

## Mechanism of forming trimer, self-assembling nano-particle and inhibiting tumor growth of small molecule CIPPCT

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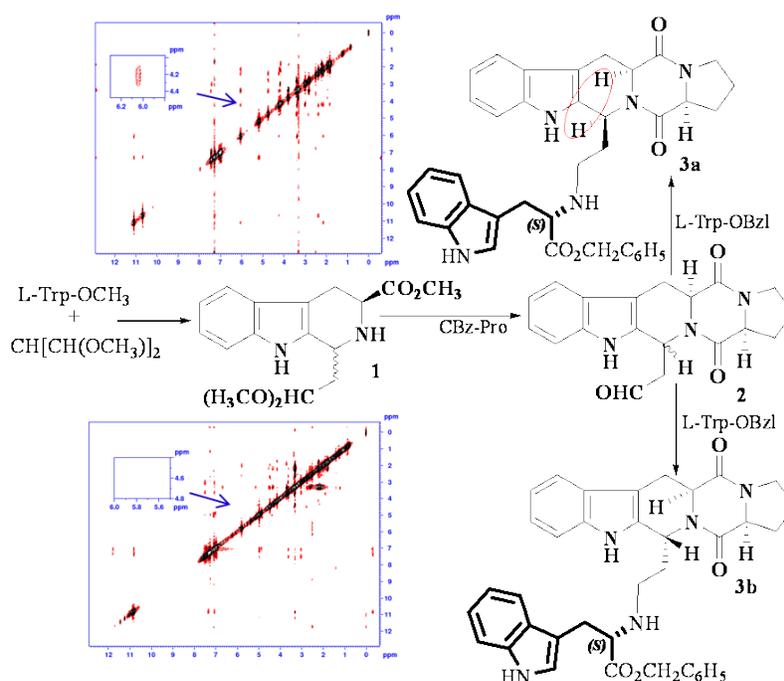
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### Supporting Information

#### Synthetic route

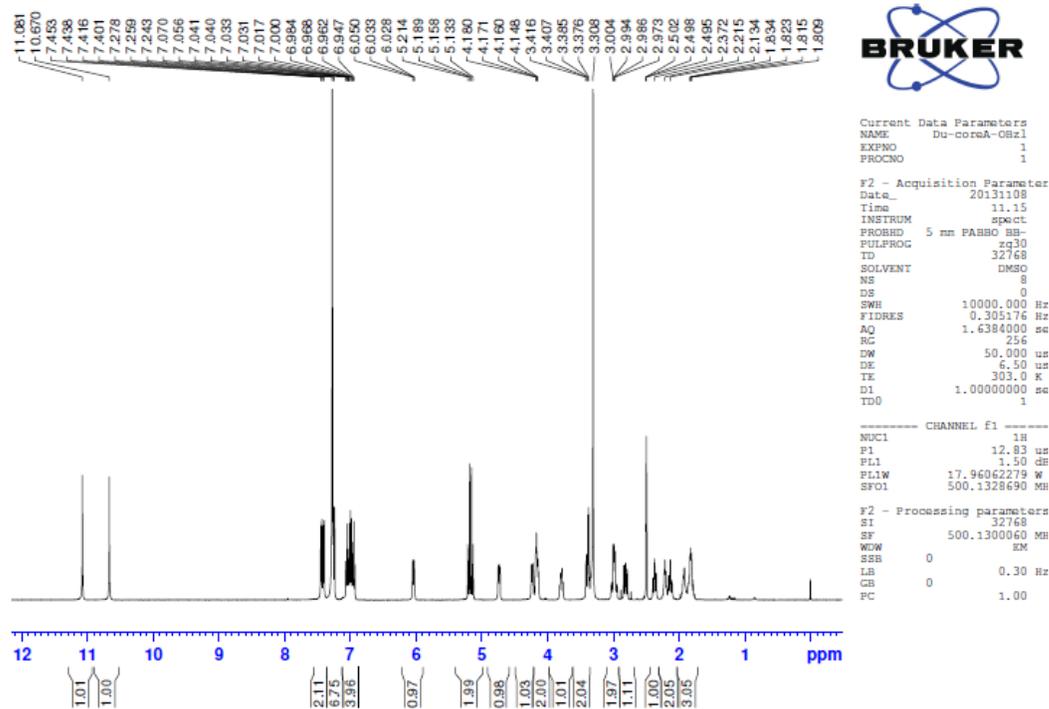
To conveniently obtain CIPPCT a 5-step reaction sequence of Scheme 2 was used, which can be divided into steps 1-3 for preparing **3a**, and steps 4,5 for preparing CIPPCT. In step 1 and 2 the cyclizations and hydrolysis of methanolacetal were performed. In brief, L-Trp-OMe (25 mmol) and 1,1,3,3-tetramethoxypropane (24 mmol) in CH<sub>3</sub>OH was adjusted to pH 2 with F<sub>3</sub>CCO<sub>2</sub>H and stirred at 66 °C for 48 h to provide methyl 1-(2,2-dimethoxyethyl)-1,2,3,4-tetrahydrocarboline-3-carboxylate (**1**, ESI-MS: m/e 318, M<sup>+</sup>) in 65% yield. Successively treating **1** with CBz-L-Pro (17 mmol)/oxalyl chloride (5 ml) for 5 h, with diisopropylamine for 24 h and with glacial acetic acid (24 ml) for 1 h to form aldehyde **2** (ESI-MS: m/e 337, M<sup>+</sup>) in 80% yield. In step 3 the reductive alkylation of

