Supporting Information

A Non-Cytotoxic Pyrrolobenzodiazepine-Ciprofloxacin Conjugate with Activity against *Mycobacterium tuberculosis*

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Table S1: Atomic level interactions of Compound 3 in binding sites of wild type Mtb GyrA

atoms	Distance	Category	Type
ARG39HE - PBD-CIP	2.68753	Hydrogen Bond	Conventional Hydrogen Bond
ARG39HH21 - PBD-CIP	2.6782	Hydrogen Bond	Conventional Hydrogen Bond
DA986H61 - PBD-CIP	2.3365	Hydrogen Bond	Conventional Hydrogen Bond
PBD-CIP - ASP94OD2	2.50891	Hydrogen Bond	Carbon Hydrogen Bond
PBD-CIP - ASP94OD1	2.35693	Hydrogen Bond	Carbon Hydrogen Bond
MN- PBD-CIP	2.3403	Other	Metal-Acceptor
ASP94OD1 - PBD-CIP	3.58727	Halogen	Halogen (Fluorine)
ARG39NH2 - PBD-CIP	4.91059	Electrostatic	Pi-Cation
ASP89OD1 - PBD-CIP	4.98341	Electrostatic	Pi-Anion
PBD-CIP - BPRO124	4.5259	Hydrophobic	Alkyl
TYR93 - PBD-CIP	4.9405	Hydrophobic	Pi-Alkyl
TYR93 - PBD-CIP	5.30015	Hydrophobic	Pi-Alkyl
PBD-CIP - BPRO124	4.96375	Hydrophobic	Pi-Alkyl

Molecular modelling data: Interactions of Ciprofloxacin and Compound 3 with M. tuberculosis DNA Gyrase

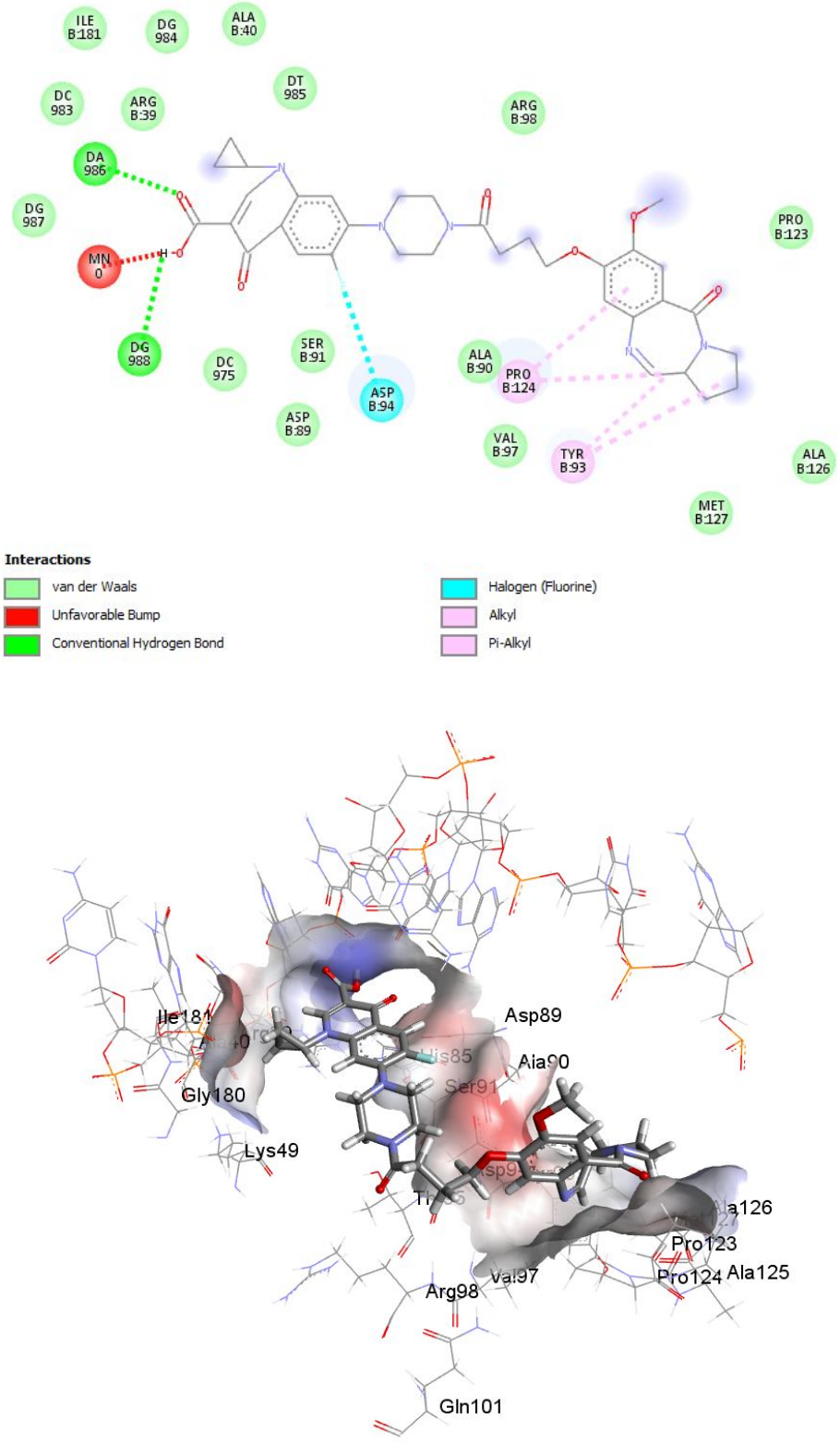


Figure S1: 2D and 3D model showing interactions of Compound 3 in binding sites of S95T Mtb GyrA

Table S2: Atomic level interactions of Compound 3 in binding sites of S95T Mtb GyrA

atoms	Distance	Category	Type
:DA986:H61 - PBD-CIP:O6	2.12545	Hydrogen Bond	Conventional Hydrogen Bond
PBD-CIP:H21 - :DG988:O6	2.68323	Hydrogen Bond	Conventional Hydrogen Bond
ASP94:OD1 - PBD-CIP:F	3.42914	Halogen	Halogen (Fluorine)
PBD-CIP - PRO124	4.77048	Hydrophobic	Alkyl
TYR93 - PBD-CIP	4.58172	Hydrophobic	Pi-Alkyl
TYR93 - PBD-CIP	5.19759	Hydrophobic	Pi-Alkyl
PBD-CIP - PRO124	4.88652	Hydrophobic	Pi-Alkyl
PBD-CIP:H21 - MN	1.34311	Other	Metal-Acceptor

