Aminoacid Based Chiral *N*-Amidothioureas. Acetate Anion Binding Induced Chirality Transfer

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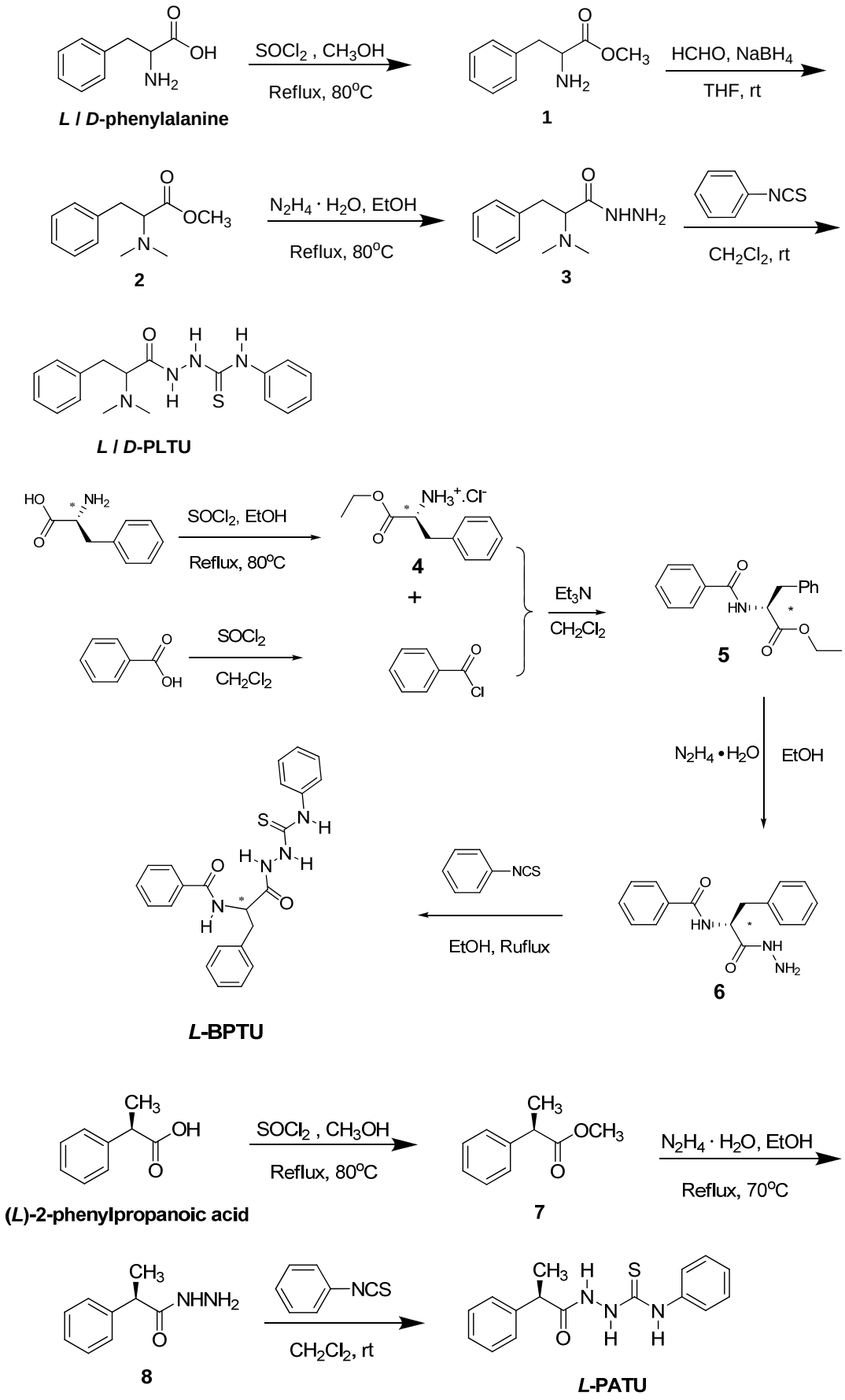
Electronic Supplementary Information (ESI)



Scheme S1. Syntheses of ***L*-/*D*-PLTU**, ***L*-BPTU** and ***L*-PATU**

Methyl 2-amino-3-phenylpropanoate (1): 21.5 ml (295.0 mmol) $SOCl_2$ was added dropwise to 9.7 g (58.8 mmol) *L*-phenylalanine in 300 ml methanol at -30 °C. After warming up to room temperature, the mixture was refluxed for 2 h. The organic solvent was removed at reduced pressure, and the pH of the residue was adjusted to ca. 9 using $NH_3 \cdot H_2O$. The mixture was then extracted by Et_2O for three times (3x15 ml). The combined organic layer was washed with little brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure, to obtain 10.0 g **1**, 95%.

***N,N*-Dimethylphenylalanine methyl ester (2):** A solution of 1.0 g (5.6 mmol) (*S*)-(+)-**1** in 56 ml THF and solid $NaBH_4$ 1.477 g (39.1 mmol) were slowly added (simultaneously) to a solution of 6.0 ml 37% formaldehyde (208 mmol) and 5.6 ml 20% H_2SO_4 in 28 ml THF over a period of 15 min at room temperature. The reaction mixture was stirred for additional 15 min and then the pH was adjusted to 9 using diluted aqueous KOH. The resulting suspension was extracted by ethyl acetate (3x15 ml) and the combined organic layer was washed with brine and dried with anhydrous Na_2SO_4. The crude product was purified using column chromatography on silica gel column eluted with petroleum ether and ethyl acetate (10:1, v/v) to give the *N,N*-dimethylphenylalanine methyl ester **2** as yellowish oil, 754 mg (65%).

2-(Dimethylamino)-3-phenylpropanehydrazide (3): Aqueous hydrazine (80%) was added to **2** in ethanol (5.0 ml) and then refluxed for 24 hours. A viscous liquid was obtained after removing solvent under reduced pressure, which was subject to chromatography on a silica gel column eluted with CH_2Cl_2/CH_3OH (20:1, v/v) to afford **3**, 621 mg (83%).

2-(2-(Dimethylamino)-3-phenylpropanoyl)-*N*-phenylhydrazinecarbothioamide (*L*-/*D*-PLTU): **3** then reacted with phenyl isothiocyanate in CH_2Cl_2. The solution was stirred at room temperature for 12 hours, after which the solvent was removed under reduced pressure. The product was purified by chromatography on a silica gel column eluted with CH_2Cl_2/CH_3OH (40:1, v/v). ***L*-PLTU:** ^{1}H NMR (400MHz, DMSO-d_6): (ppm), 10.01 (s, 1H), 9.73 (s, 1H), 8.88 (s, 1H), 7.42 (s, 2H), 7.34 (t, 2H, J = 8.0 Hz), 7.21-7.27 (m, 4H), 7.13-7.18 (m, 2H), 3.47 (t, 1H, J = 6.0 Hz), 2.98-3.03 (m, 1H), 2.85-2.90 (m, 1H), 2.32 (s, 1H); ^{13}C NMR (100MHz, $CDCl_3$): (ppm), 178.0, 168.5, 138.5, 137.4, 129.1, 128.6, 126.6, 126.3 124.6, 69.7, 42.3, 32.7; HRMS (ESI): calcd for [$C_9H_9F_3N_3OS^+$]: 343.1593, found: 343.1591. ***D*-PLTU**: ^{1}H NMR (400MHz, DMSO-d_6): (ppm), 10.01 (s, 1H), 9.70 (s, 1H), 8.83 (s, 1H), 7.41 (s, 2H), 7.32 (t, 2H, J = 8.0 Hz), 7.21-7.26 (m, 4H), 7.12-7.17 (m, 2H), 3.45 (t, 1H, J = 6.0 Hz), 2.97-3.01 (m, 1H), 2.84-2.89 (m, 1H), 2.31 (s, 1H); ^{13}C NMR (100MHz, $CDCl_3$): (ppm), 178.0, 168.4, 138.5, 137.5, 129.1, 128.6, 126.6, 126.2 124.5, 69.7, 42.3, 32.7; HRMS (ESI): calcd for [$C_9H_9F_3N_3OS^+$]: 343.1593, found: 343.1579.

