10 / 1) to afford product **12** (5.50 g, 17.3 mmol, 98 %) as a white solid. m.p. 96-98 $^oC$

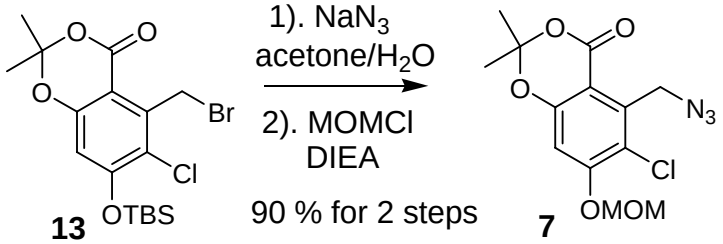
**Analytical data:** $^1$H NMR (400MHz, $CDCl_3$): δ 6.37 (d, 1H, *J* = 2.4 Hz), 6.23 (d, 1H, *J* = 2.4 Hz), 2.59 (s, 3H), 1.66 (s, 6H), 1.01 (s, 9H), 0.22 (s, 6H); $^{13}$C NMR (100MHz, $CDCl_3$): δ 161.3, 160.2, 158.4, 118.0, 105.8, 105.5, 104.7, 25.4, 25.3, 22.0, 17.9, -4.6. MS (EI+) calcd for [M+H] $C_{17}H_{27}O_4Si$: 323.1679; found 323.1686.




**12** **13**

**Procedure:** To a solution of compound **12** (2.0 g, 6.2 mmol, 1.0 eq.) in 10.0 mL of anhydrous chlorobenzene was added 915 mg of *N*-chlorosuccinimide (6.8 mmol, 1.1 eq.). The reaction mixture was stirred at 100 $^{o}$C for 12 h. After the reaction mixture was cooled to rt, freshly purified *N*-bromosuccinimide (1.65g, 9.3 mmol, 1.5 eq.) and benzoyl peroxide (750 mg, 3.1 mmol, 0.5 eq.) were added. The reaction mixture was stirred at 100 $^{o}$C for 16 h. Then the reaction mixture was cooled to rt, and quenched with 10 mL sat. $NaHSO_3$, extracted with ether (3 x 20 mL). The combined organic phase was washed with brine, dried over $MgSO_4$, concentrated and purified by flash chromatography (Hexane / EA: 10 / 1) to afford product **13** (1.94 g, 4.4 mmol, 72%) as a white solid. m.p. 102-103 $^{o}$C

**Analytical data:** $^{1}$H NMR (400MHz, $CDCl_3$): δ 6.42 (s, 1H), 5.34 (bs, 2H), 1.69 (s, 6H), 1.04 (s, 9H), 0.28 (s, 6H); $^{13}$C NMR (100MHz, $CDCl_3$): δ 158.7, 157.6, 156.4, 140.1, 130.0, 128.4, 122.8, 107.8, 105.3, 26.8, 25.4, 25.2, 18.1, -4.5, -4.6; MS (EI+) calcd for [M+H] $C_{17}H_{25}BrClO_4Si$: 435.0395; found 435.0382.

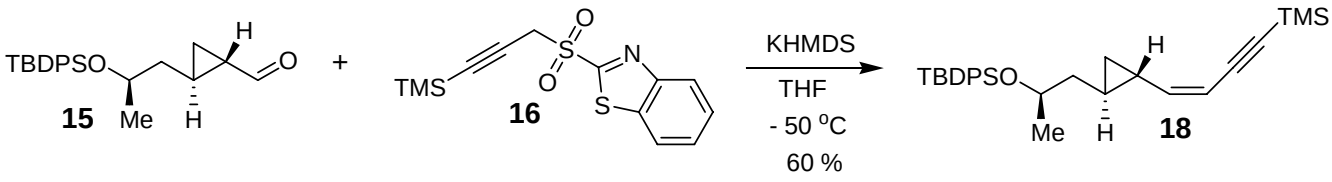



**13** **7**

**Procedure:** To a solution of benzylbromide **13** (1.23 g, 2.8 mmol, 1.0 eq.) in 6 mL of acetone and 2 mL of water was added 360 mg of sodium azide (5.6 mmol, 2.0 eq.) at 0 $^{o}$C. The reaction mixture was stirred at rt for 1 h. Then the reaction mixture was concentrated *in vacuo*, and extracted with EtOAc (3 x

20 mL). The combined organic phase was washed with water and brine, dried over $MgSO_4$, concentrated *in vacuo*. The crude product was directly used for the next step. To a solution of the crude material in 20 mL of anhydrous $CH_2Cl_2$ was added MOMCl (260 μL, 3.4mmol, 1.2 eq.), followed by DIEA (630 μL, 3.6 mmol, 1.3 eq.) at 0 $^oC$. The reaction mixture was stirred at rt for 2h, before it was quenched by water. The organic layer was separated and the aqueous layer was extracted with $CH_2Cl_2$ (3 x 20 mL). The combined organic layers were washed with brine and dried over $MgSO_4$, concentrated and purified via flash chromatography (Hexane / EA 5 / 1) to afford benzylazide **7** (820 mg, 2.5 mmol, 90 %) as a white solid. m.p. 86-88 $^oC$

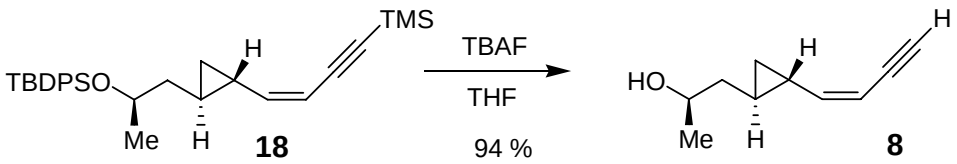
**Analytical data:** $^1H$ NMR (400MHz, $CDCl_3$): δ 6.80 (s, 1H), 5.29 (s, 2H), 5.05 (s, 2H), 3.49 (s, 3H), 1.69 (s, 6H); $^{13}C$ NMR (100MHz, $CDCl_3$): δ 159.0, 158.3, 156.6, 136.8, 120.2, 106.1, 105.4, 103.7, 94.7, 56.5, 47.2, 39.0, 25.1; MS (EI+) calcd for [M-$N_2$] $C_{13}H_{14}ClNO_5$: 299.0561; found 299.0537.




