Supporting Information

Synthesis and Initial Evaluation of YM-08, a Blood-Brain Barrier Permeable Derivative of the Heat Shock Protein 70 (Hsp70) Inhibitor MKT-077, Which Reduces Tau Levels

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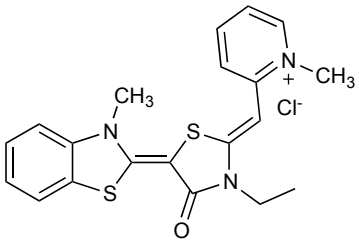
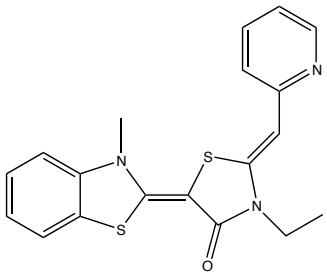
Compound Synthesis and Characterization. Compounds **MKT-077** (1-ethyl-2-((Z)-((E)-3-ethyl-5-(3-methylbenzo[d]thiazol-2(3H)-ylidene)-4-oxothiazolidin-2-ylidene)methyl)pyridin-1-ium), **YM-02** ((*E*)-3-ethyl-5-(3-methylbenzo[*d*]thiazol-2(3*H*)-ylidene)-2-thioxothiazolidin-4-one), **YM-03** ((*E*)-3-ethyl-5-(3-methylbenzo[*d*]thiazol-2(3*H*)-ylidene)-2-(methylthio)-4-oxo-4,5-dihydrothiazol-3-ium), **YM-04** ((*Z*)-2-((3-ethyl-4-oxothiazolidin-2-ylidene)methyl)-1-methylpyridin-1-ium) and **YM-07** ((*Z*)-3-ethyl-2-(pyridin-2-ylmethylene)thiazolidin-4-one) were synthesized as previously reported[32]. Characterization by ^{1}H NMR and mass spectrometry confirmed the reported values.

2-((*Z*)-((*E*)-3-ethyl-5-(3-methylbenzo[*d*]thiazol-2(3*H*)-ylidene)-4-oxothiazolidin-2-ylidene)methyl)-1-methylpyridin-1-ium (**YM-01**). ^{1}H *d6*-DMSO 8.67 (1H, d, *J* = 6.3 Hz), 8.26 (1H, t, *J* = 8.2 Hz), 8.04 (1H, d, *J* = 8.6 Hz), 7.87 (1H, d, *J* = 7.8 Hz), 7.61 (1H, d, *J* = 8.2 Hz), 7.49 (1H, t, *J* = 7.4 Hz), 7.42 (1H, t, *J* =7.4 Hz), 7.30 (1H, t, *J* = 7.4 Hz), 5.96 (1H, t), 4.14 (3H, s), 4.10, (2H, q, *J* = 7.4, 6.7 Hz), 4.04 (3H, s), 1.26 (3H, t, *J* = 6.7 Hz). ^{13}C *d6*-DMSO 163.80, 154.42, 150.60, 150.51, 145.33, 142.67, 140.33, 127.01, 125.61, 123.53, 122.80, 122.06, 118.69, 111.72, 84.19, 78.26, 45.18, 38.23, 34.48, 11.87. MS (ESI): calculated for $C_{20}H_{20}N_3OS_2^+$ $[M\text{-}Cl^-]^+$ m/z 382.1, found 382.1. Purity: >95 % (determined by ^{1}H NMR).



(2*Z*,5*E*)-3-ethyl-5-(3-methylbenzo[*d*]thiazol-2(3*H*)-ylidene)-2-(pyridin-2-ylmethylene)thiazolidin-4-one (**YM-08**). ^{1}H NMR (600 MHz, DMSO-*d*6): *δ* 8.53 (1H, d, *J*=4.2 Hz), 7.65 (1H, d, *J*=7.8 Hz), 7.61 (1H, t, *J*=7.8 Hz), 7.35 (1H, t, *J*=7.8 Hz), 7.31 (1H, d, *J*=7.8 Hz), 7.22 (1H, d, *J*=7.8 Hz), 7.14 (1H, t, *J*=7.8 Hz), 6.93 (1H, t, *J*=6.0 Hz), 6.16 (1H, s), 3.94 (3H, s), 3.89 (2H, q, *J*=7.2 Hz), 1.20 (3H, t, 7.2 Hz); ^{13}C NMR (150 MHz, DMSO-*d*6): *δ* 165.08, 155.92, 149.81, 147.41, 140.90, 140.18, 135.78, 126.40, 125.87, 122.38, 121.94, 121.44, 117.32, 110.41, 93.44, 84.10, 37.14, 34.24, 12.09.; ESI-MS:m/z calculated for $[C_{19}H_{18}N_3OS_2]^+$ 368.09, found 368.1 $[M+H]^+$. Purity: >95 % (determined by ^{1}H NMR).