1-Ethoxy-1-oxo-3-phenylpropan-2-aminium chloride (**4**): To a 50 ml round-bottom flask

equipped with magnetic stirring were added 1.65 g (10 mmol) *L*-phenylalanine and 25 ml of ethanol. The solution was stirred in an ice bath for 10 min, sulfuryl dichloride 2 ml was added dropwise. The reaction mixture stirred for 0.5 h at room temperature, and then was heated at reflux for 3 h. The solvent was removed and the crude product was purified to afford pure **4** (0.198 g, 65% yield).

Ethyl 2-benzamido-3-phenylpropanoate (5): To a 25 ml round-bottom flask equipped with magnetic stirring were added 0.12 g (1 mmol) benzoic acid and 15 ml of dichloromethane. The solution was stirred in an ice bath for 10 min, sulfuryl dichloride 0.5 ml was added dropwise. The reaction mixture stirred for 0.5 h at room temperature, and then was heated at reflux for 3 h. The solvent was removed to give a white solid residue (benzoyl chloride).

0.25 g (1.5 mmol) of **4**, 1 ml triethylamine and 25 ml of dichloromethane were added to a 50 ml round-bottom flask equipped with magnetic stirring. Benzoyl dichloride in 5 ml dichloromethane was added dropwise. The reaction mixture stirred in an ice bath for 0.5 h and then stirred at room temperature for another 4 h. The solvent was removed and the crude product was washed with dilute sodium carbonate solution and diethylether for several times to afford crude product **5** (0.23 g, 77% yield).

2-Benzamido-3-phenylpropanehydrazide (6): 0.23 g of **5**, 2 ml hydrazine hydrate (80%) and 20 ml of ethanol was added to a 50 ml round-bottom flask equipped with magnetic stirring. The reaction mixture was heated at reflux for 5 h. The solvent was removed, and the crude product was washed with diethylether several times to afford crude product **6** (0.2 g, 90% yield).

1-(2-Benzamido-3-phenylpropanoyl)-4-phenylthiosemicarbazide (*L*-BPTU): 0.2 g of **3**, 0.5 ml 1-isothiocyanatobenzene and 20 ml of ethanol was added to a 50 ml round-bottom flask equipped with magnetic stirring. The reaction mixture was stirred for 12 h. The solvent was removed, and the crude product was washed with ether several times to afford pure ***L*-BPTU** (0.24 g, 80% yield). ^{1}H NMR (500 MHz, DMSO-d_6, TMS): δ=10.45 (s, 1H), 9.78 (s, 1H), 9.25 (s,1H), 8.89 (s,1H), 7.79 (d, J = 7.5 Hz, 2H), 7.61 (d, J = 6.6 Hz, 2H), 7.53 (t, J = 7.0 Hz, 1H), 7.45 (t, J = 7.3 Hz, 2H), 7.35 (t, J = 7.0 Hz, 4H), 7.28 (t, J = 7.3 Hz, 2H), 7.18 (m, J = 13.7, 7.0 Hz, 2H), 4.59 (s, 1H), 3.21 (s, 1H), 3.15 – 3.07 (m, 1H). ^{13}C NMR (500 MHz, DMSO-d_6, TMS): δ 180.26, 170.73, 167.35, 138.93, 137.78, 133.44, 131.50, 129.11, 128.13, 128.11, 127.41, 126.28, 124.77, 124.21, 54.50, 36.01. HRMS (ESI): calcd for $C_{23}H_{22}O_2N_4S$ m/z 419.1536 [M+H+]; found 419.1530 [M+H$^+$].

(*L*)-Methyl 2-phenylpropanoate (7): To a mixture of 0.15 g (1.0 mmol) (*R*)-2-phenylpropanonic acid in 10 ml of methanol was added dropwise $SOCl_2$ 0.5 ml at -30 °C. After warming up to room temperature, the reaction mixture was heated to 70 °C for 8 h. The organic solvent was concentrated under reduced pressure and the residue was washed with water. The mixture was

extracted three times with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure, to obtain 0.16g 7, 95%.

(*L*)-2-Phenylpropanehydrazide (8): Aqueous hydrazine (80%) was added to 7 in ethanol (5.0 ml) and then refluxed for 24 hours. After removing solvent under reduced pressure, white solide was obtained which was purified on a silica gel column eluted with CH_2Cl_2/CH_3OH (60:1, v/v) to afford 8, 0.12g (80% yield).

(*L*)-*N*-Phenyl-2-(2-phenylpropanoyl)hydrazinecarbothioamide (*L*-PATU): 8 then reacted with phenyl isothiocyanate in CH_2Cl_2. The solution was stirred at room temperature for 12 hours, after which the solvent was removed under reduced pressure. The product was purified by chromatography on a silica gel column eluted with CH_2Cl_2/CH_3OH (80:1, v/v). ^{1}H NMR (400MHz, CD_3CN): (ppm), 8.46 (s, 1H), 8.38 (s, 1H), 7.92 (s, 1H), 7.43 (s, 1H), 7.40 (t, 4H, J = 4.0 Hz), 7.35-7.39 (m, 3H), 7.29-7.33 (m, 1H), 7.25 (t, 1H, J = 8.0 Hz), 3.72-3.78 (m, 1H), 1.50 (d, 3H, J = 4.0 Hz); ^{13}C NMR (100MHz, CD_3CN: (ppm), 182.3, 174.0, 141.1, 138.3, 128.7, 128.5, 127.6, 127.4, 127.2, 126.0, 125.3, 117.4, 44.3, 17.9.

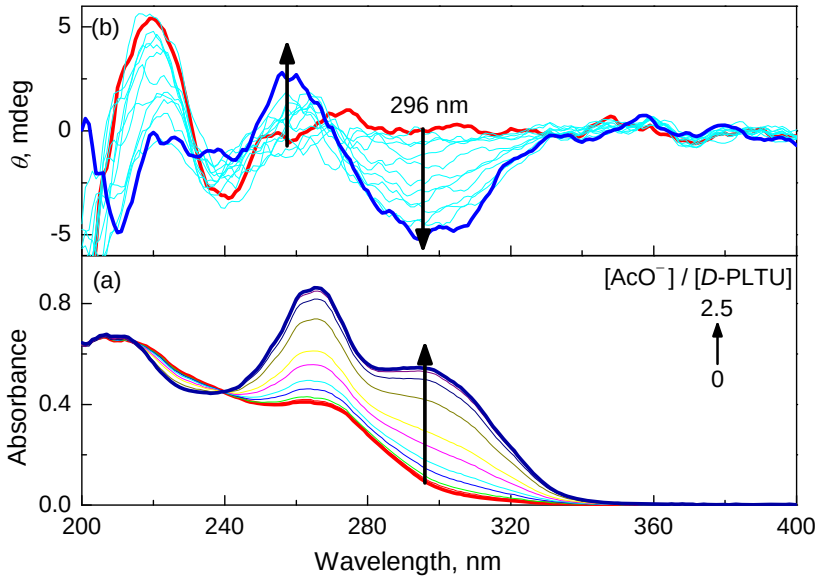


Figure S1. Absorption (a) and CD (b) spectra of ***D*-PLTU** in acetonitrile in the presence of acetate anion. [***D*-PLTU**] = 40 μM.