**Procedure:** To a solution of aldehyde **15** (2.3 g, 6.3 mmol, 1.0 eq) and sulfone **16** (2.5 g, 8.2 mmol, 1.3 eq.) in 30 mL of anhydrous THF was slowly added KHMDS 0.5 M in toluene (16.4 mL, 8.2 mmol, 1.3 eq.) at -78 $^oC$ under argon during 1 hour. The reaction mixture was stirred at -50 $^oC$ for 6 hours, before it was quenched by sat. $NH_4Cl$. The mixture was diluted with $Et_2O$, washed with water and brine, dried over $MgSO_4$, concentrated and purified via flash chromatography (Hexane / EA 20 / 1) to afford enyne **18** (1.7 g, 3.8 mmol, 60 %) as a yellow oil.

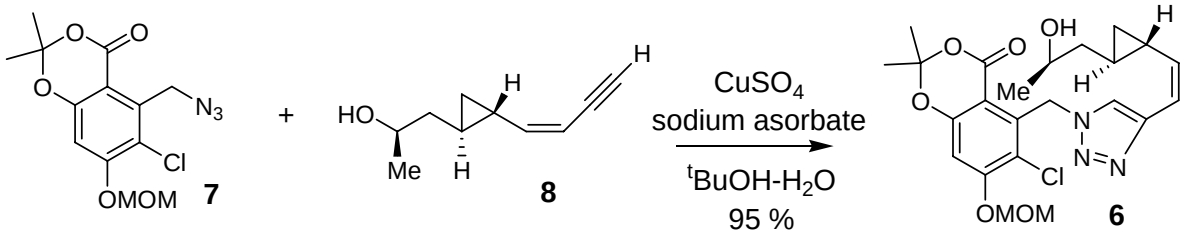
**Analytical data:** $^1H$ NMR (400MHz, $CDCl_3$): δ 7.66 (m, 4H), 7.35 (m, 6H), 5.31 (d, $J$ = 10.8 Hz, 1H), 5.22 (t, $J$ = 10.8 Hz, 1H), 3.88 (dd, $J$ = 12.8, 6.0 Hz, 1H), 1.65 (m, 1H), 1.51 (m. 1H), 1.34 (m, 1H), 1.08

(d, $J$ = 5.6 Hz, 3H), 1.02 (s, 9H), 0.83 (m, 1H), 0.58 (m, 2H), 0.18 (s, 9H),; $^{13}$C NMR (100MHz, $CDCl_3$): δ 148.9, 135.8, 134.7, 134.3, 129.4, 127.5, 105.9,102.7, 97.6, 69.8, 43.6, 27.0, 23.4, 21.2, 19.2, 18.7, 14.9, 0.06. MS (EI+) calcd for [M] $C_{29}H_{40}OSi_2$: 460.2618; found 460.2619. $[\alpha]_D^{23}$ = -55.6$^o$ (c = 2.2, $CHCl_3$)




**Procedure:** To a solution of enyne **18** (1.4 g, 3.0 mmol, 1.0 eq) in 3 mL of anhydrous THF was slowly added TBAF 1.0 M in THF (9.0 mL, 9.0 mmol, 3.0 eq.) at 0 $^o$C . The reaction mixture was stirred at rt for 8 hours. The mixture was concentrated and purified via flash chromatography (Hexane / Ether 5 / 1) to afford alcohol **8** (420 mg, 2.8 mmol, 94 %) as a yellow oil.

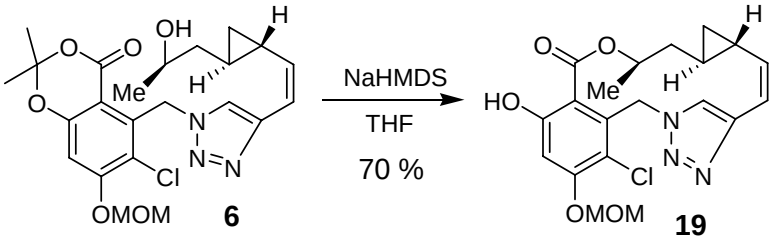
**Analytical data:** $^1$H NMR (400MHz, $CDCl_3$): δ 5.34 (m, 2H), 3.90 (dd, $J$ = 12.0, 6.0 Hz, 1H), 3.70 (dd, $J$ = 14.0, 6.8 Hz, 1H), 3.07 (s, 1H), 1.79 (m, 1H), 1.56 (m. 2H), 1.42 (m, 1H), 1.25 (d, $J$ = 5.6 Hz, 3H), 0.95 (m, 1H), 0.75 (m, 2H),; $^{13}$C NMR (100MHz, $CDCl_3$): δ 149.0, 104.9, 80.9, 80.6, 67.9, 67.8, 65.7, 57.8, 42.7, 22.9, 20.4, 18.3, 18.1, 14.8. MS (EI+) calcd for [M+H] $C_{10}H_{15}O$: 151.1124; found 151.1132. $[\alpha]_D^{23}$ = -90.5$^o$ (c = 0.25, $CHCl_3$)




**Procedure:** To a solution of benzylazide **7** (730 mg, 2.2 mmol, 1.0 eq.) and alkyne **8** (370 mg, 2.4 mmol, 1.1 eq.) in 2.0 mL of $^t$BuOH and 2.0 mL of $H_2O$ was added $CuSO_4$ (8.0 mg, 0.05 mmol, 0.02 eq.) followed by sodium asorbate (90 mg, 0.5 mmol, 0.5 eq.) at rt. The reaction mixture was stirred at rt for

12 h. The resulting mixture was diluted with 50 mL EtOAc, washed with water and brine, dried over $MgSO_4$, concentrated and purified via flash chromatography (Hexane / EA 1 / 1) to afford triazole **6** (1.01 g, 2.1 mmol, 95 %) as a colorless oil.