aldehyde **2** with L-Trp-OBzl/triethylamine (7 mmol/1 mL) for 0.5 h, with sodium cyanoborohydride (10 mmol) for 2 h and the product was separated on silica gel column chromatography to provide **3a** and **3b** 34% and 17% yield, respectively. The 12C of **3a** was assigned S configuration due to a positive NOE signal between 5aS-H and 12-H occurring in its ROESY 2D NMR spectrum, and the 12C of **3b** was assigned R configuration due to no such a positive NOE signal between 5aS-H and 12-H occurring in its ROESY 2D NMR spectrum. Steps 1-3 are shown in Scheme 1. In step 4 the hydrolysis of **3a** provided CIPPC. In step 5 the coupling reaction of Thr-OBzl and CIPPC provided CICCPT.

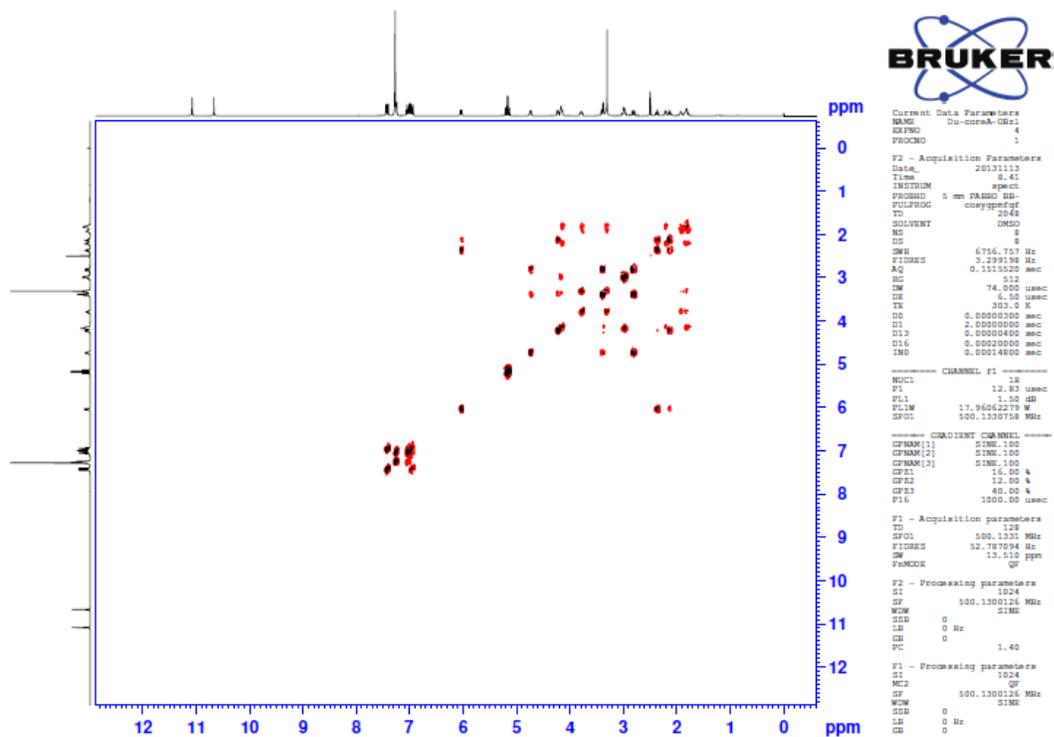


Scheme 1 Synthetic route and NOE between 5aS-H and 12-H of **3a**, (5aS,12S,14aS)-5,14-dioxo-12-(2-tryptophanbenzylester-N-ylethyl-1-yl)-1,2,3,5,5a,6,11,12,14,14a-decahydro-5H,14H-pyrolo[1,2:4,5]pyrazino[1,2:1,6]pyrido[3,4-b]indole. For **3b**, (5aS,

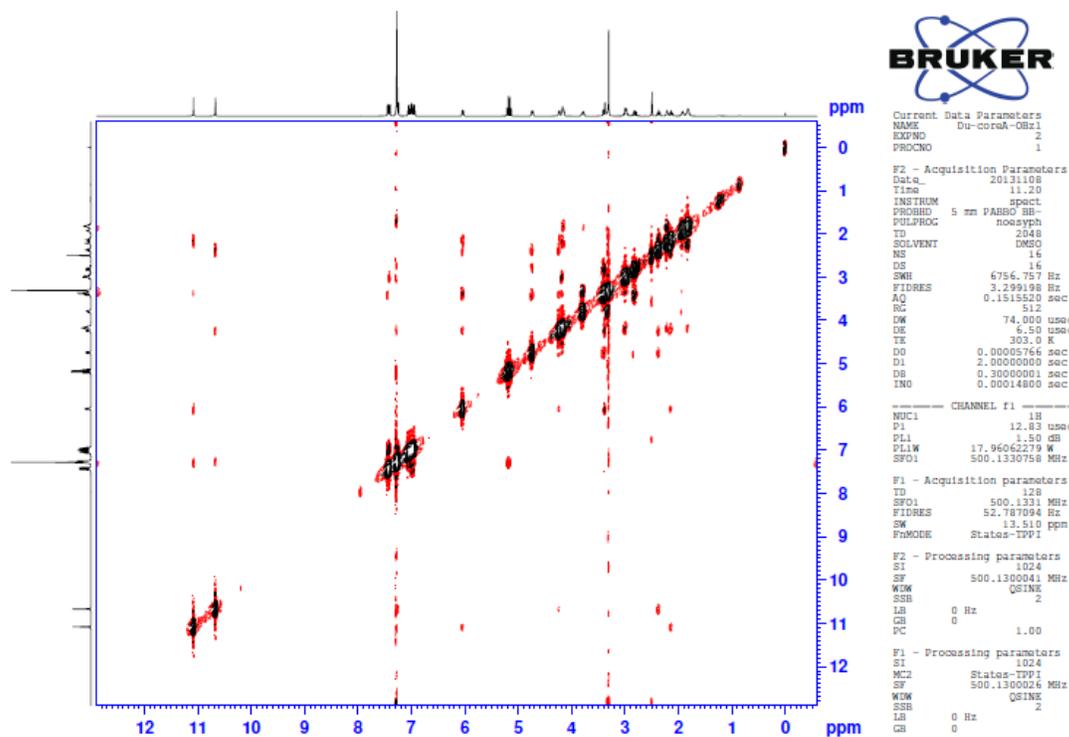
12R,14aS)-5,14-dioxo-12-(2-tryptophanbenzylester-N-ylethyl-1-yl)-1,2,3,5,5a,6,11,  
 12,14,14a-decahydro-5H,14H-pyrol[1,2:4,5]pyrazino[1,2:1,6]pyrido[3,4-b]indole, no  
 NOE between 5aS-H and 12-H was observed.