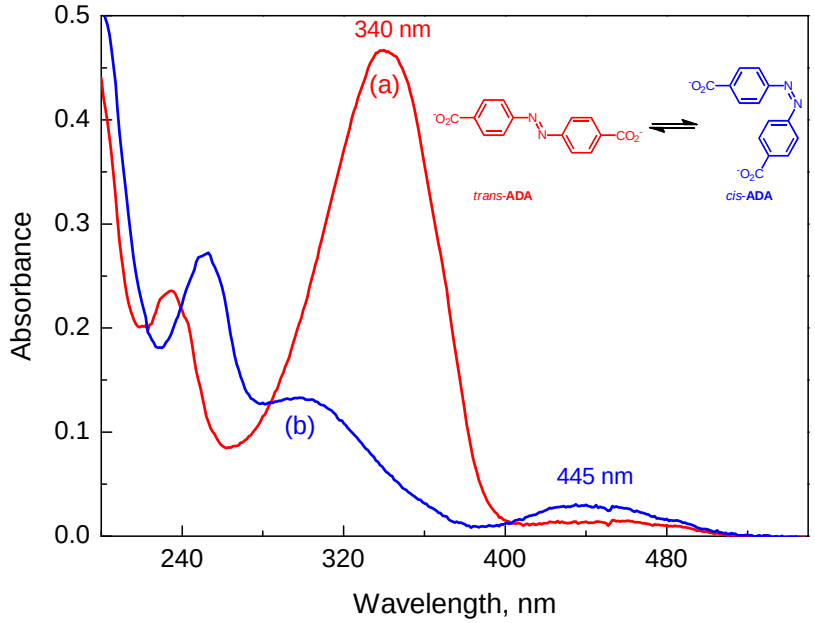


Figure S2. Absorption spectra of *trans*- (a) and *cis*-ADA (b) in acetonitrile. [ADA] = 20 μM.

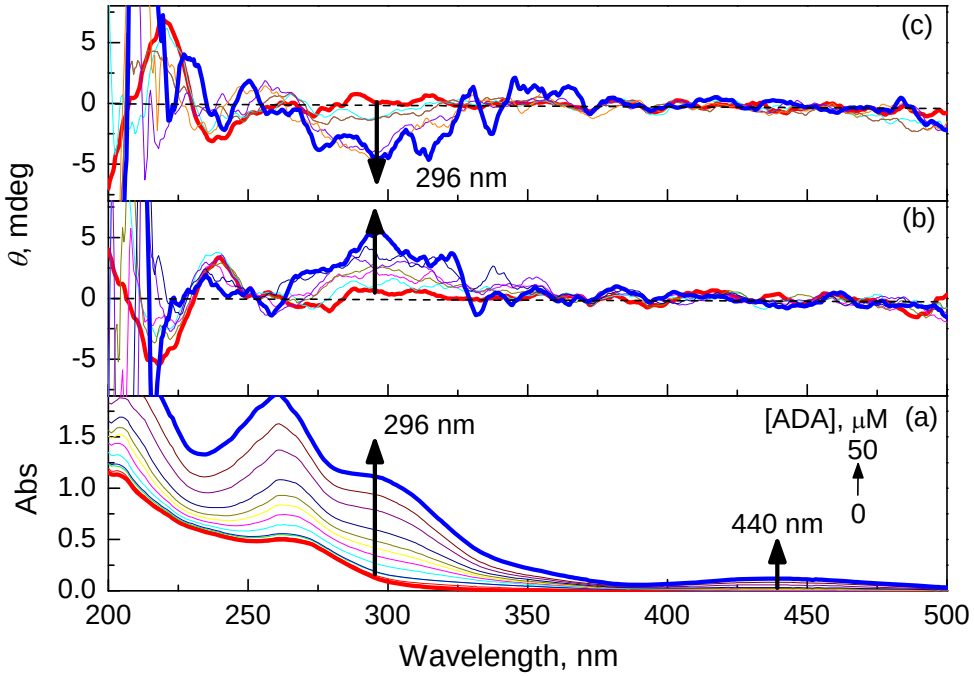


Figure S3. Absorption (a) and CD (b, c) spectra of **PLTU** in acetonitrile in the presence of *cis*-ADA. ***L***- (a, b) and ***D*-PLTU** (c). [**PLTU**] = 40 μM, [ADA] = 0-50 μM.

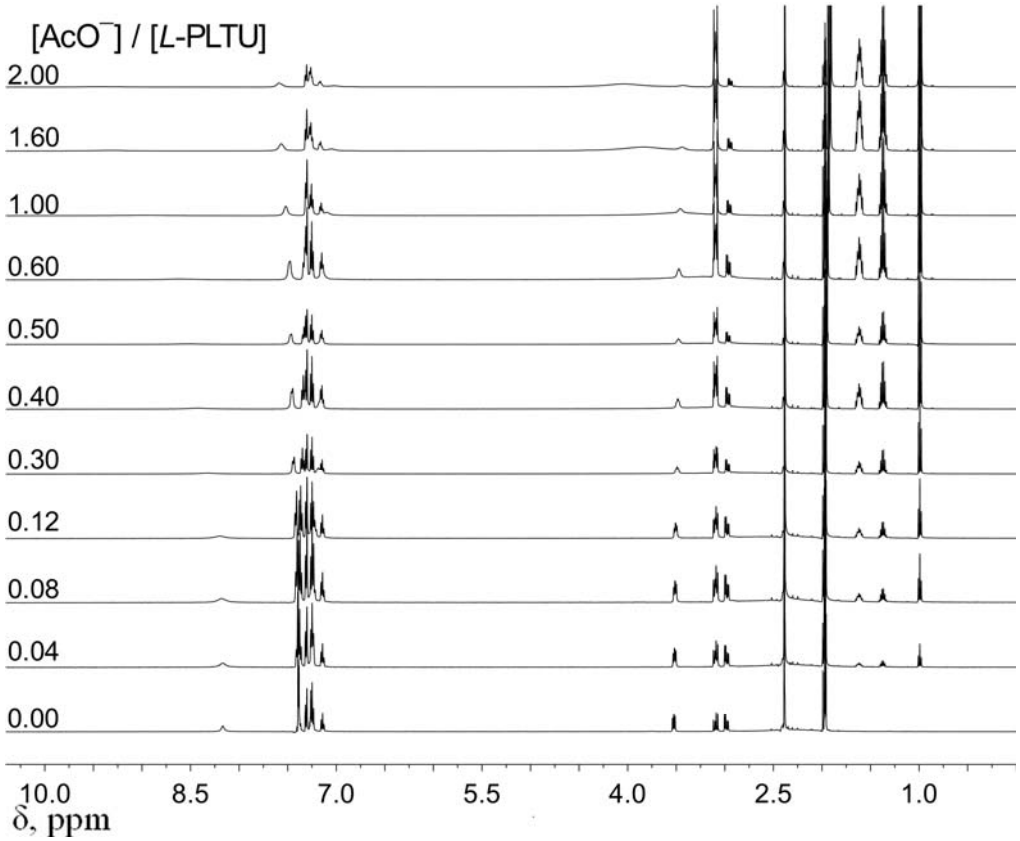


Figure S4. NMR traces of ***L*-PLTU** in CD_3CN in the presence of acetate anion. [***L*-PLTU**] = 10 mM.