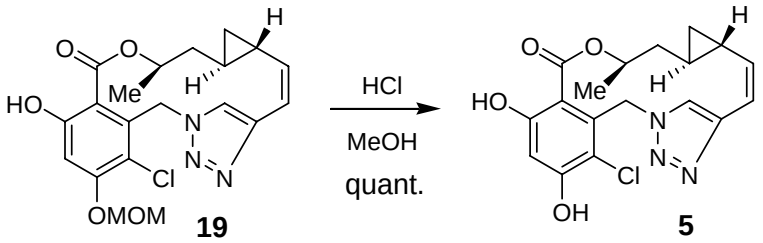
**Analytical data:** $^1$H NMR (400MHz, $CDCl_3$): δ 7.66 (s, 1H), 6.83 (s, 1H), 6.23 (d, *J* = 4.4 Hz, 2H), 6.17 (d, *J* = 11.2 Hz, 1H), 5.29 (s, 2H), 5.10 (t, *J* = 10.0 Hz, 1H), 3.91 (d, *J* = 5.6 Hz, 1H), 3.50 (s, 3H), 2.36 (bs, 1H), 2.18 (m, 1H), 1.68 (s, 6H), 1.61 (m. 1H), 1.46 (m, 1H), 1.24 (d, *J* = 5.6 Hz, 3H), 0.90 (m, 1H), 0.66 (m, 2H),; $^{13}$C NMR (100MHz, $CD_3OD$): δ 161.1, 160.1, 158.5, 145.5, 138.9, 136.6, 124.1, 122.4, 115.9, 108.1, 107.4, 105.6, 96.4, 68.7, 57.2, 43.9, 25.6, 23.4, 20.4, 19.7, 15.5, 15.2. MS (EI+) calcd for [M+H] $C_{23}H_{29}ClN_3O_6$: 478.1746; found 478.1742. $[\alpha]_D^{23}$ = -51.5$^o$ (c = 0.76, $CHCl_3$)




**Procedure:** To a solution of triazole **6** (750 mg, 1.6 mmol, 1.0 eq.) in 80 mL of anhydrous THF was slowly added NaHMDS 1.0 M in THF (4.8 mL, 4.8 mmol, 3.0 eq.) at -78 $^o$C. The reaction mixture was stirred at -20 $^o$C for 3 h, before it was quenched by dilute HCl aq. The mixture was extracted with EtOAc (3x50 mL) and the combined organic layers were washed twice with brine, dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by flash chromatography (Hexane / EA: 2 / 1) to afford phenol **19** (460 mg, 1.1 mmol, 70 %) as a white solid. m.p. 181-183 $^o$C

**Analytical data:** $^1$H NMR (400MHz, $CDCl_3$): δ 11.5 (bs, 1H), 7.64 (s, 1H), 6.88 (s, 1H), 6.57 (dd, *J* = 11.2, 2.0 Hz, 1H), 6.10 (d, *J* = 13.6 Hz, 1H), 5.63 (dd, *J* = 11.2, 2.0 Hz, 2H), 5.34 (s, 1H), 5.26 (s, 2H), 3.48 (s, 3H), 2.02 (m, 1H), 1.26 (m, 2H), 1.21 (d, *J* = 5.6 Hz, 3H), 0.62 (m, 1H), 0.55 (m, 1H), 0.53 (m,

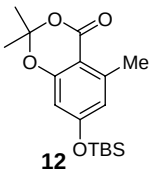
1H); $^{13}$C NMR (100MHz, $CDCl_3$): δ 168.1, 162.3, 157.8, 143.3, 134.1, 132.3, 124.9, 122.3, 119.2, 108.8, 104.9, 94.8, 72.9, 56.8, 49.8, 39.0, 29.9, 18.5, 17.2, 14.4. MS (EI+) calcd for [M+H] $C_{20}H_{23}ClN_3O_5$: 420.1327; found 420.1350. $[\alpha]_D^{23} = +64.0^o$ (c = 0.08, $CHCl_3$)




**19** **5**

**Procedure:** To the solution of phenol **19** (460 mg, 1.1 mmol) in 3 mL of MeOH was added 1 mL of 2 M HCl at room temperature. The reaction mixture was stirred at 50 $^o$C for 8 hours. The solution was concentrated in *vacuo* and the residue was dissolved with EtOAc (50 mL). The solution was washed with water and brine, dried over anhydrous $MgSO_4$, and filtrated. After evaporation of the solvent, the product was collected and further recrystalized by $CHCl_3$/EtOH(10:1) to afford the pure triazole-cycloproparadicicol **5** (410 mg, 1.1 mmol, quant.) as a white solid. m.p. 240-242 $^o$C