Table S3: Atomic level interactions of Ciprofloxacin in binding sites of wild type Mtb GyrA

atoms	Distance	Category	Type
CIP:H13 - SER118:O	2.88992	Hydrogen Bond	Conventional Hydrogen Bond
:DA990:H8 - CIP:O2	2.76806	Hydrogen Bond	Carbon Hydrogen Bond
CIP:H5 - ASP94:OD2	2.85189	Hydrogen Bond	Carbon Hydrogen Bond
CIP:H10 - ASP122:O	2.99041	Hydrogen Bond	Carbon Hydrogen Bond
CIP:H9 - ASP122:O	2.93845	Hydrogen Bond	Carbon Hydrogen Bond
CIP:H7 - ASP122:O	2.3897	Hydrogen Bond	Carbon Hydrogen Bond
CIP:H12 - GLY120:O	3.08744	Hydrogen Bond	Carbon Hydrogen Bond
MN- CIP:O2	2.53214	Other	Metal-Acceptor
ARG98:NH2 - CIP	4.8887	Electrostatic	Pi-Cation
VAL97 - CIP	4.18269	Hydrophobic	Alkyl
PRO124 - CIP	4.38312	Hydrophobic	Alkyl

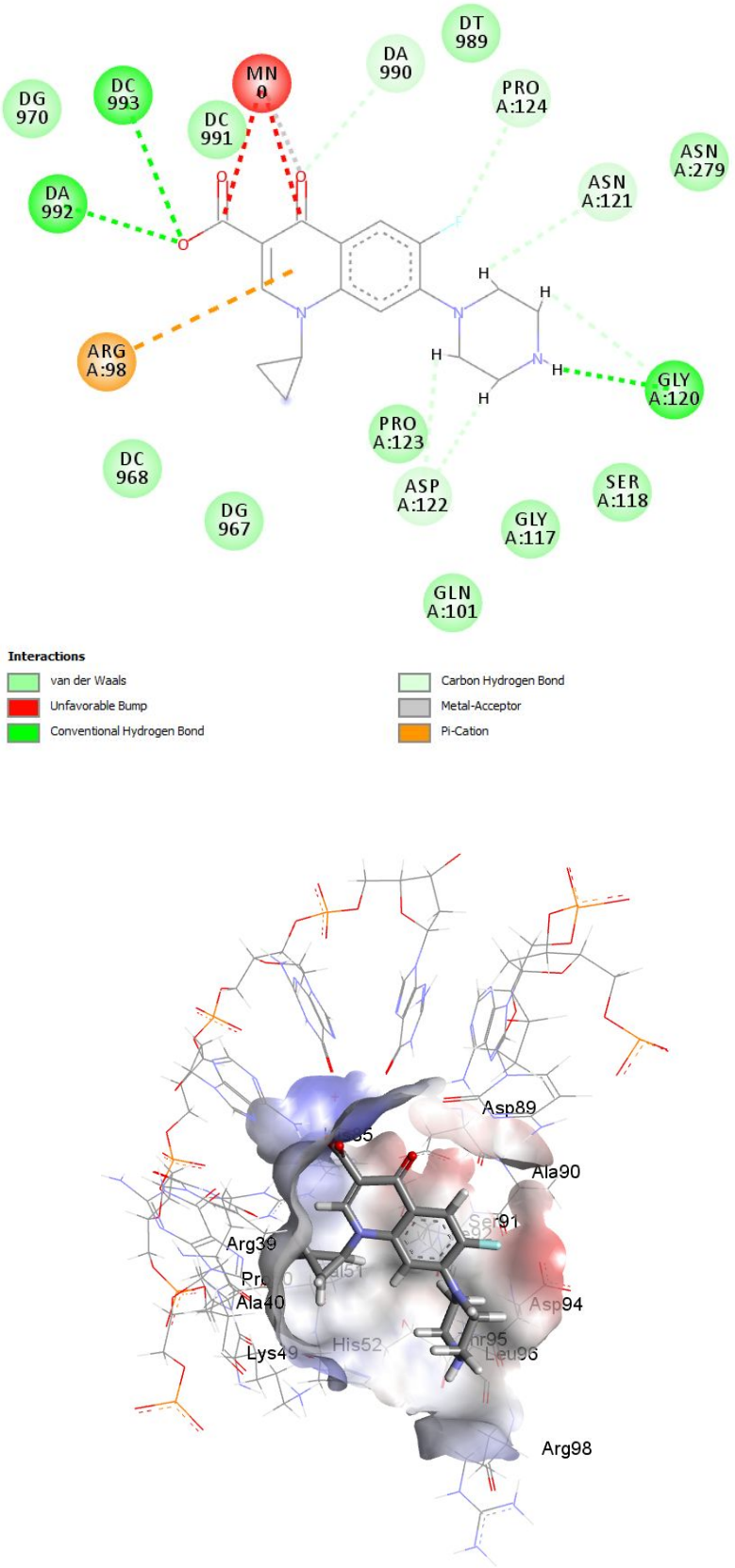


Figure S2: 2D and 3D model showing interactions of Ciprofloxacin in binding sites of S95T Mtb GyrA

Table S4: Atomic level interactions of Ciprofloxacin in binding sites of S95T Mtb GyrA

atoms	Distance	Category	Type
:DA992:H61 - CIP:O	2.58625	Hydrogen Bond	Conventional Hydrogen Bond
:DC993:H41 - CIP:O	2.98835	Hydrogen Bond	Conventional Hydrogen Bond
CIP:H13 - GLY120:O	2.32821	Hydrogen Bond	Conventional Hydrogen Bond
PRO124:HD1 - CIP:F	2.79004	Hydrogen Bond	Carbon Hydrogen Bond
:DA990:H8 - CIP:O2	2.89251	Hydrogen Bond	Carbon Hydrogen Bond
CIP:H9 - ASP122:O	2.67972	Hydrogen Bond	Carbon Hydrogen Bond
CIP:H7 - ASP122:O	2.9912	Hydrogen Bond	Carbon Hydrogen Bond
CIP:H12 - GLY120:O	3.01378	Hydrogen Bond	Carbon Hydrogen Bond
CIP:H3 - ASN121:O	2.50594	Hydrogen Bond	Carbon Hydrogen Bond
MN- CIP:O2	1.95309	Other	Metal-Acceptor
ARG98:NH2 - CIP	4.93434	Electrostatic	Pi-Cation

Table S5: Mutations conferring antibiotic resistance to MDR-*M. tuberculosis* strain 08/00483E