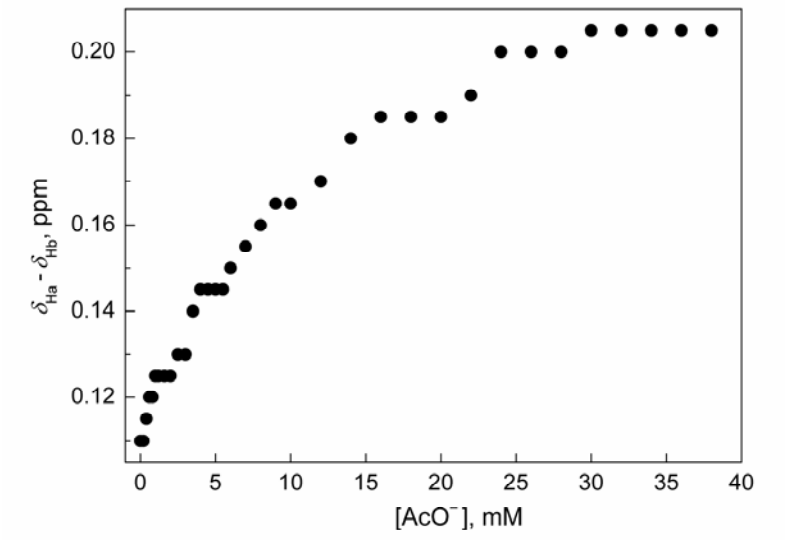
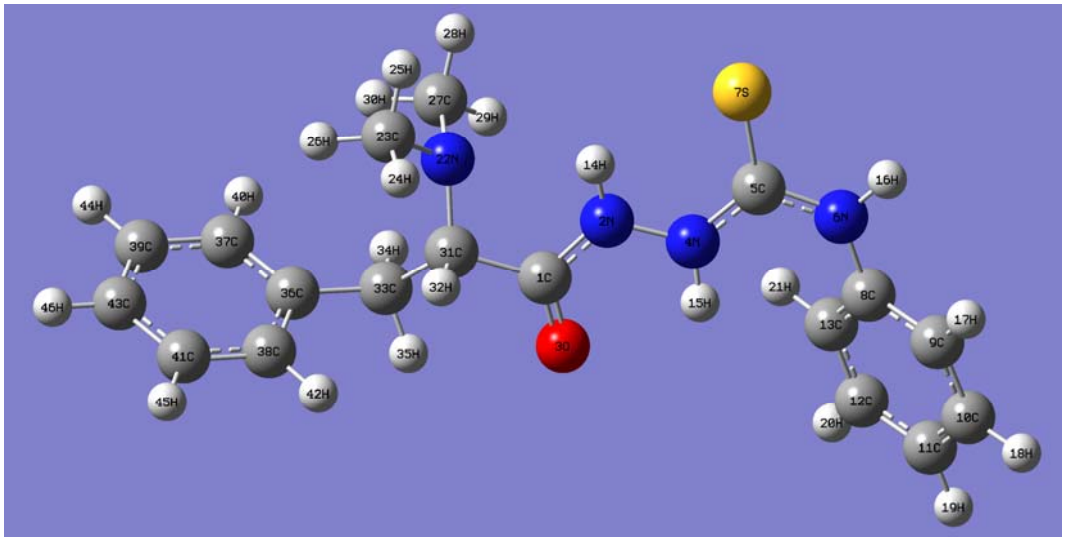


Figure S5. Splitting of NMR signals of gemini protons H_a and H_b next to chiral α-carbon centre in ***L*-PLTU** in the presence of acetate of increasing concentration in CD_3CN. [PLTU] = 10 mM. For numbering of protons H_a and H_b see Scheme 2 in the main text.



Scheme S2. X3LYP/6-311++G(d,p)-optimized structure of **PLTU** with Me_2N...HNC(O) five-membered ring intramolecular hydrogen bond. Hydrogen bond length: N(22)…H(14), 2.27 Å; ond angle: N(22)-H(14)-N(2): 100.26^{o} ; Dihedral angle: N(22)-H(14)-N(2)-C(1): -10.78^{o} .

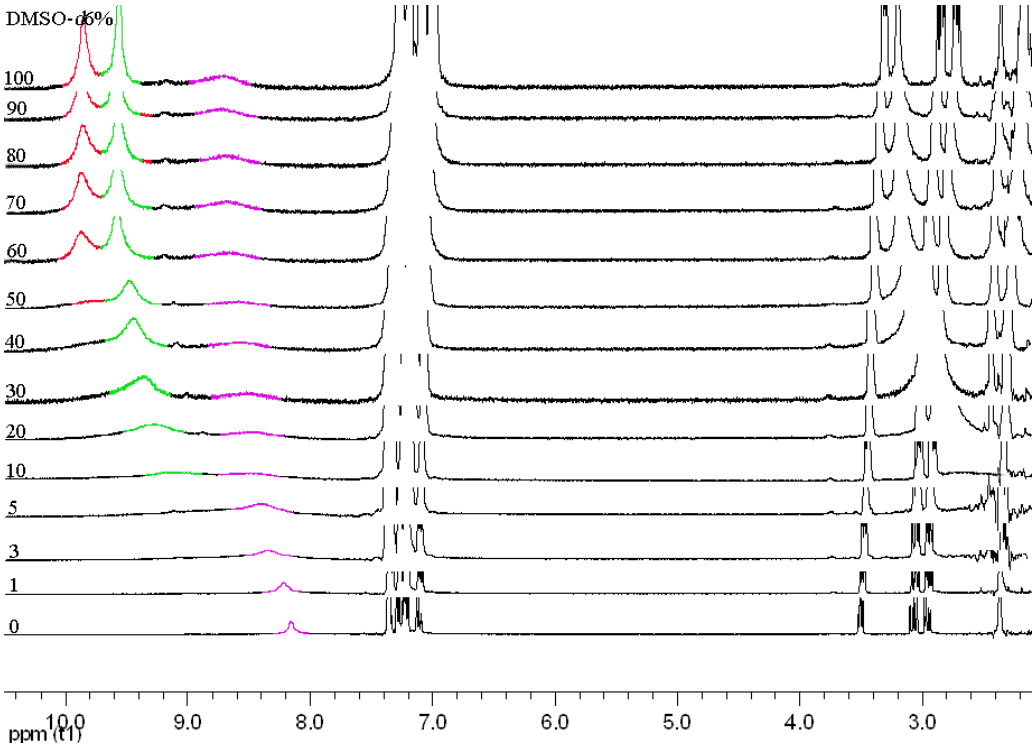


Figure S6. Portion of NMR traces of ***L*-PLTU** in DMSO-d_6/CD_3CN binary solvents of increasing volume fraction of DMSO-d_6. Pink and green peaks are signals of thioureido -NH protons and the red one is that of the *N*-amido -NH proton.