**Analytical data:** $^1$H NMR (400MHz, $CD_3OD$): δ 7.91 (s, 1H), 6.55 (s, 1H), 6.38 (d, *J* = 11.2 Hz, 1H), 5.93 (d, *J* = 13.6 Hz, 1H), 5.78 (t, *J* = 8.0 Hz, 2H), 5.18 (m, 1H), 1.84 (m, 2H), 1.21 (d, *J* = 6.4 Hz, 3H), 0.86 (m, 1H), 0.58 (m, 1H), 0.52 (m, 2H); $^{13}$C NMR (100MHz, $CD_3OD$): δ 168.2, 157.2, 144.3, 135.6, 132.1, 129.4, 128.3, 124.8, 119.6, 104.4, 73.1, 60.8, 38.9, 29.4, 17.3, 16.1, 14.8, 13.5. MS (EI+) calcd for [M+H] $C_{18}H_{19}ClN_3O_4$: 376.1065; found 376.1045. $[\alpha]_D^{23} = +47.5^o$ (c = 0.14, MeOH)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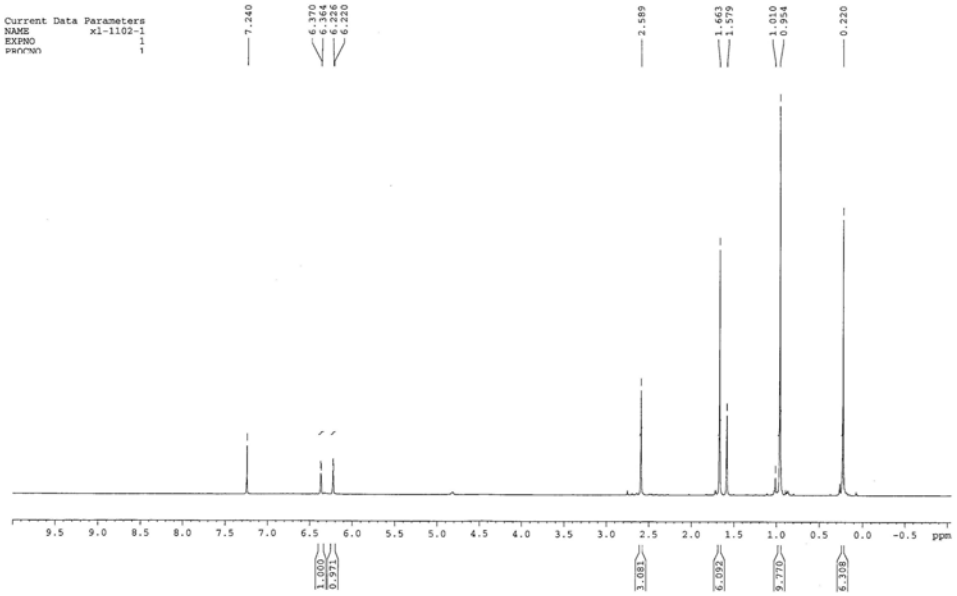
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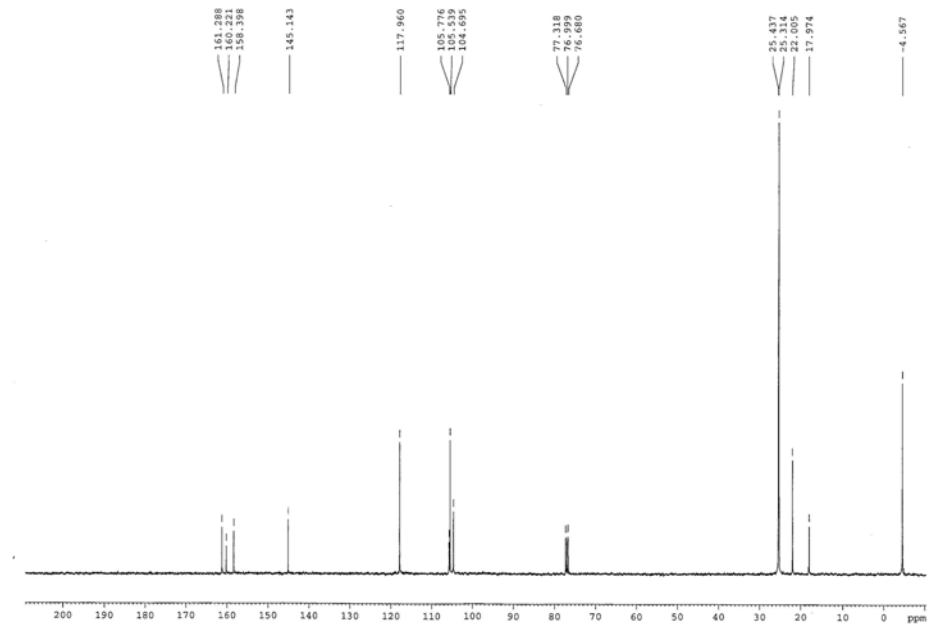