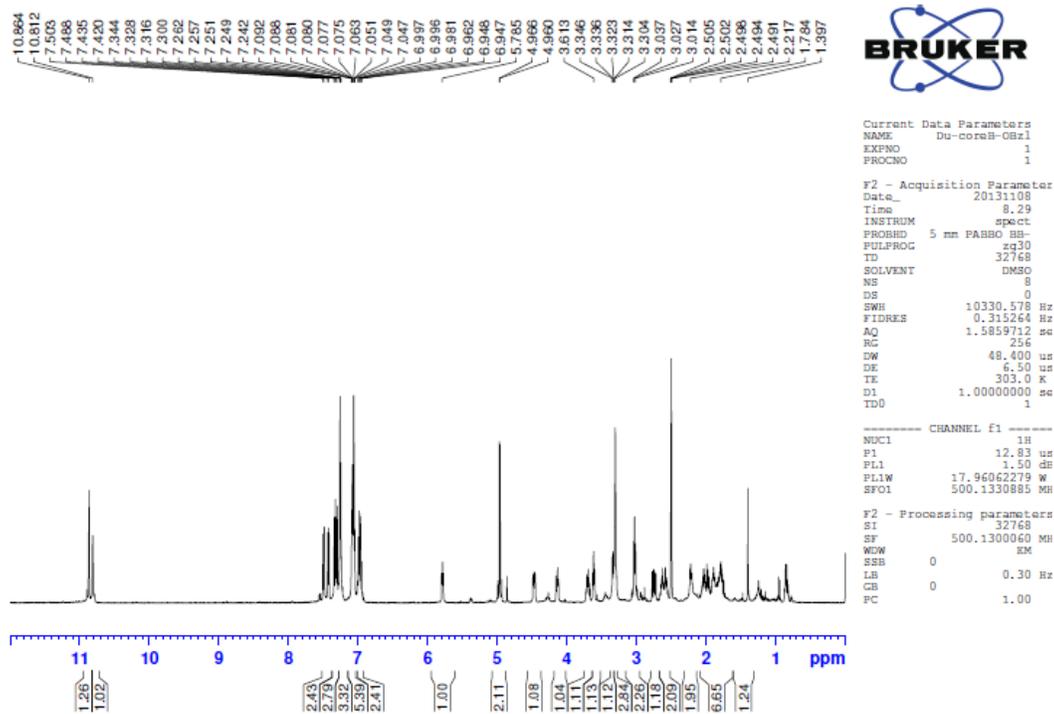
FigureS1. <sup>1</sup>H NMR of 3a



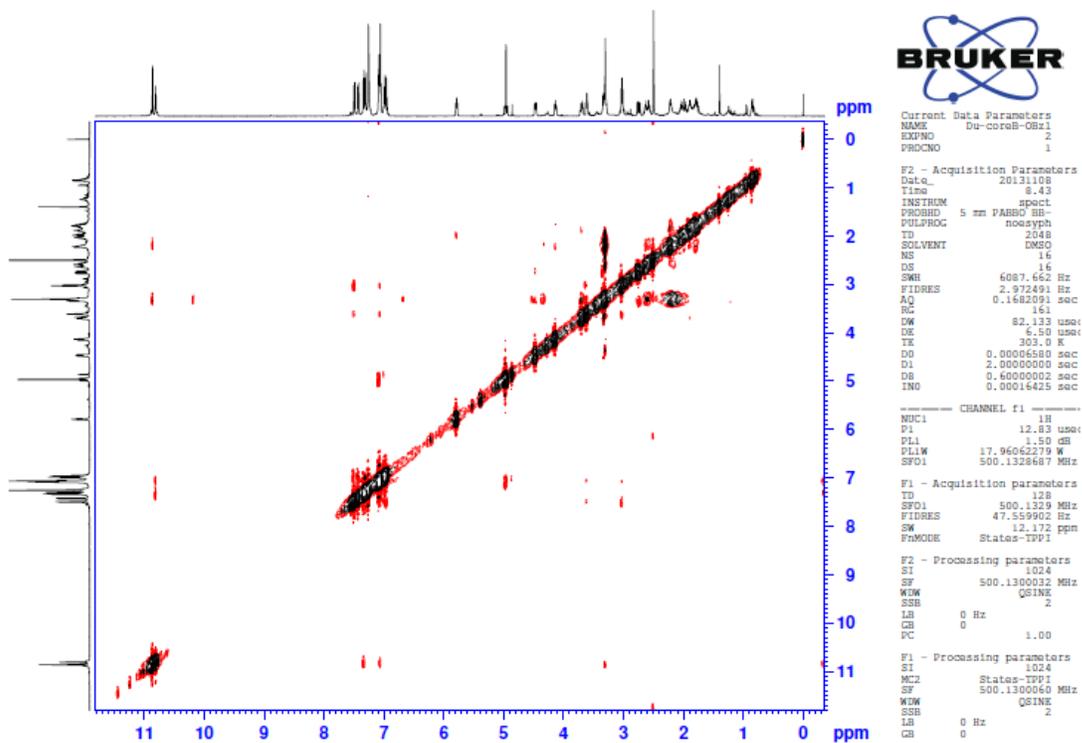
FigureS2. Cosy of 3a