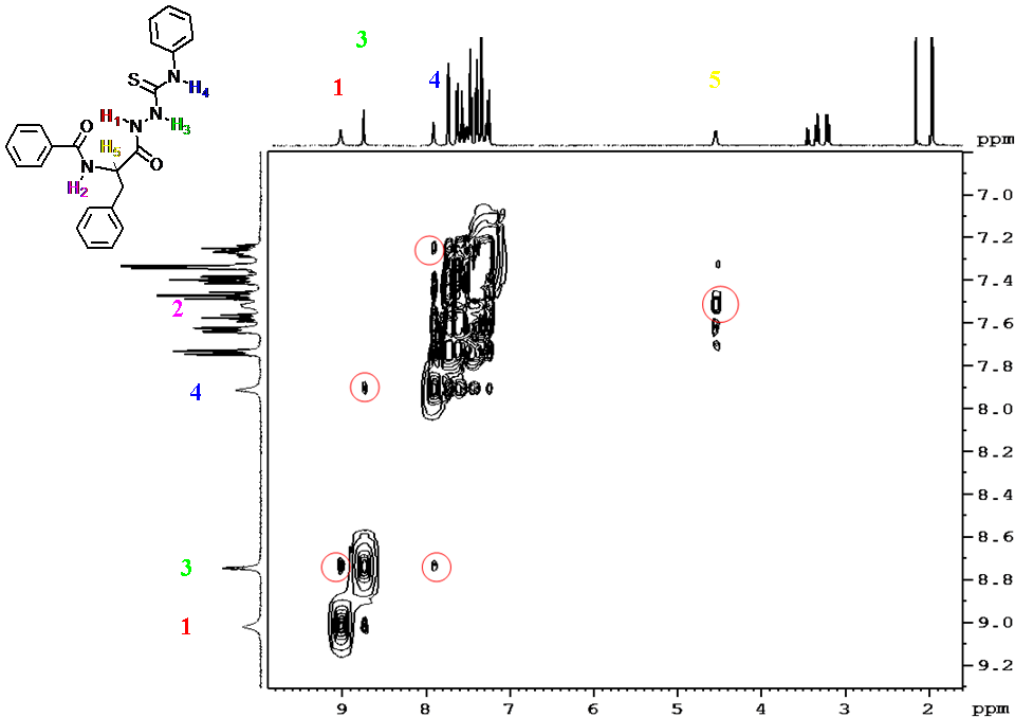


Figure S7. ^{1}H-^{1}H COSY spectrum of **BPTU** in CD_3CN. [**BPTU**] = 10 mM. Crossing peaks highlighted by red circles allow the assignment of the signals to the indicated protons.

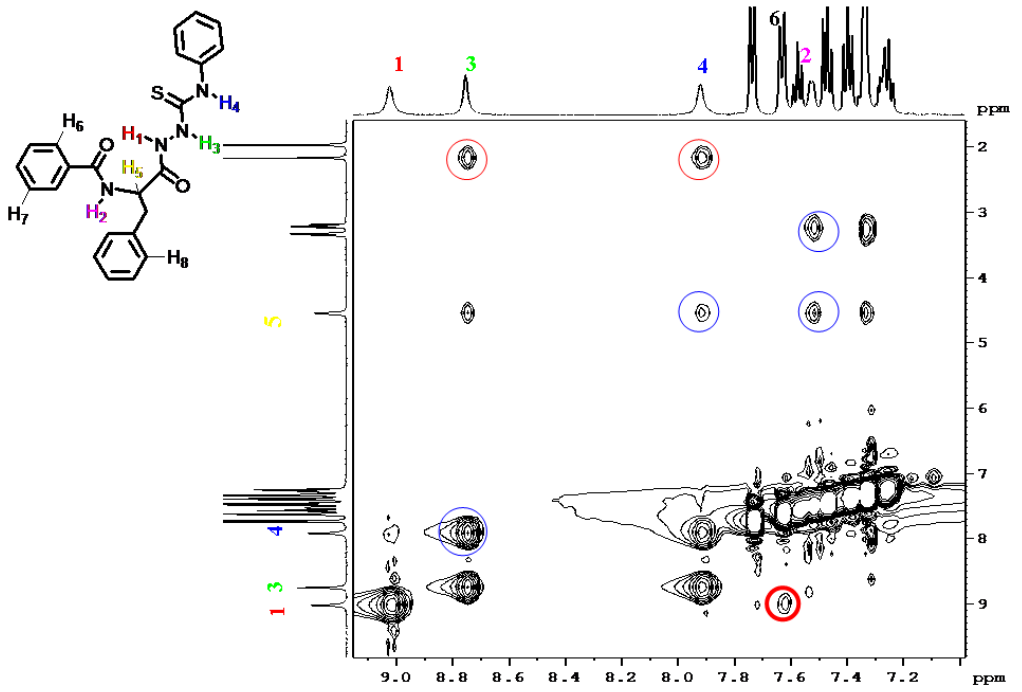


Figure S8. ^{1}H-^{1}H NOESY spectrum of **BPTU** in CD_3CN. Coupling of signals of NH_1 and phenyl CH_6 shown in the bold red circle is a support of the seven-membered intramolecular hydrogen bond between -N$\underline{H}_1$ and benzamido C=$\underline{O}$.

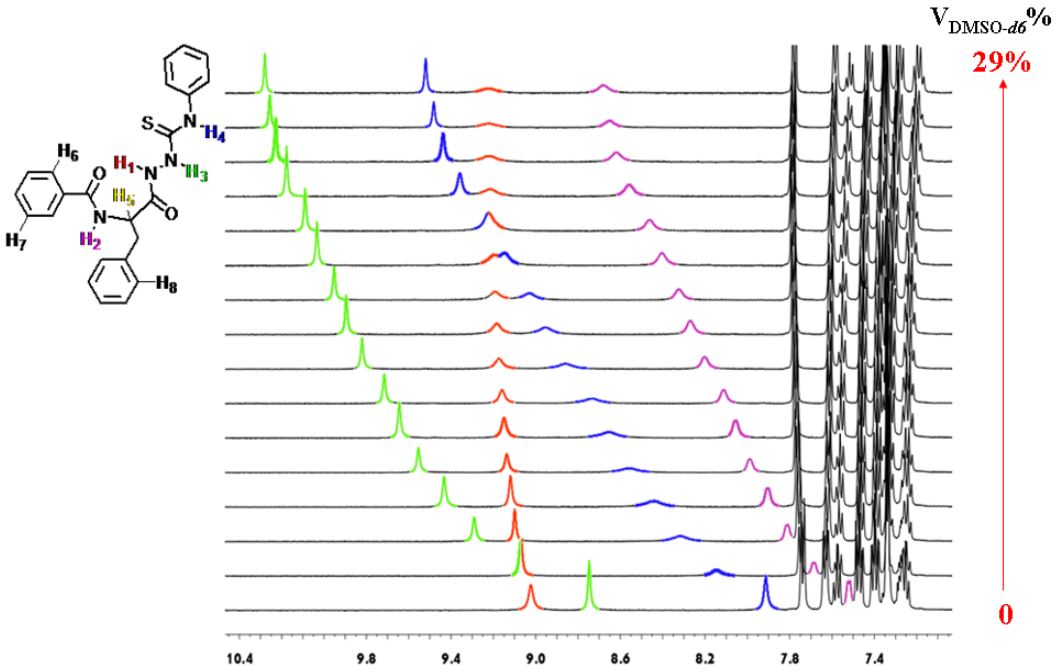


Figure S9. Portion of ^{1}H NMR spectra of ***L*-BPTU** in CD_3CN-DMSO-d_6 binary solvents. [**BPTU**] = 10 mM. The reluctant response of the -NH_1 signal (red peak) towards the solvent composition suggests its involving in an intramolecular hydrogen bond.