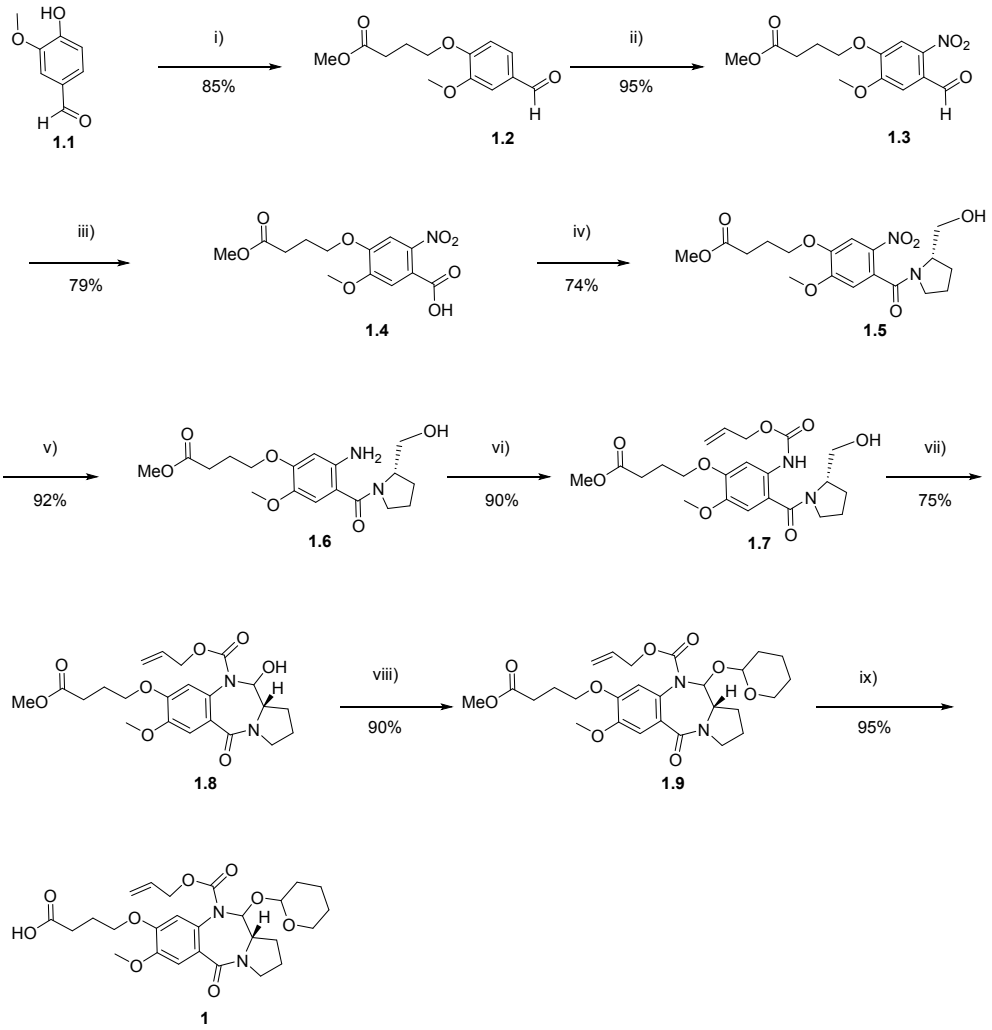
Position	Mutation*	Annotation	Gene**	Description	Antibiotic resistance
761155	C→T	S450L (TCG→TTG)	*rpo*B →	DNA-directed RNA polymerase subunit beta	Rifampicin
781687	A→G	K43R (AAG→AGG)	*rps*L →	30S ribosomal protein S12	Streptomycin
2155168	C→G	S315T (AGC→ACC)	*kat*G ←	Catalase-peroxidase	Isoniazid
2289056	+T[#]	coding (186/561 nt)	*pnc*A ←	Pyrazinamidase/nicotinamidase	Pyrazinamide
3861920	G→A	P11S (CCG→TCG)	*rps*I ←	30S ribosomal protein S9	Streptomycin
4247429	A→G	M306V (ATG→GTG)	*emb*B →	Arabinosyltransferase B	Ethambutol

* Mutations called with reference to forward DNA strand

** Arrow indicates polarity of gene transcription product

Insertion

Synthesis of PBD Core 1



i) K_2CO_3, DMF, Methyl 4-bromobutyrate ii) KNO_3, TFA, iii) $KMnO_4$, Acetone, H_2O, iv) Oxalyl chloride, *S* pyrrolidine methanol, DCM
v) Ammonium formate, Pd/C, MeOH, vi) Allylchloroformate, Pyridine, DCM, vii) TEMPO, BAIB, DCM viii) pTSA, DHP, THF ix) NaOH, Dioxane, H_2O

Scheme 1. The Synthesis of a N10-C11 protected PBD core subunit.

*Synthesis of methyl 4-(4-formyl-2-methoxyphenoxy)butanoate (**1.2**).* A suspension of **1.1** (20 g, 131 mmol), methyl 4-bromobutanoate (24.986 g, 1.05 equiv.) and potassium carbonate (27.25 g, 1.5 equiv.) was prepared in DMF (100 ml) and stirred at room temperature for six hours. After completion of reaction was confirmed by LC-MS analysis, the reaction mixture was diluted with water (500 ml). A white precipitate formed. This precipitate was filtered and washed with cold water to yield a white solid product which was dried in a vacuum oven at 40 °C to yield 28.1 g of **1.2** (85% yield). ^{1}HNMR (400 MHz, $CDCl_3$): δ 9.84 (s, 1H), 7.43 (dd,

1H, J= 8.2, 2.0 Hz), 7.40 (d, 1H, J= 1.6 Hz), 6.97 (d, 1H, J= 8 Hz), 4.16 (t, 2H, J= 6.4 Hz), 3.91 (s, 3H), 3.69 (s, 3H), 2.56 (t, 2H, J= 7.2 Hz), 2.20 (p, 2H, J= 6.0 Hz). ^{13}CNMR (100 MHz, $CDCl_3$): δ 191.0, 173.4, 153.8, 149.8, 130.1, 126.8, 111.5, 109.2, 67.8, 56.0, 51.7, 30.3, 24.2 . EIMS (m/z): 252.9 $(M+H)^+$.

*Synthesis of methyl 4-(4-formyl-2-methoxy-5-nitrophenoxy)butanoate (**1.3**)*. **1.2** (5g, 19.8 mmol) was dissolved in trifluoroacetic acid (12 ml). This solution was added drop wise at 0-5 °C to a stirred solution of potassium nitrate (2.5 g, 1.25 equiv.) in TFA (12 ml). A colour change from colourless to pale yellow occurred on addition. The reaction mix was stirred at room temperature for 20 mins at which point TLC (15% ethyl acetate/n-hexane) showed completion of reaction. The product was concentrated using a rotary evaporator and the residue dissolved in ethyl acetate (200 ml). The solution was washed with brine (3 x 50ml) and dried over magnesium sulphate. The material was concentrated using a rotary evaporator and dried in a vacuum oven at 40 °C to yield 5.81 g of **1.3**, a bright yellow solid (95% yield). The product was taken to the next step without further purification. ^{1}HNMR (400 MHz, $CDCl_3$): δ 10.30 (s, 1H), 7.50 (s, 1H), 7.21 (s, 1H), 4.11 (t, 2H, J= 6.4 Hz), 3.89 (s, 3H), 3.59 (s, 3H), 2.46 (t, 2H, J=7.2 Hz), 2.11 (quin., 2H, J= 6.4 Hz). ^{13}CNMR (100 MHz, $CDCl_3$): δ 187.7, 173.1, 153.4, 151.6, 143.0, 125.4, 109.8, 108.1, 68.6, 56.6, 51.7, 30.9, 24.0. EIMS (m/z): 297.8 $(M+H)^+$.