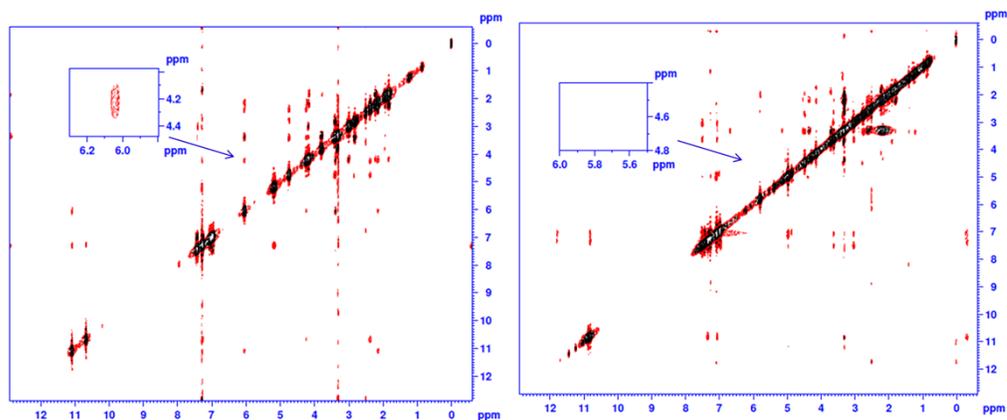
FigureS3. Noesy of 3a



FigureS4. <sup>1</sup>H NMR of 3b



FigureS5. Noesy of 3b