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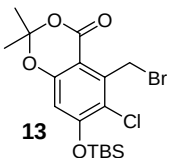
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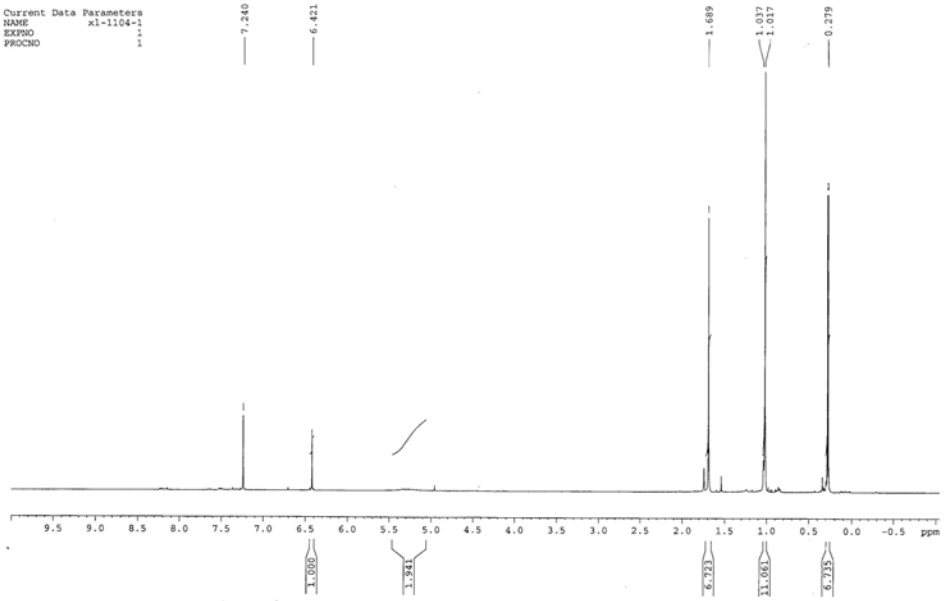
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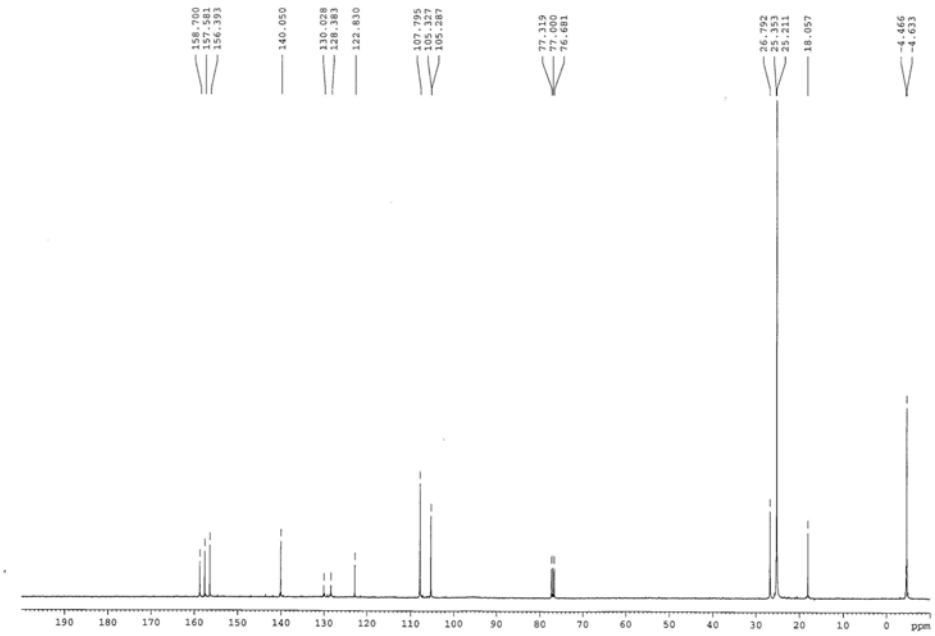
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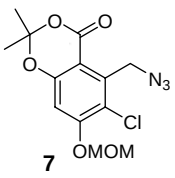
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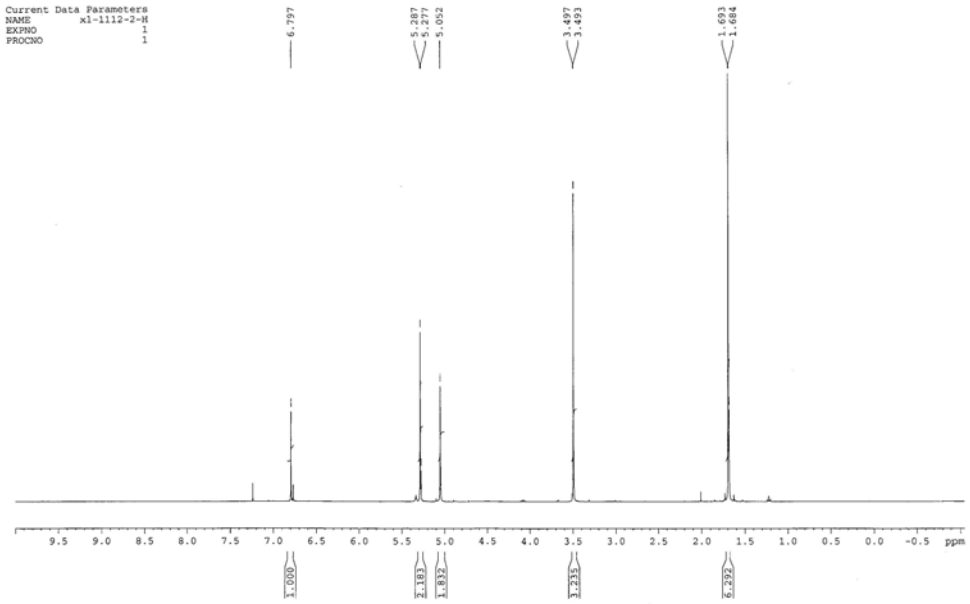
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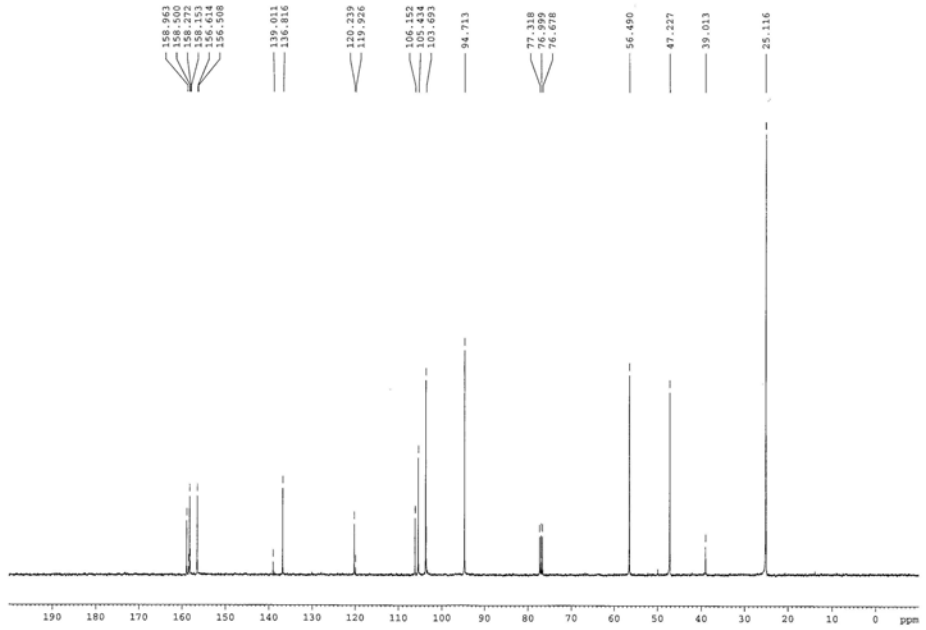