*Synthesis of 5-methoxy-4-(4-methoxy-4-oxobutoxy)-2-nitrobenzoic acid (**1.4**)*. **1.3** (5g, 16.83 mmol) was dissolved in acetone (160 ml) and placed in a three necked round bottomed flask with fitted with a reflux condenser. A solution of potassium permanganate (10% w/v, 100 ml) was prepared and heated to 70 °C. This solution was quickly added to the stirred solution of **1.3** and the reaction mix was heated at 70 °C. The reaction mix was left for three hours and completion of reaction observed by TLC (15% ethyl acetate/hexane) and colour change from purple to brown. The reaction vessel was allowed to cool and the reaction mix passed filtered through celite packed into a sintered funnel. The brown residue on the celite was washed with hot water (300 ml). A solution of sodium bisulphite (10 g) in hydrochloric acid (1M, 160 ml) was then added to the filtrate. The pH of the product was then adjusted to 1 through the addition of 1M hydrochloric acid. This caused partial precipitation of **1.4**. The product was extracted from the filtrate with dichloromethane (400 ml) and dried using magnesium sulphate. The DCM extract was concentrated using a rotary evaporator and dried at 40 °C in a vacuum oven to yield 4.155 g of **1.4** as a pale yellow solid (79% yield). ^{1}HNMR (400 MHz, $CDCl_3$): δ 7.38 (s, 1H), 7.21 (s, 1H), 4.16 (t, 2H, J= 6.0 Hz), 3.97 (s, 3H), 3.71 (s, 3H), 2.57 (t, 2H, J=7.2 Hz),

2.11 (quin, 2H, J= 6.6 Hz). ^{13}CNMR (100 MHz, $CDCl_3$): δ 173.4, 169.1, 152.3, 150.4, 119.6, 111.5, 108.1, 68.5, 56.6, 51.9, 30.2, 24.1. EIMS (m/z): 314.1 $(M+H)^+$.

*Synthesis of (S)-methyl 4-(4-(2-(hydroxymethyl)pyrrolidine-1-carbonyl)-2-methoxy-5-nitrophenoxy)butanoate (**1.5**)*. **1.4** (5 g, 15.9 mmol) was placed in a round bottomed flask to which a gas bubbler was attached. Oxalyl chloride (4.4 g) was added to the flask as a solvent and the formation of HCl gas was observed through the bubbler. After 20 minutes, the bubbling ceased and the reaction mix was concentrated in a rotary evaporator. The resulting residue was dissolved in toluene (10 ml) and the solution concentrated once more to remove any excess oxalyl chloride. The resulting residue was dissolved in dichloromethane (10 ml) and added drop wise to a solution of + (*S*)-pyrrolidinemethanol (1.05 equiv.) and triethylamine (1.5 equiv.) in dichloromethane (20 ml) at 0 °C. The reaction allowed to warm to room temperature and left until TLC/LC-MS (2% methanol/ethyl acetate) showed completion of the reaction at about three hours. The reaction mix was washed with hydrochloric acid (1M, 10 ml) and brine (10 ml) and dried over magnesium sulphate. The solution was concentrated using a rotary evaporator and the crude product purified by flash column chromatography 0.02:0.98 methanol/ethyl acetate to yield **1.5** as a yellow solid in 74% yield. ^{1}HNMR (400 MHz, $CDCl_3$): δ 7.72 (s, 1H), 6.82 (s, 1H), 4.17 (t, 2H, J= 6.0 Hz), 3.98 (s, 3H), 3.91 (m, 1H) 3.89 (m, 1H) 3.72 (s, 3H), 3.18 (t, 2H, J=6.8 Hz), 2.58 (t, 2H J=7.2 Hz), 2.22 (m, 3H), 1.86 (m, 4H). ^{13}CNMR (100 MHz, $CDCl_3$): δ 173.3, 154.8, 148.4, 137.1, 127.8, 117.8, 109.1, 108.3, 68.4, 61.6, 56.3, 51.8, 49.5, 30.3, 28.6, 24.1. EIMS (m/z): 397.1 $(M+H)^+$.

*Synthesis of (S)-methyl 4-(5-amino-4-(2-(hydroxymethyl)pyrrolidine-1-carbonyl)-2-methoxyphenoxy)butanoate (**1.6**)*. **1.5** (2 g, 5.4 mmol) was dissolved in methanol. Ammonium formate (5 equiv.) was then added to the flask, together with a catalytic amount of palladium on carbon (10% wt. loading). The solution was refluxed at 60 °C for 30 minutes, after which LC-MS/TLC (2% methanol/ethyl acetate) showed completion of the reaction. The solution was then filtered through Celite, with the Pd/C residue remaining on the Celite washed with methanol. The filtrate was concentrated using a rotary evaporator to yield **6** as a red oil which upon exposure to hard vacuum formed a foam in 92% yield. ^{1}HNMR (400 MHz, $CDCl_3$): δ 6.74 (s, 1H), 6.26 (s, 1H), 4.35 (bs, 1H) 4.01 (t, 2H, J= 6.4 Hz), 3.76 (s, 3H), 3.68 (s, 3H), 3.60 (m, 1H), 3.53 (m, 1H), 2.53 (t, 2H, J= 7.2 Hz), 2.15 (m, 3H), 1.87 (m, 3H), 1.73 (m, 2H). ^{13}CNMR (100 MHz, $CDCl_3$): δ 173.6, 171.2, 151.2, 141.4, 113.1, 102.2, 67.5, 66.8, 60.9, 57.2, 51.7, 30.4, 28.5, 24.9, 21.0. EIMS (m/z): 367.2 $(M+H)^+$.