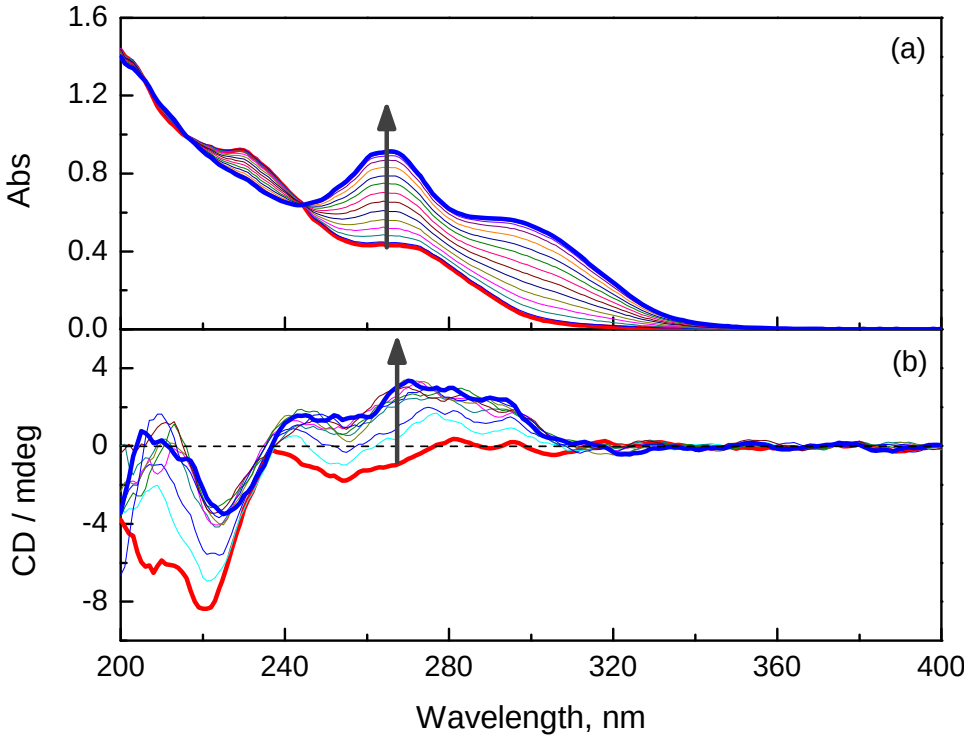


Figure S10. Absorption (a) and CD (b) spectra of ***L*-BPTU** in acetonitrile in the presence of AcO^{-}. [**BPTU**] = 40 μM; [AcO^{-}] = 0 to 200 μM.

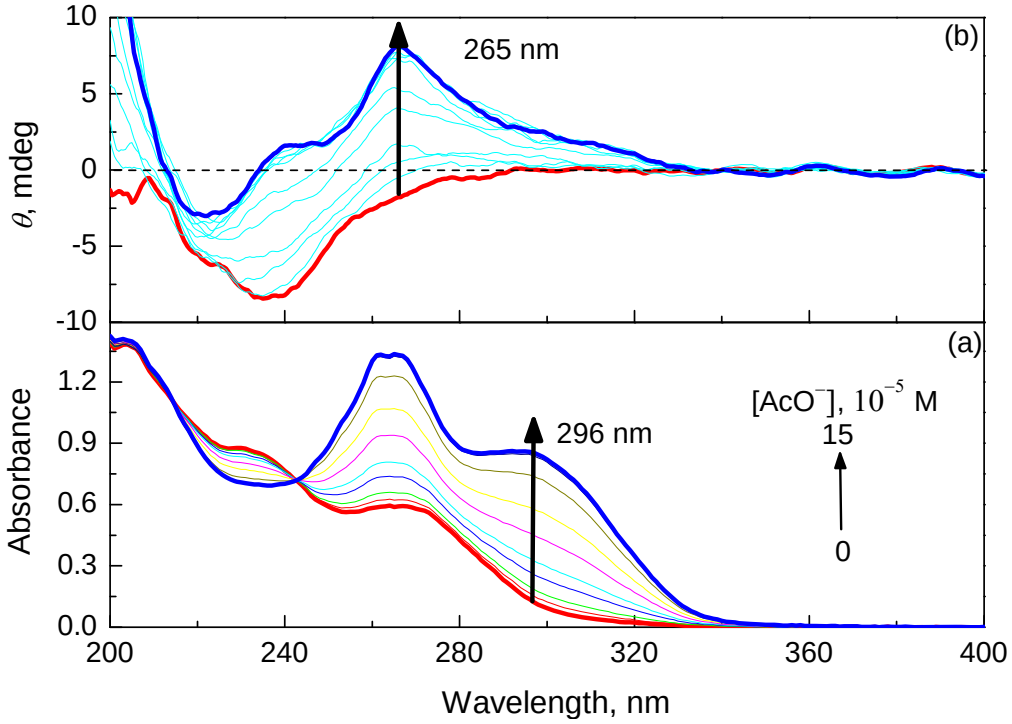
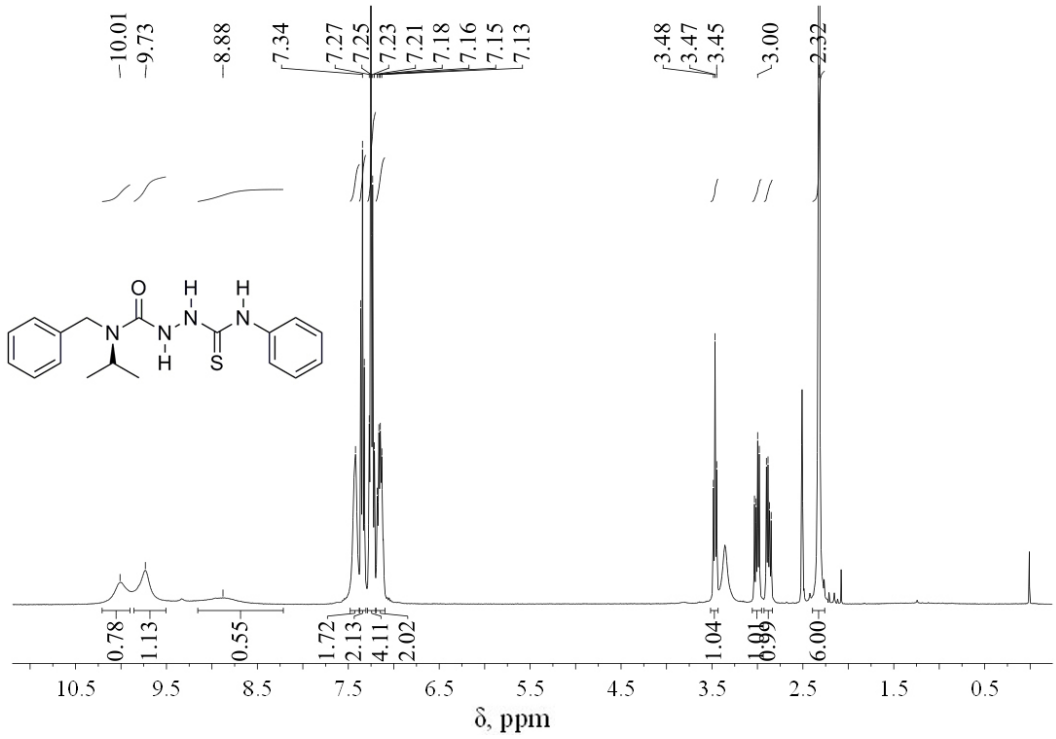