FigureS6. Comparison of noesy spectra of 3a and 3b

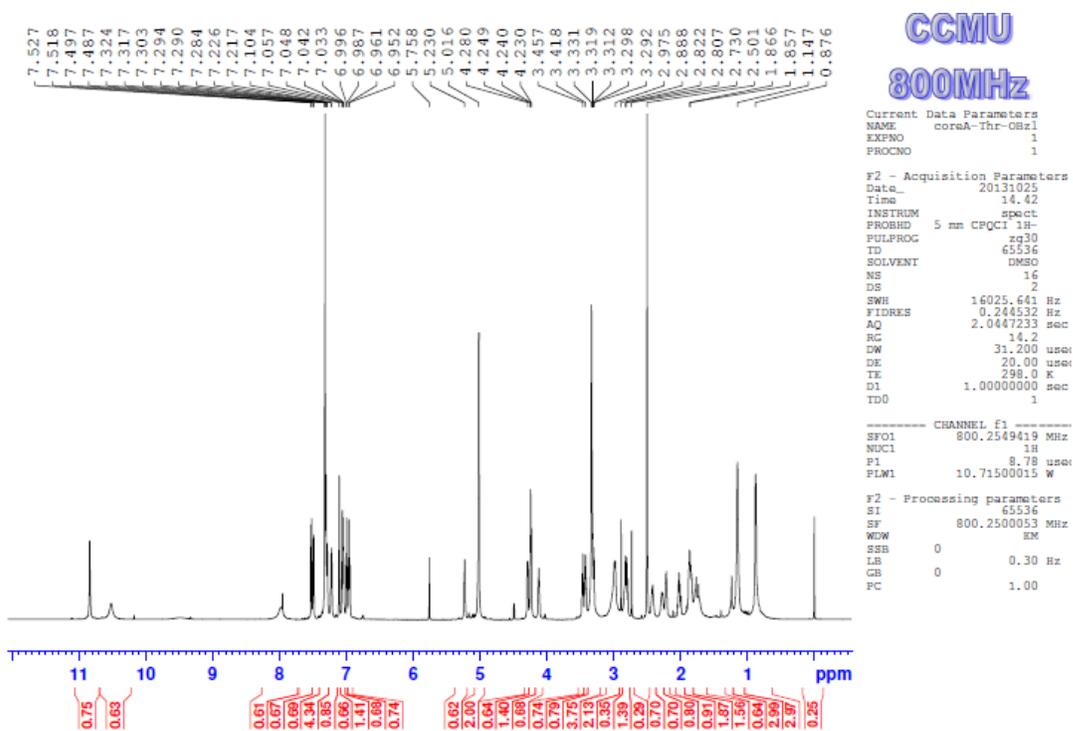
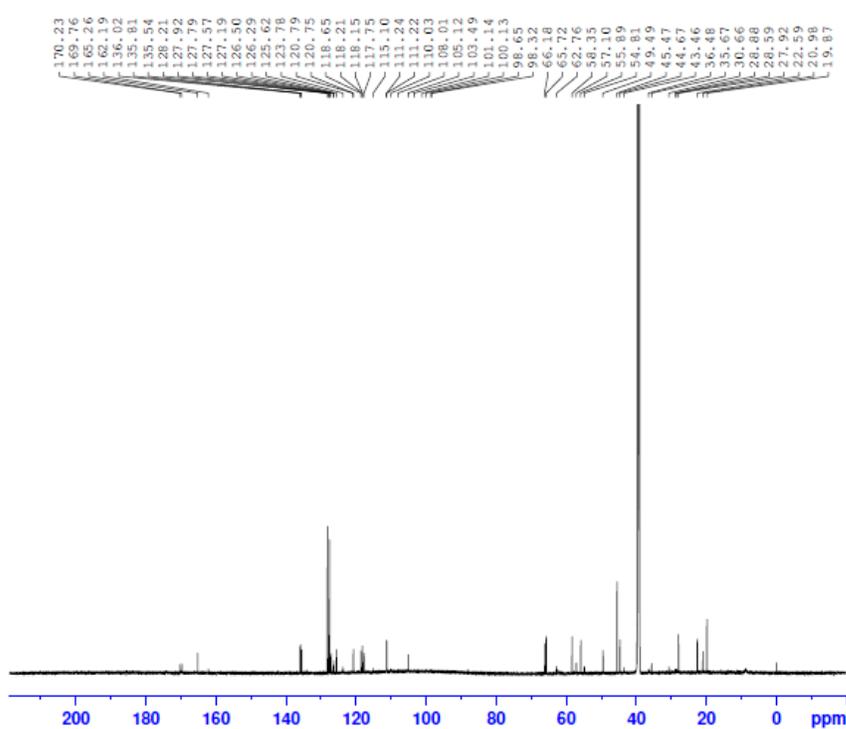