*Synthesis of (S)-methyl 4-(5-(((allyloxy)carbonyl)amino)-4-(2-(hydroxymethyl)pyrrolidine-1-carbonyl)-2-methoxyphenoxy)butanoate (**1.7**)*. **1.6** (5 g, 13.7 mmol) was dissolved in anhydrous dichloromethane (100 ml) and anhydrous pyridine (2.54 ml, 2.3 equiv.) under nitrogen and the resulting solution cooled to -10 °C. A solution of allyl chloroformate (1.73 g, 1.05 equiv.) was dissolved in anhydrous dichloromethane (100 ml) and added drop wise to the solution of **1.6**. The reaction mix was then allowed to reach room temperature and reaction progression monitored using TLC (5% acetone/DCM). After about two hours, the reaction was complete. The reaction mix was sequentially washed with saturated copper sulphate solution (100 ml), water (100 ml) and sodium bicarbonate solution (100 ml). The reaction mix was dried over magnesium sulphate and concentrated in a rotary evaporator to yield **1.7** in 90% yield as a red oil. ^{1}HNMR (400 MHz, $CDCl_3$): δ 8.75 (s, 1H), 7.77 (s, 1H), 6.81 (s, 1H), 5.98 (m, 1H), 5.35 (dd, 1H, J= 13.2 Hz, 1.6Hz), 5.25 (dd, 1H, J= 10.4Hz, 1.2 Hz), 4.63 (dd, 2H, J= 5.6Hz, 1.2 Hz) 4.41 (bs, 1H), 4.11 (t, 2H, J=5.6), 3.82 (s, 3H), 3.69 (s, 3H), 3.59 (m, 1H), 3.50 (m, 1H), 2.54 (t, 2H, J= 7.6 Hz), 2.17 (m, 4H), 1.89 (m, 1H), 1.65 (m, 3H). ^{13}CNMR (100 MHz, $CDCl_3$): δ 172.4, 169.5, 152.6, 149.5, 143.0, 131.5, 131.3, 118.1, 117.1, 110.6, 104.6, 67.1, 66.7, 64.8, 60.1, 55.6, 50.6, 29.5, 28.7, 27.4, 24.1, 23.4. EIMS (m/z): 451.1 $(M+H)^+$.

*Synthesis of allyl (11aS)-11-hydroxy-7-methoxy-8-(4-methoxy-4-oxobutoxy)-5-oxo-2,3,11,11a-tetrahydro-1H-benzo[e]pyrrolo[1,2-a][1,4]diazepine-10(5H)-carboxylate (**1.8**)*. **1.7** (3.5 g, 7.8 mmol) was dissolved in dichloromethane (175 ml). To this solution, (2,2,6,6-tetramethylpiperidine-1-yl)oxyl (TEMPO) (0.122 g, 0.1 equiv.) and bis(acetoxy)iodobenzene

(BAIB) (3.01 g, 1.2 equiv.) were added and the reaction mix monitored for reaction progression via TLC (5% acetone/DCM) and LC-MS. After six hours the reaction went to completion. The reaction mixture was washed sequentially with saturated sodium metabisulphite (75 ml), saturated sodium bicarbonate solution (75 ml), water (75 ml) and brine (75 ml). The solution was concentrated using a rotary evaporator and the crude product was purified using flash column chromatography using a 50:50 Ethyl acetate/n-hexane gradient as a yellow oil. The product was recrystallized using diethyl ether overnight to form **1.8** as a white powder with a yield of 75%. . ^{1}HNMR (400 MHz, $CDCl_3$): δ 7.22 (s, 1H), 6.67 (s, 1H), 5.79 (m, 1H), 5.60 (d, 1H, J= 9.6 Hz), 5.14 (d, 2H, J= 11.2 Hz), 4.67 (dd, 1H, J= 13.6Hz, 5.2 Hz), 4.45 (d, 1H, J= 12.4 Hz), 4.06 (m, 2H), 3.90 (s, 3H), 3.68 (s, 3H), 3.54 (m, 1H), 3.46 (m, 1H), 2.53 (t, 2H, J= 7.2 Hz), 2.12 (m, 4H), 2.03 (m, 2H). ^{13}CNMR (100 MHz, $CDCl_3$): δ 173.5, 167.1, 156.1, 150.0, 148.7, 131.8, 128.3, 125.9, 118.0, 114.0, 110.7, 86.0, 67.9, 66.8, 60.3, 60.0, 56.1, 53.5, 51.7, 50.8, 46.4, 30.3, 28.7, 24.2, 23.1. EIMS (m/z): 449.3 $(M+H)^+$.

*Synthesis of allyl (11aS)-7-methoxy-8-(4-methoxy-4-oxobutoxy)-5-oxo-11-((tetrahydro-2H-pyran-2-yl)oxy)-2,3,11,11a-tetrahydro-1H-benzo[e]pyrrolo[1,2-a][1,4]diazepine-10(5H)-carboxylate (**1.9**)*. **1.8** (3.5 g, 7.8 mmol) was dissolved in ethyl acetate (50 ml). Dihydropyran (6.571 g, 10 equiv.) and a catalytic amount of PTSA (35 mg) were added to the reaction mix. The progression of the reaction was monitored using TLC (5% acetone/DCM) and LC-MS and after two hours the reaction was complete. The reaction mix was diluted with a further amount of ethyl acetate (50 ml) and washed sequentially with saturated sodium bicarbonate solution (50 ml) and brine (75 ml). The ethyl acetate layer was dried using magnesium sulphate and concentrated using a rotary evaporator to produce **1.9** in 90% yield. ^{1}HNMR (400 MHz, $CDCl_3$): δ 7.22 (s, 1H), 7.19 (s, 1H), 6.85 (s, 1H), 6.59 (s, 1H), 5.85-5.71 (m, 4H), 5.28-4.80 (m, 8H), 4.65-4.31 (m, 4H), 4.05-4.00 (m, 5H), 3.88-3.89 (m, 10H), 3.66-3.66 (m, 9H), 3.53-3.46 (m, 13H), 2.55-2.50 (m, 4H), 2.14-1.86 (m, 8H), 1.84-1.70 (m, 8H), 1.66-1.43 (m, 14H). ^{13}CNMR (100 MHz, $CDCl_3$): 173.4, 167.4, 149.1, 132.0, 114.9, 100.0, 98.4, 96.1, 94.6, 91.7, 88.6, 68.0, 67.7, 66.5, 63.6, 62.9, 60.1, 56.1, 51.6, 51.2, 46.3, 30.9, 30.2, 29.0, 25.4, 24.2, 20.0. EIMS (m/z): 533.1 $(M+H)^+$.