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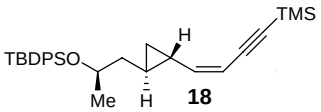
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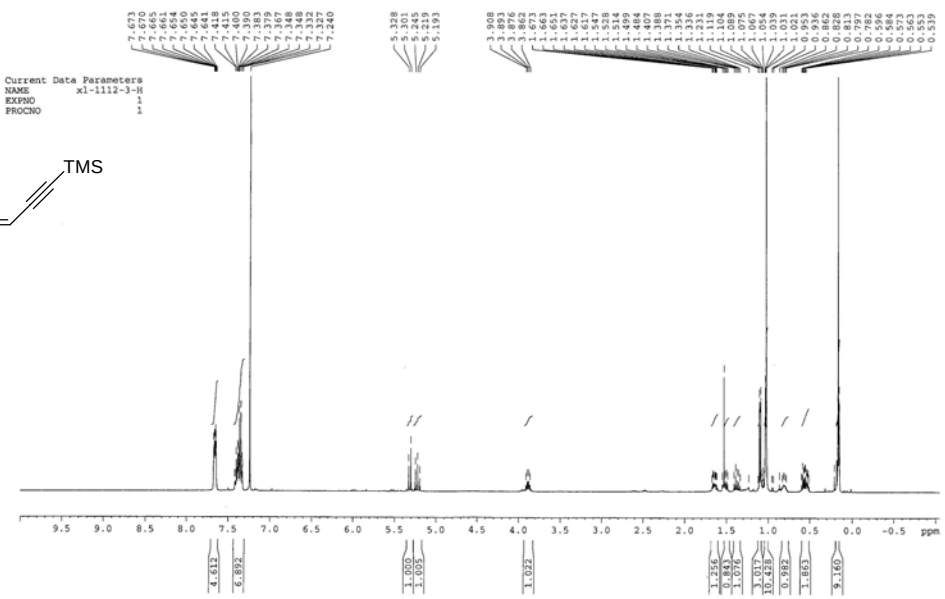
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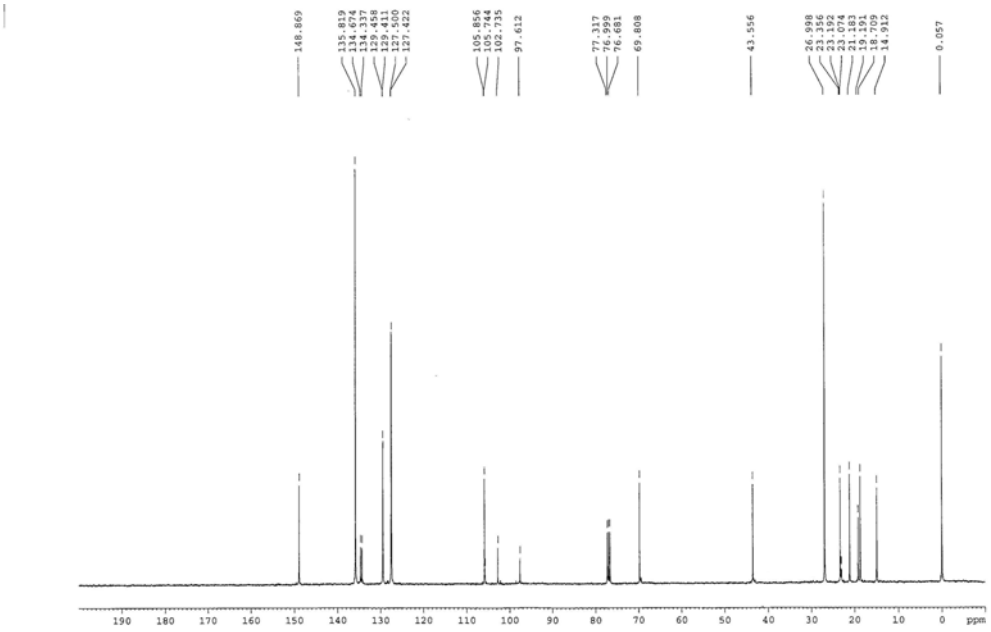
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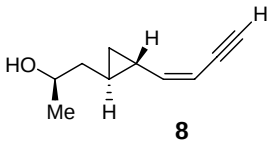
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Me
H
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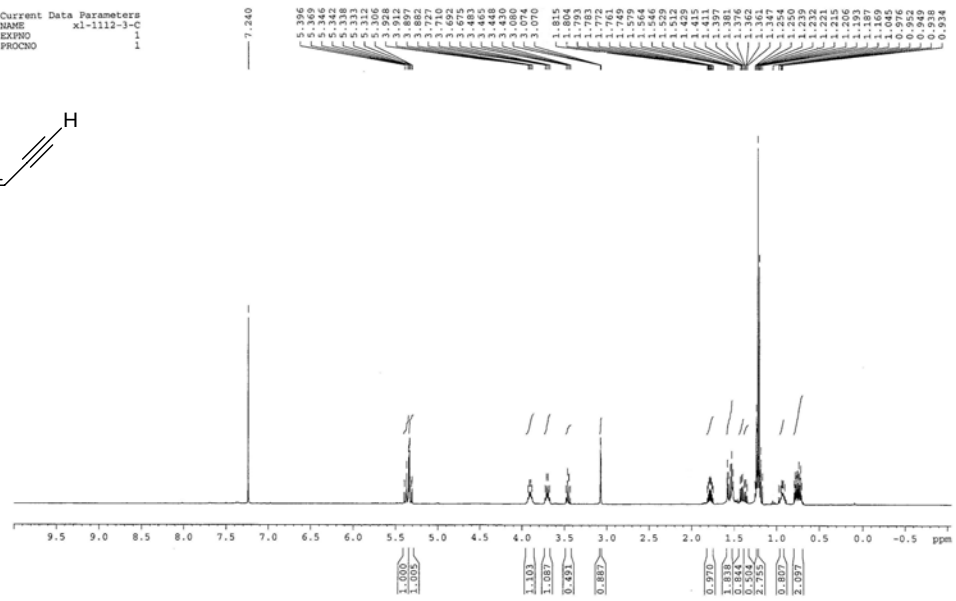
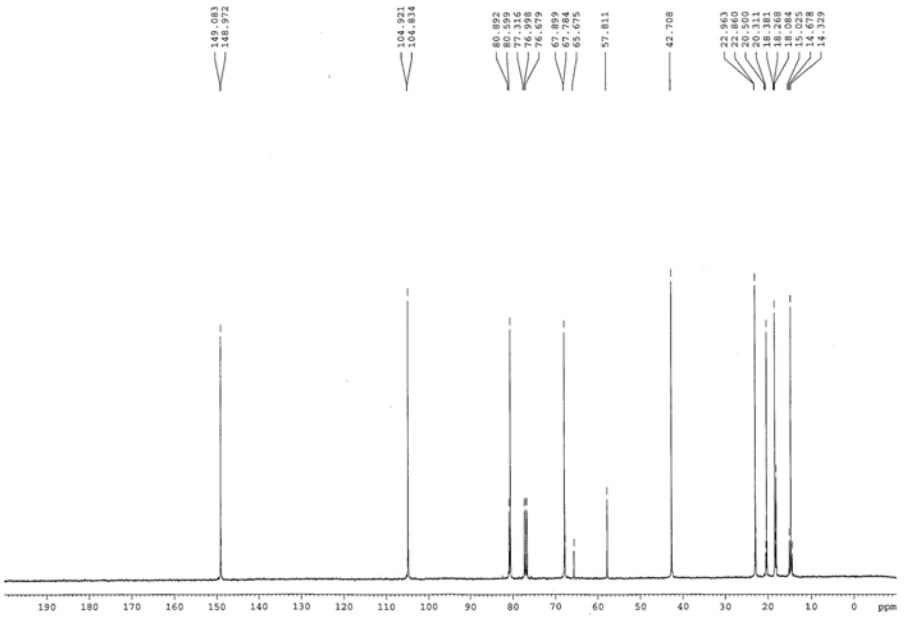
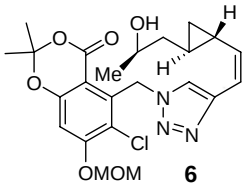
H