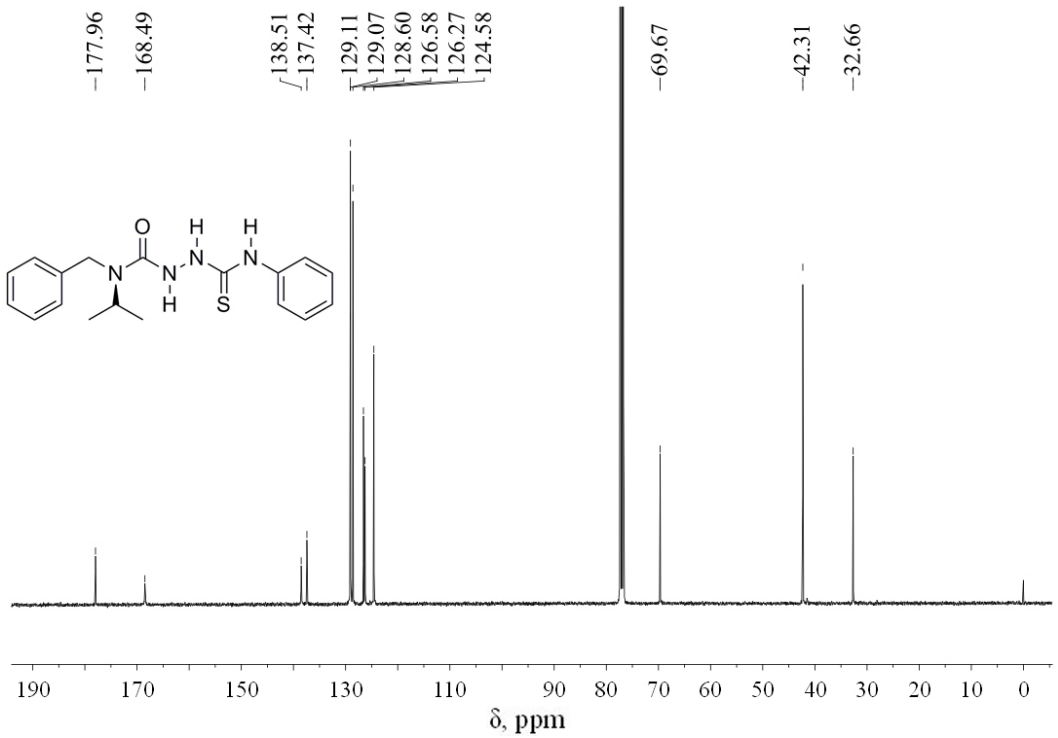
Figure S11 Absorption (a) and CD (b) spectra of ***L*-PATU** in acetonitrile in the presence of acetate anion. [***L*-PATU**] = 40 μM.

^{1}H NMR and ^{13}C NMR spectra of *L*-/*D*-PLTU, *L*-BPTU and *L*-PATU

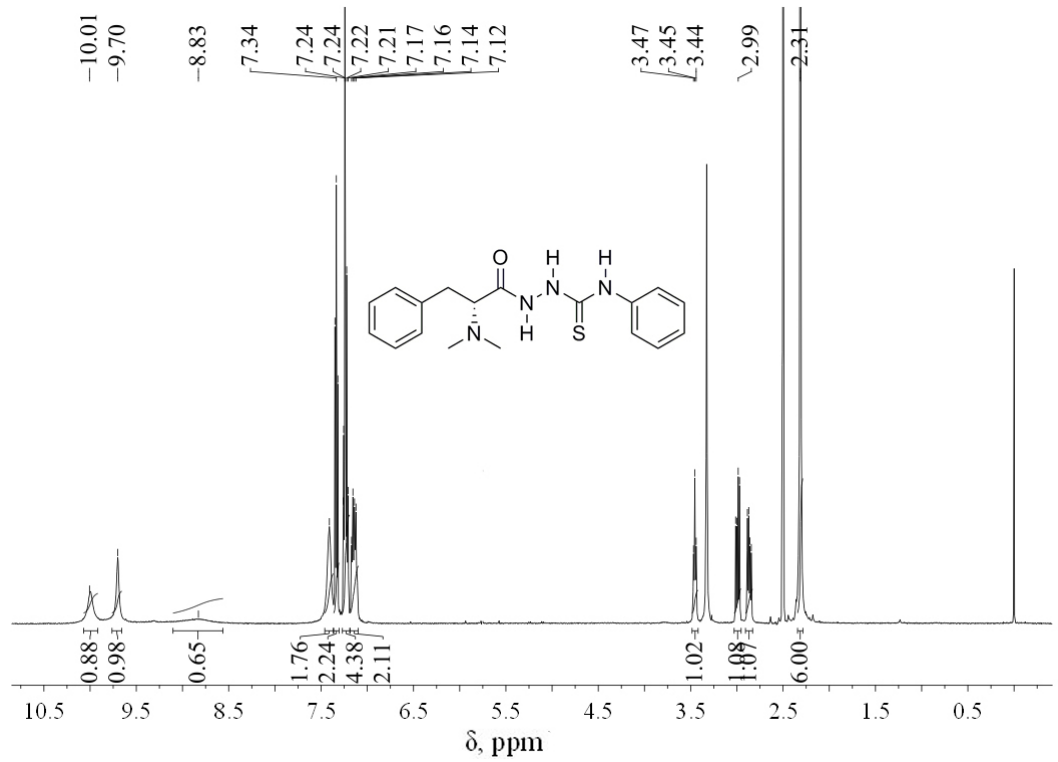
^{1}H NMR of *L*-PLTU (400 MHz, DMSO-d_6)



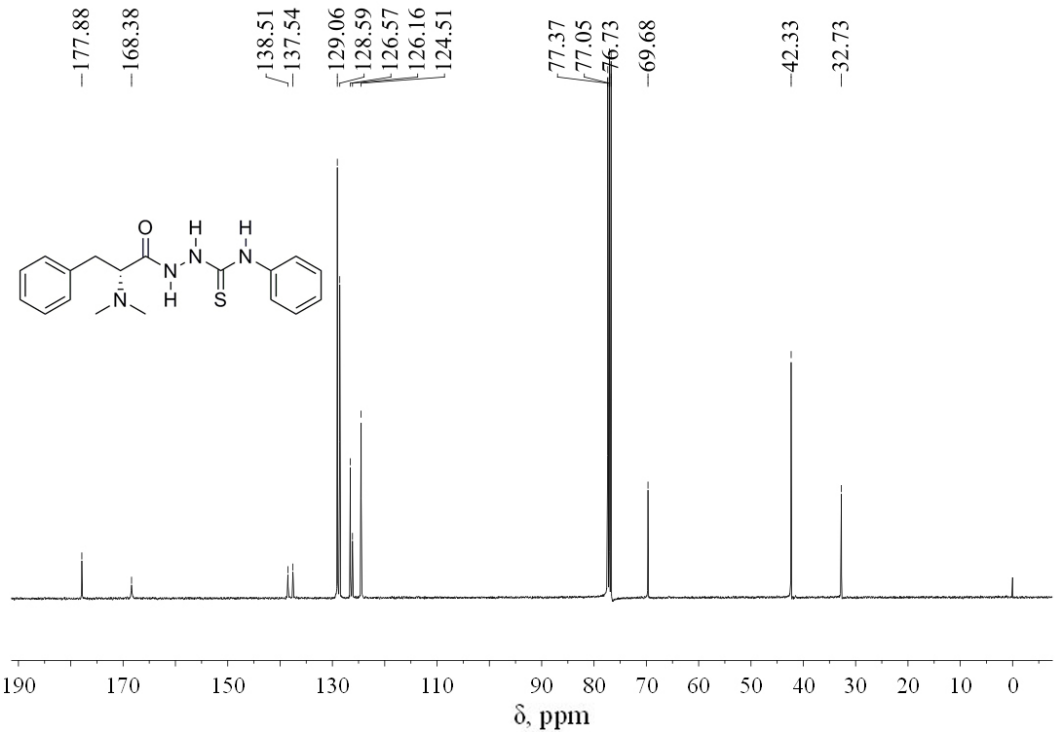
^{13}C NMR of *L*-PLTU (100 MHz, $CDCl_3$)