*Synthesis of 4-(((11aS)-10-((allyloxy)carbonyl)-7-methoxy-5-oxo-11-((tetrahydro-2H-pyran-2-yl)oxy)-2,3,5,10,11,11a-hexahydro-1H-benzo[e]pyrrolo[1,2-a][1,4]diazepin-8-yl)oxy)butanoic acid (**1**).* **1.9** (3.5 g, 6.571 mmol) was dissolved in dioxane (70 ml), and a solution of sodium hydroxide (0.5 M) was added in excess to the solution. The reaction was monitored using LC-MS and went to completion after 5 hours. The dioxane was removed from the reaction mix using a rotary evaporator, and the remaining residue was diluted with water (25 ml). The solution was acidified using citric acid solution (1M, 25 ml). The acid was extracted using ethyl acetate (2 x 50 ml) and the combined organic fractions then washed with brine (50 ml). The resulting solution was dried over magnesium sulphate and concentrated over a rotary evaporator. The resulting white solid **2** was resolved in 95% yield. . ^{1}HNMR (400 MHz, $CDCl_3$): δ 7.24 (s, 1H), 7.21 (s, 1H), 6.88 (s, 1H), 6.57 (s, 1H), 5.87 (d, 2H, J= 9.2 Hz), 5.75 (d, 2H, J= 5.2Hz, 5.14-4.93 (m, 6H), 4.93-4.76 (m, 1H), 4.67-4.34 (m, 5H), 4.07-4.02 (m, 6H), 3.99-3.82 (m, 9H), 3.70-3.50 (m, 12H), 2.60-2.53 (m, 5H), 2.14-1.95 (m, 9H), 1.86-1.68 (m, 6H), 1.62-1.15 (m, 8H). ^{13}CNMR (100 MHz, $CDCl_3$): 177.3, 167.5, 149.1, 131.9, 117.1, 114.4, 110.5, 94.7, 67.9, 67.5, 66.4, 63.0, 56.1, 46.5, 30.9, 30.2, 30.1, 29.0, 25.4, 25.3, 25.1, 24.0, 23.3, 20.2, 20.0, 19.8. EIMS (m/z): 519.1 $(M+H)^+$.

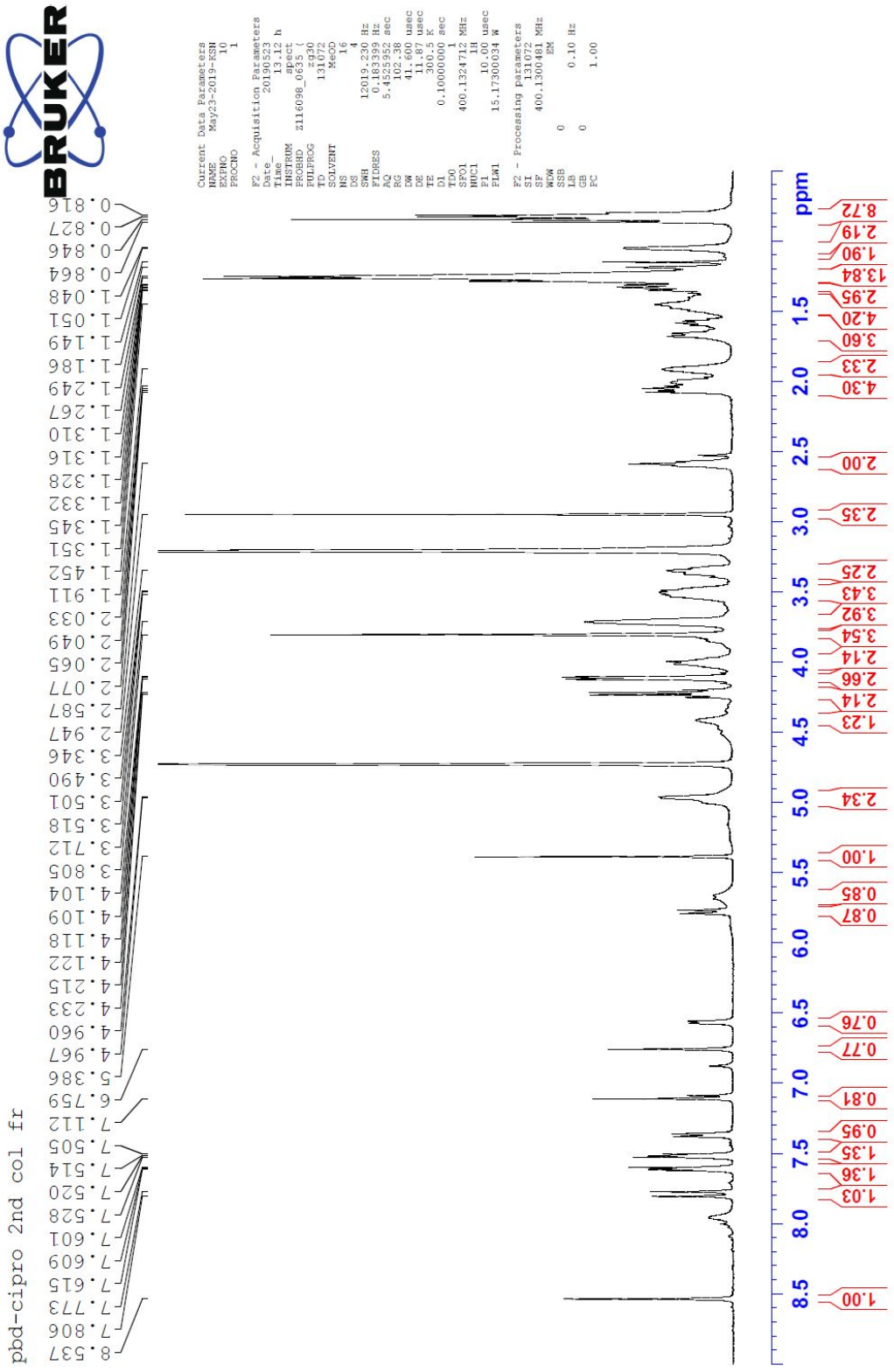


Figure S3: ^{1}H-NMR of C8-linked PBD-Ciprofloxacin ethyl ester conjugate (3a)