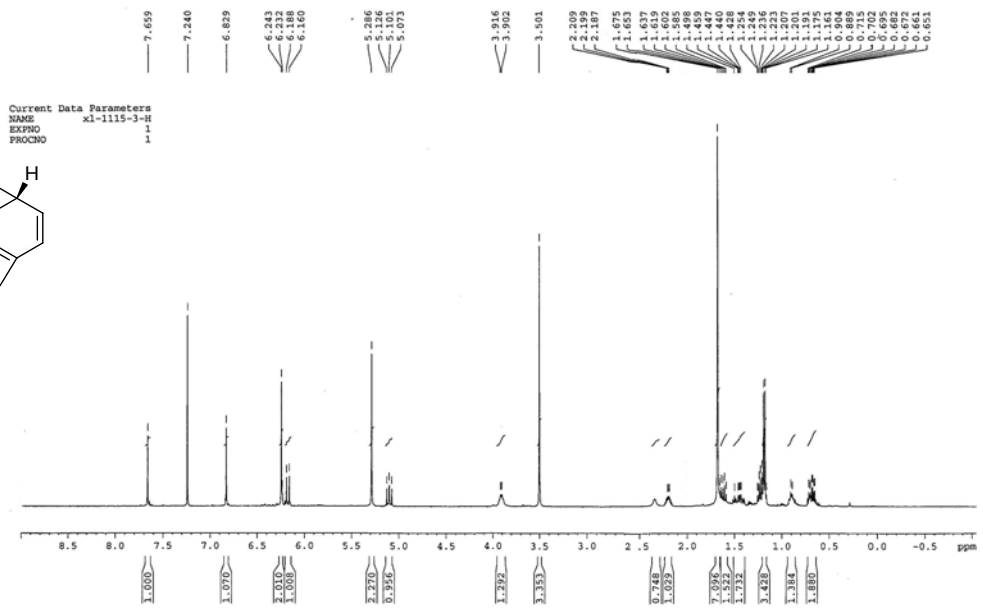
**8**


Current Data Parameters
NAME xl-1112-3-C
EXPNO 1
PROCNO 1
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 ppm


190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


OH
H
O
O
O
Me
H
N
N=N
Cl
OMOM

**6**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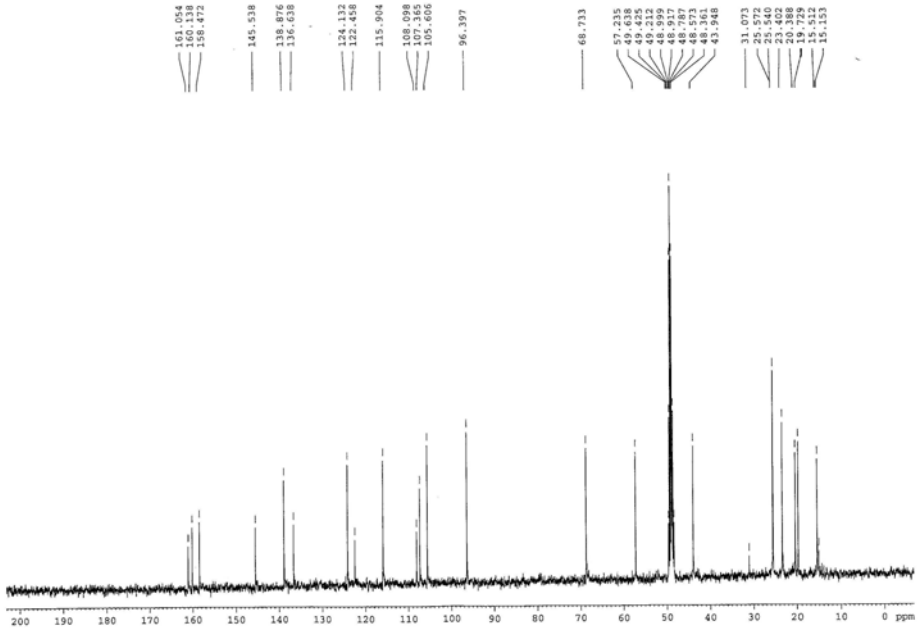
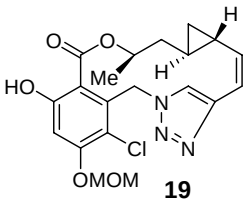
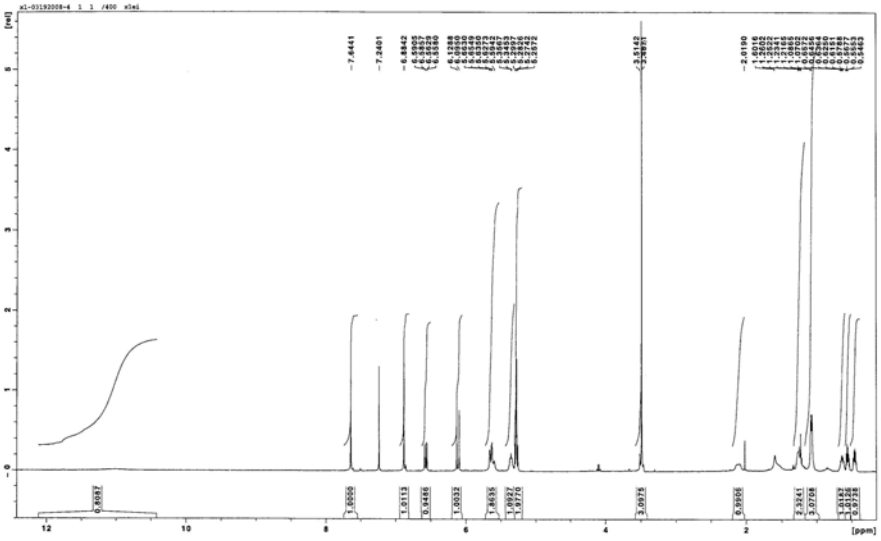
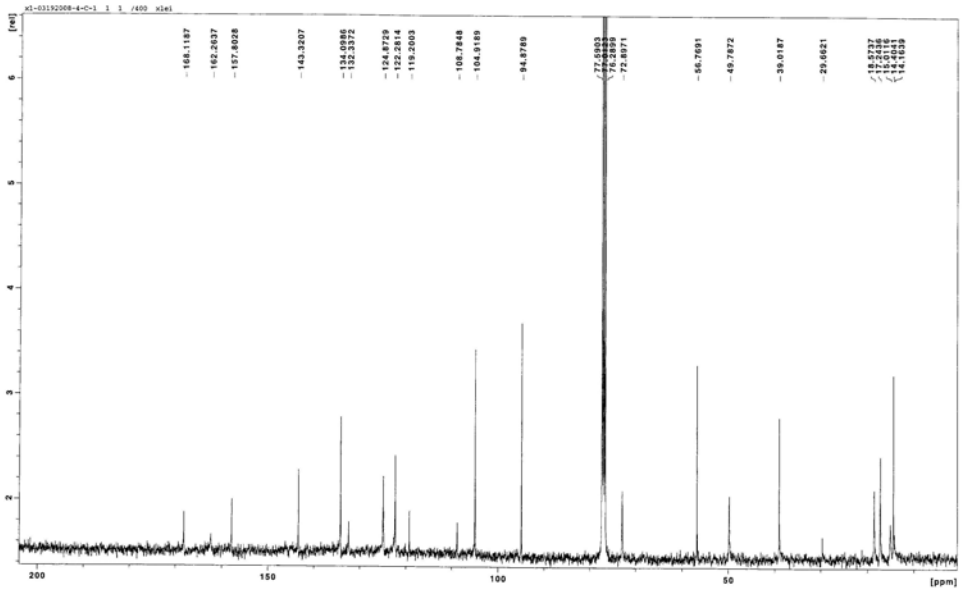
EXPNO 1
PROCNO 1
ppm