YM08_H1
STANDARD 1H OBSERVE - profile

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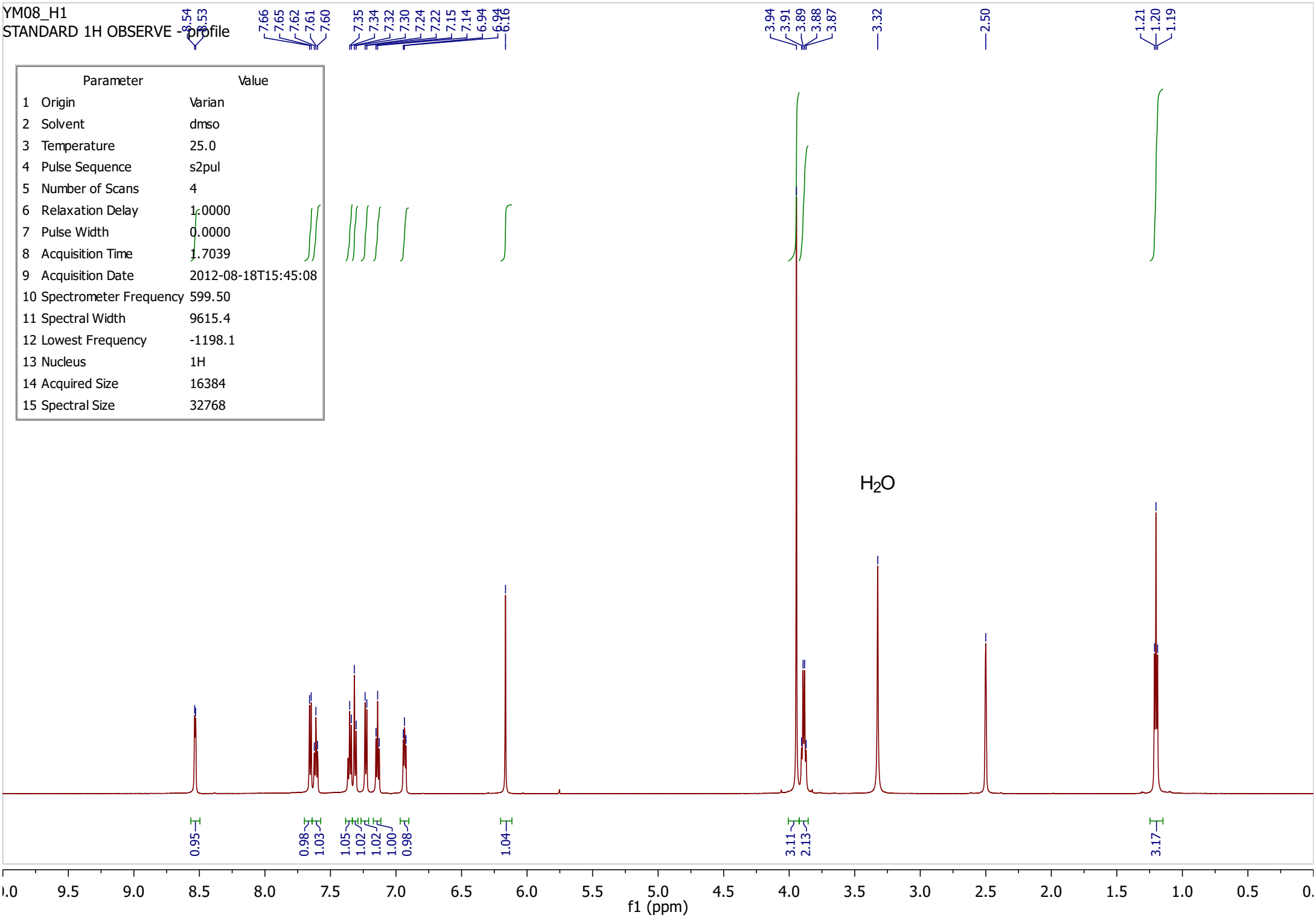
2	Solvent	dmso
3	Temperature	25.0
4	Pulse Sequence	s2pul
5	Number of Scans	4
6	Relaxation Delay	1.0000
7	Pulse Width	0.0000
8	Acquisition Time	1.7039
9	Acquisition Date	2012-08-18T15:45:08
10	Spectrometer Frequency	599.50
11	Spectral Width	9615.4
12	Lowest Frequency	-1198.1
13	Nucleus	1H
14	Acquired Size	16384
15	Spectral Size	32768



YM08_C13
STANDARD 1H OBSERVE - profile

	Parameter	Value
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2	Solvent	dmso
3	Temperature	25.0
4	Pulse Sequence	s2pul
5	Number of Scans	992
6	Relaxation Delay	1.0000
7	Pulse Width	0.0000
8	Acquisition Time	0.8651
9	Acquisition Date	2012-08-18T15:12:18
10	Spectrometer Frequency	150.76
11	Spectral Width	37878.8
12	Lowest Frequency	-2428.0
13	Nucleus	13C
14	Acquired Size	32768
15	Spectral Size	65536