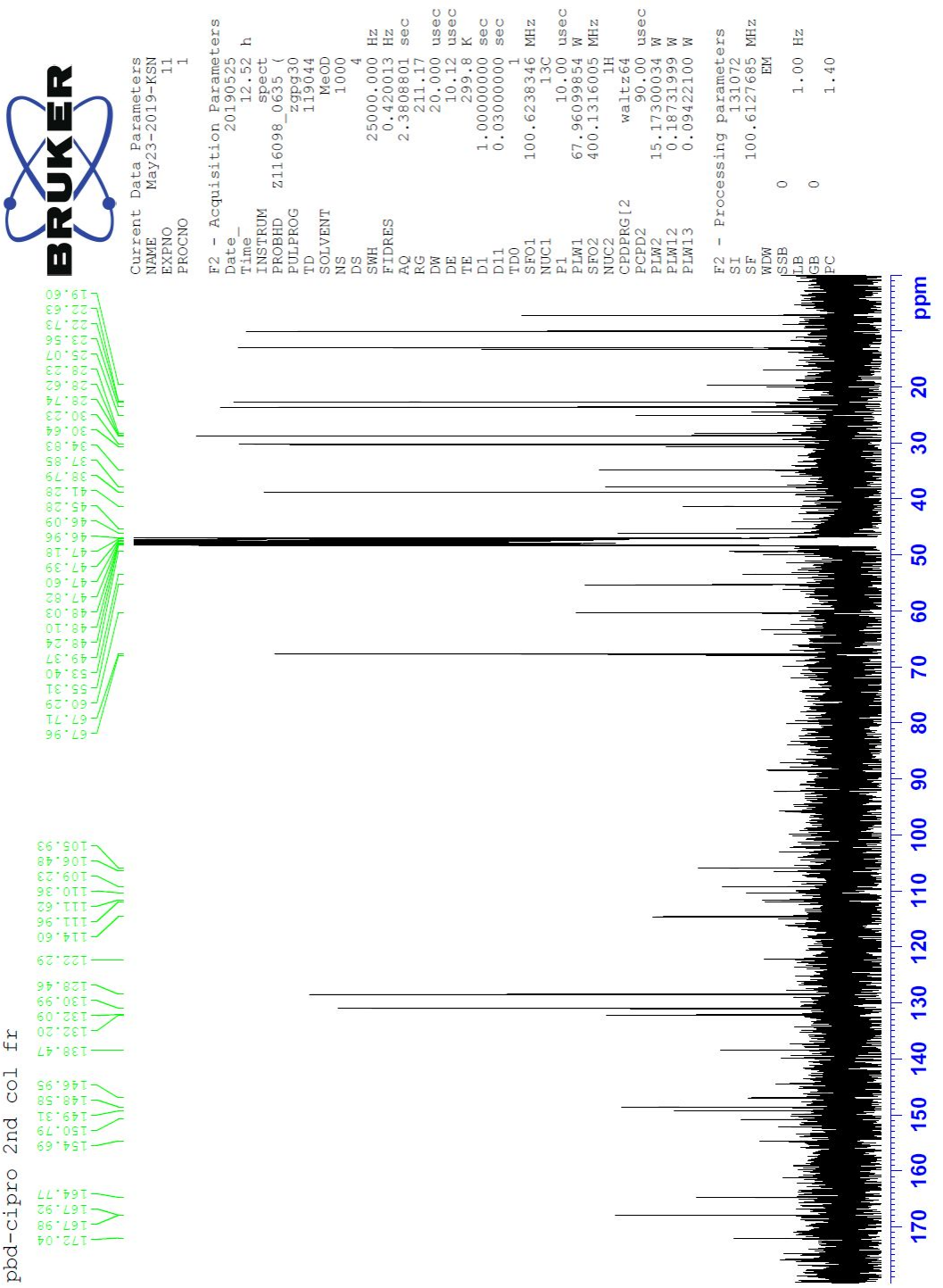


Figure S4: ^{13}C-NMR of C8-linked PBD-Ciprofloxacin ethyl ester conjugate (3a)

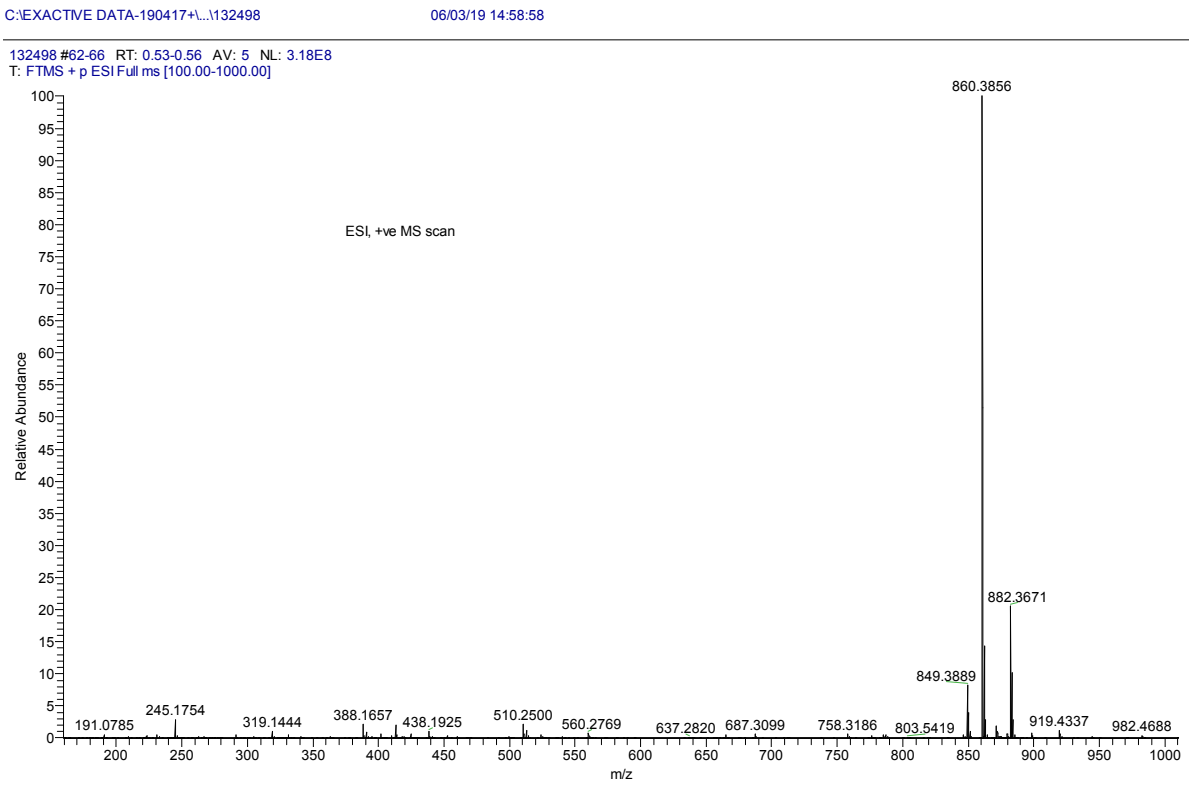


Figure S5: HRMS of C8-linked PBD-Ciprofloxacin ethyl ester conjugate (3a)