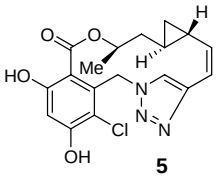

ppm



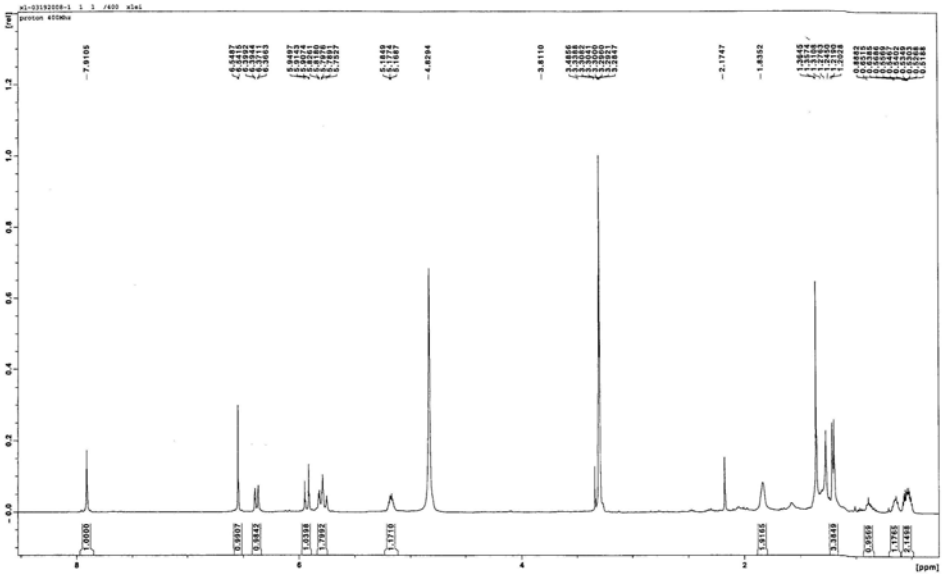

**19**

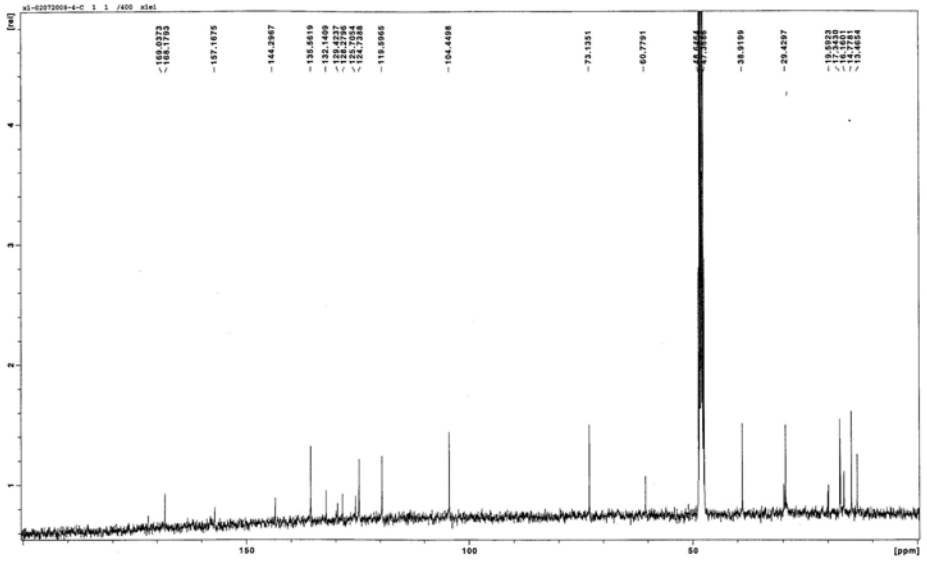


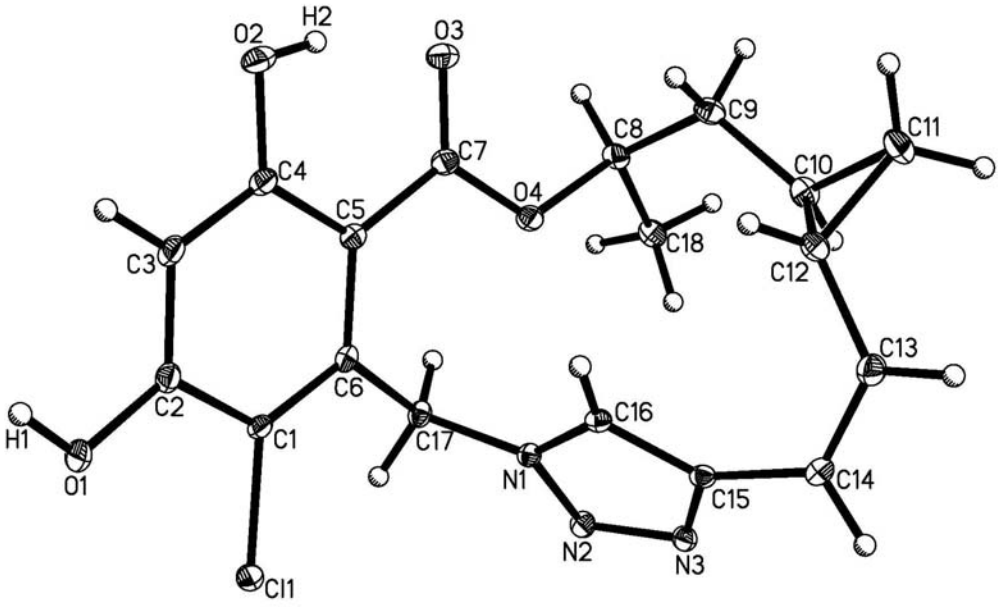





**5**








X-ray structure of **5**

CCDC 682086

Formula: C22 H26 Cl1 N3 O6

Unit cell parameters: a 7.2034(6) b 8.1459(6) c 9.9024(8)

alpha 82.8420(10) beta 75.2760(10) gamma 89.1210(10)

space group P1

CCDC 682086 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033

Hsp90 Inhibition by **5**