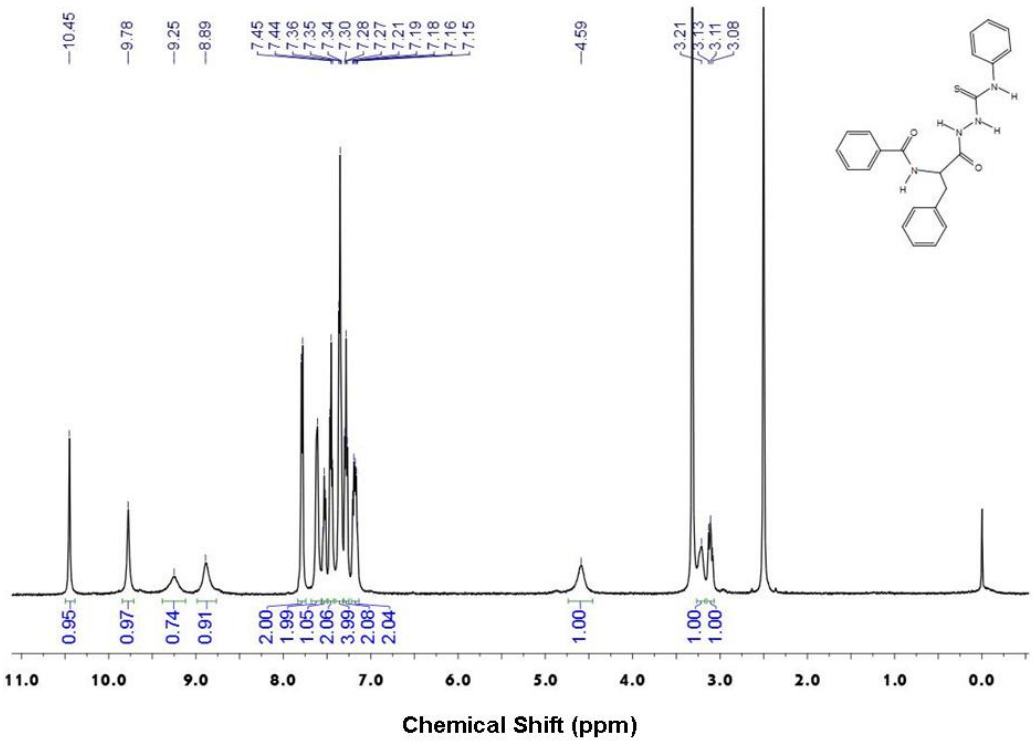
^{1}H NMR of *D*-PLTU (400 MHz, DMSO-d_6)



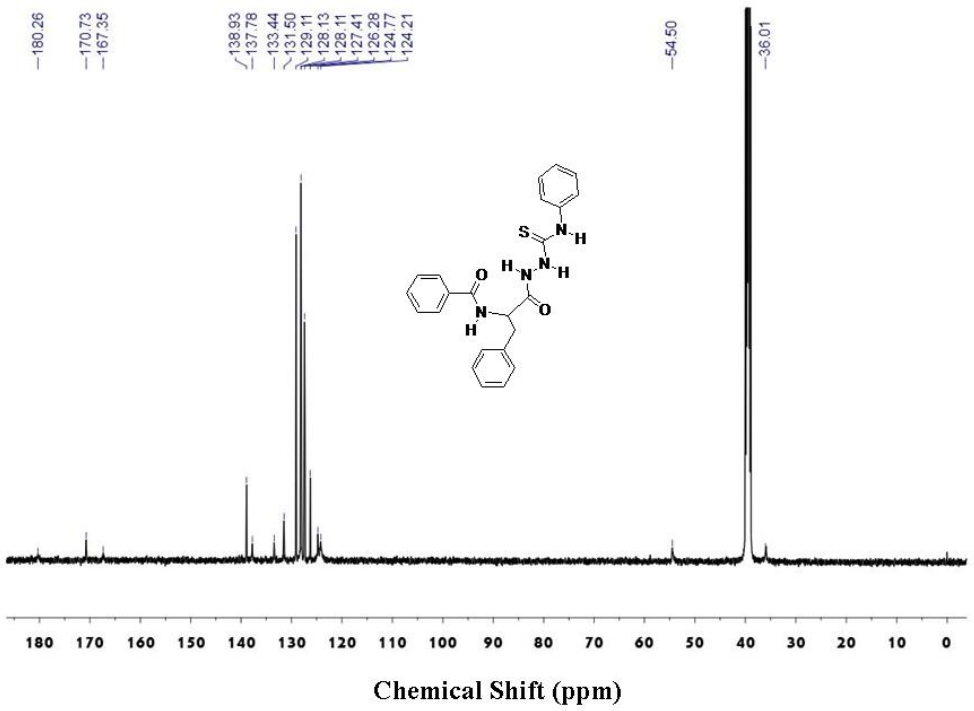
^{13}C NMR of *D*-PLTU (100 MHz, $CDCl_3$)



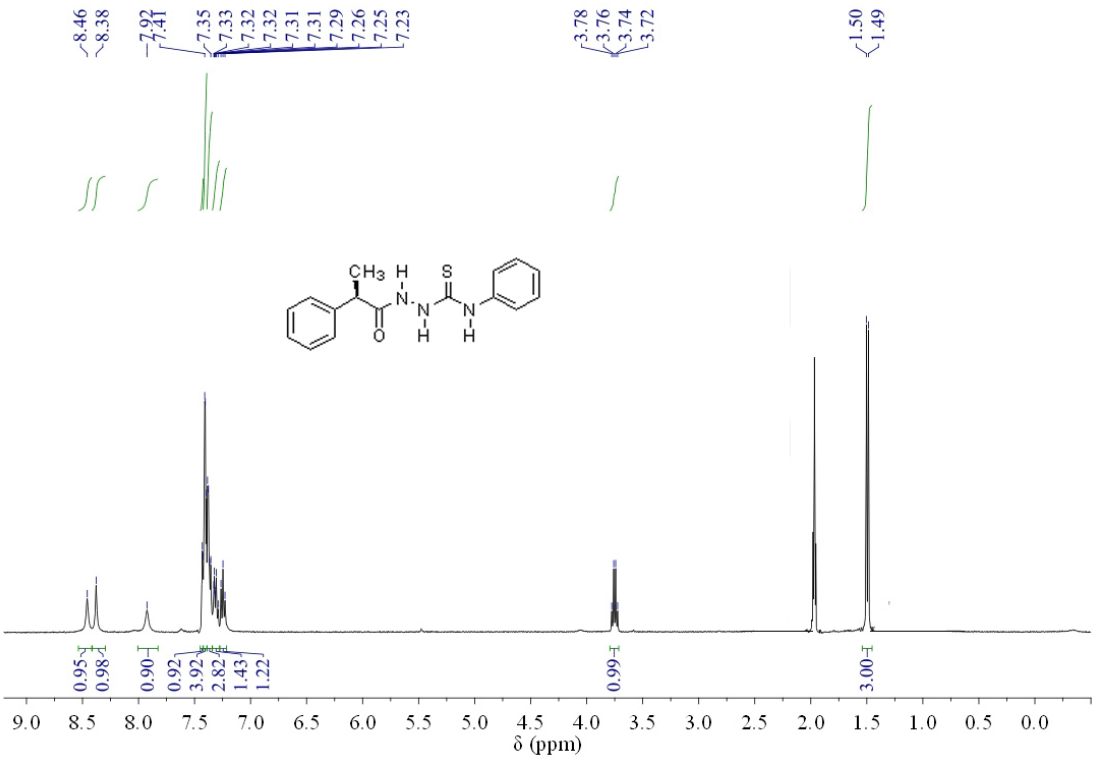
^{1}H NMR of *L*-BPTU (500 MHz, DMSO-d_6)



^{13}C NMR of *L*-BPTU (125 MHz, DMSO-d_6)



^{1}H NMR of *L*-PATU (400 MHz, CD_3CN)



^{13}C NMR of *L*-PATU (100 MHz, CD_3CN)