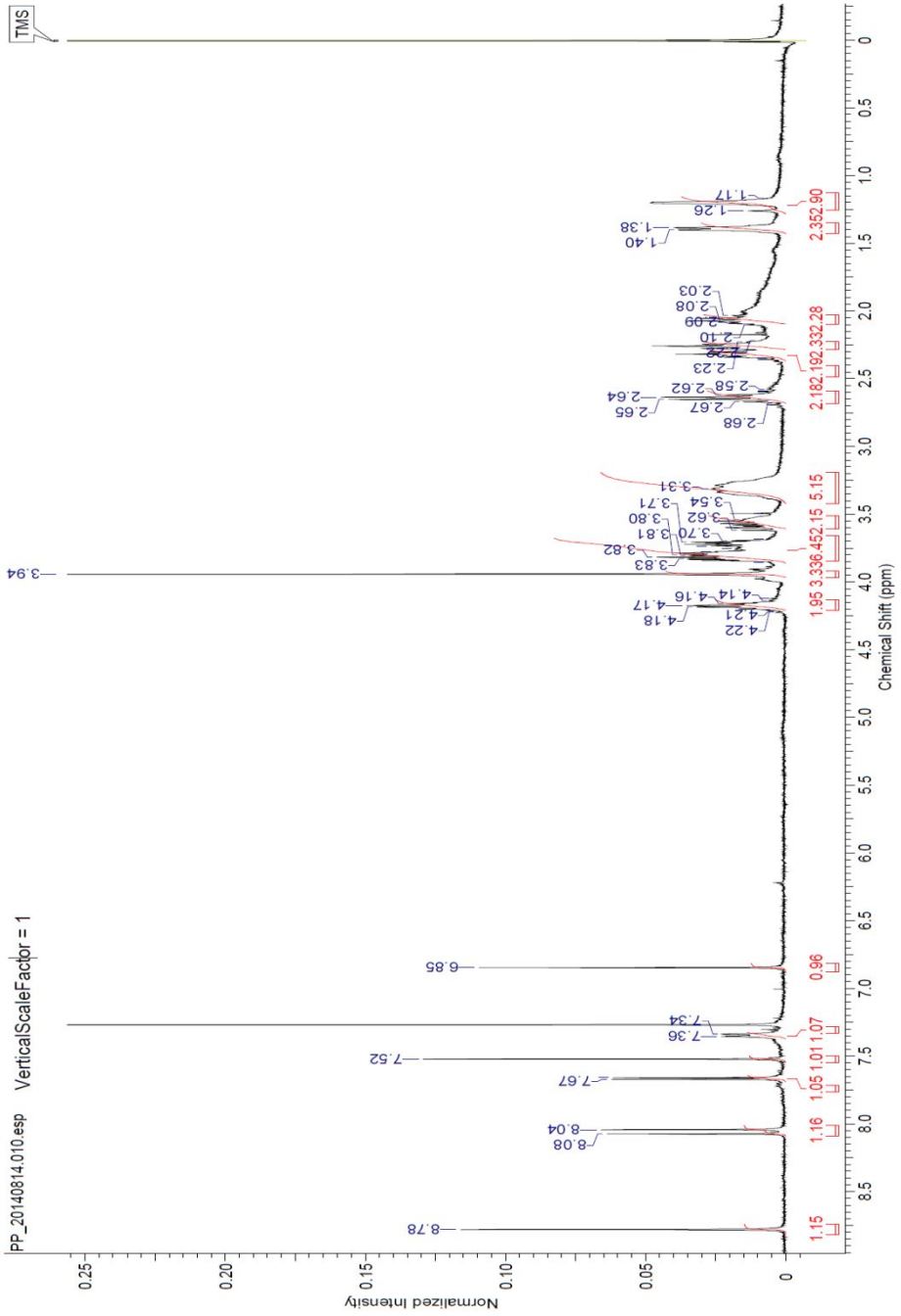


Figure S6: ^{1}H-NMR of C8-linked PBD-Ciprofloxacin Hybrid Compound 3

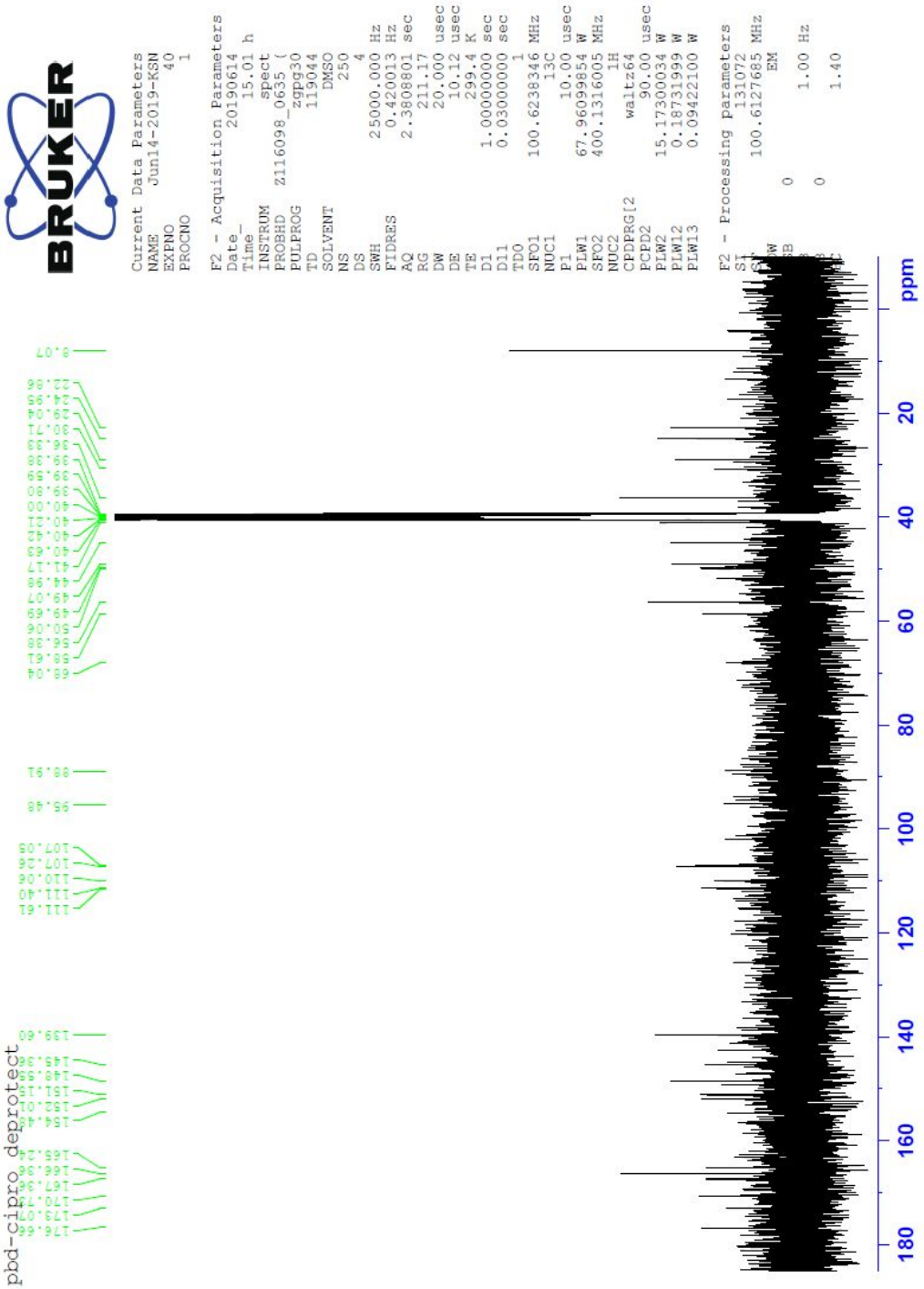


Figure S7: ^{13}C-NMR of C8-linked PBD-Ciprofloxacin Hybrid Compound 3