Figure S7.  $^1\text{H}$ NMR of CIPPCT



**CCMU**  
**800MHz**

Current Data Parameters  
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EXPNO 2  
PROCNO 1

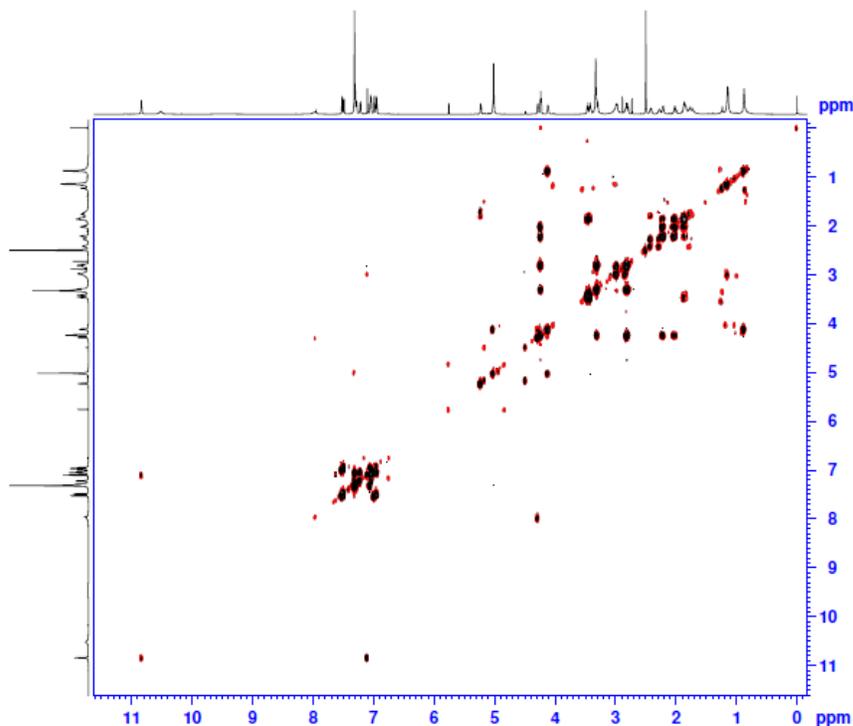
F2 - Acquisition Parameters  
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TD 85536  
SOLVENT DMSO  
NS 1024  
DS 4  
SWH 48076.922 Hz  
FIDRES 0.733596 Hz  
AQ 0.6815744 sec  
RG 3620  
DW 10.400 usec  
DE 18.00 usec  
TE 298.0 K  
D1 2.00000000 sec  
D11 0.03000000 sec  
TD0 1

CHANNEL f1  
SFO1 201.2431439 MHz  
NUC1 13C  
P1 11.04 usec  
PLW1 128.82000732 W

CHANNEL f2  
SFO2 800.2532010 MHz  
NUC2 1H  
CPDPRG2 waltz16  
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PLW2 10.71500015 W  
PLW12 0.12906000 W  
PLW13 0.08260000 W

F2 - Processing parameters  
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SF 201.2231395 MHz  
WDW EM  
SSB 0  
LB 1.00 Hz  
GB 0  
PC 1.40

Figure S8.  $C^{13}$  NMR of CIPPCT



**BRUKER**

Current Data Parameters  
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EXPNO 6  
PROCNO 1

F2 - Acquisition Parameters  
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Time 16.55  
INSTRUM spect  
PROBHD 5 mm CPQCI 1H-  
PULPROG zgpg30  
TD 2048  
SOLVENT DMSO  
NS 4  
DS 8  
SWH 9433.962 Hz  
FIDRES 4.606427 Hz  
AQ 0.1080440 sec  
RG 2050  
DM 53.900 usec  
DE 20.00 usec  
TE 298.0 K  
D0 0.00000000 sec  
D1 1.98730195 sec  
D13 0.00000400 sec  
D14 0.00000000 sec  
IND 0.00010600 sec

CHANNEL f1  
SFO1 800.2545805 MHz  
NUC1 1H  
P1 8.78 usec  
PLW1 10.71500015 W

GRADIENT CHANNEL  
GPNAM[1] DMSQ10.100  
GPNAM[2] DMSQ10.100  
GPNAM[3] DMSQ10.100  
CPE1 16.00 %  
CPE2 12.00 %  
CPE3 40.00 %  
P16 1000.00 usec

F1 - Acquisition parameters  
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SFO1 800.2546 MHz  
FIDRES 73.702827 Hz  
SW 11.789 ppm  
PnMODE QF

F2 - Processing parameters  
SI 1024  
SF 800.2499977 MHz  
WDW SINE  
SSB 0  
LB 0 Hz  
GB 0  
PC 1.40

F1 - Processing parameters  
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MC2 QF  
SF 800.2499995 MHz  
WDW SINE  
SSB 0  
LB 0 Hz  
GB 0

Figure S9. Cosy of CIPPCT

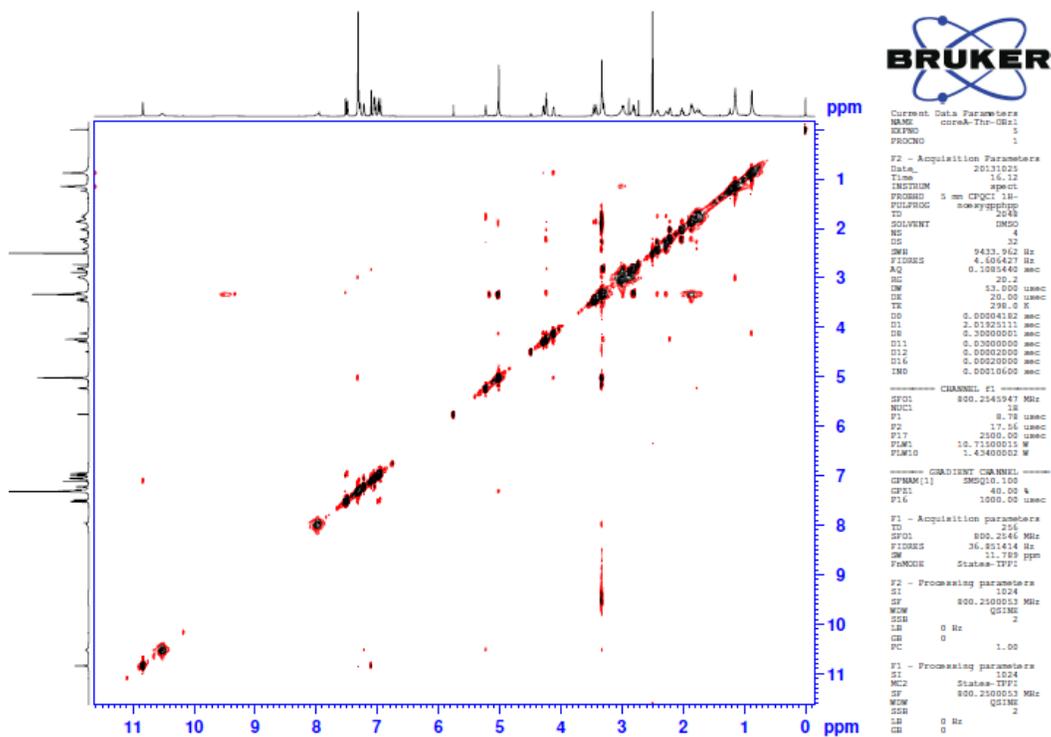


Figure S10. Noesy of CIPPCT