Chemical Science & Engineering Research

Supporting Information

Synthesis, Antimicrobial Evaluation and Molecular Docking Studies of Tetrazole Containing Hybrid Levofloxacin Derivatives

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Figure legend for supplementary materials

Experimental:

***Materials and analysis*:**

Melting points (°C, uncorrected) of the synthesized compounds were checked in the open capillary tubes using a digital auto melting point apparatus (Labtronics 110, India) and found uncorrected. All the chemicals and solvents were purchased from Sigma– Aldrich, Merck and Himedia, India. Purity of all the products was checked by thin layer chromatography on a TLC silica gel 60 F254 using eluting solvents such as ethyl acetate and chloroform (1:1). The synthesized compounds were purified by column chromatography using the column, packed with silica gel 100–200 mesh and eluted with (ethyl acetate: chloroform, 1:2) mixture. All the compounds were characterized employing a FT-IR spectrometer (Thermo Nicolet-Avatar-330 FT-IR spectrophotometer) using KBr pellets. ^{1}H NMR spectroscopy in DMSO-d_6 (400 MHz, Bruker), ^{13}C NMR spectroscopy in DMSO-d_6 (100 MHz, Bruker) using tetramethylsilane (TMS) as internal standard were also carried out. The Coupling constant (J values) is reported in Hz. Elemental analyses (C, H and N) were performed using the Thermo Scientific Flash 2000 organic elemental analyzer.

All the reactions routinely monitored by Thin-layer chromatography (TLC). All the reported melting points were taken in open capillaries and were uncorrected. Infrared (IR) spectra were recorded in KBr (pellet forms) on a Thermo Nicolet-Avatar-330 Fourier Transform Infrared (FT-IR) spectrophotometer and only noteworthy absorption values (cm^{-1}) were listed. ^{1}H and ^{13}C NMR (nuclear magnetic resonance) were recorded with Bruker AMX-400 spectrometer at 400 and 100 MHz respectively. NMR spectra were obtained in DMSO-d_6 solutions and are reported as parts per million (ppm) downfield from a tetramethylsilane internal standard. Mass spectrometry is recorded with Applied Biosystem mass spectrometer. Elemental analyses (C, H and N) were performed using the Thermo Scientific Flash 2000 organic elemental analyzer. Merck silica gel (100-200 mesh) was used for column chromatography.

General procedure for synthesis of 1-aryl-1H-tetrazoles (*2a-2g*):

A 100 mL RB flask was charged with sodium azide (1.2 mmol), triethylorthoformate (1.5 mmol) and corresponding aryl aniline (1 mmol) in acetic acid (25 mL). The reaction mixture was heated to 80°C for 5-6 hrs. The flow of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was quenched with crushed ice and the solid thrown out was filtered, washed with water and dried under vacuum to obtain crystalline solid.

***Typical procedure for synthesis of 2-chloro-1-(1-aryl-1H-tetrazol-5-yl)ethanone* (3a-3g)**

A 100 mL RB flask was charged with 1-aryl-1*H*-tetrazole (1 mmol), chloroacetylchloride (2.5mmol) and pyridine (0.1 mmol) in tedrahydrofuran (25 mL) at 0°C. The reaction mixture was reflux for 6 hrs. The flow of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was quenched with crushed ice and the solid thrown out

was filtered, washed with water and dried under vacuum to obtain white solid. Finally the crude product was purified through the column chromatography.

***General procedure for synthesis of* 1-*(1-aryl-1H-tetrazol-5-yl)-2-(piperazin-1-yl)ethanone* (5a-5g)**

A 150 mL conical flask was charged with 2-chloro-1-(1-aryl-1*H*-tetrazol-5-yl)ethanone(1 mmol), piperazine (3 mmol) and triethylamine (0.1 mmol) in acetonitrile (25 mL). The reaction mixture was stirred for 6 hrs at room temperature. The reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was quenched with crushed ice and the solid was filtered, washed with water and dried under vacuum to get novel 1-(1-aryl-1*H*-tetrazol-5-yl)-2-(piperazin-1-yl)ethanone. Finally the crude product was purified through the column chromatography.

***General procedure for synthesis of 9-fluoro-3,7-dihydro-3-methyl-7-oxo-10-(4-(2-oxo-2-(1-phenyl-1H-tetrazol-5-yl)ethyl)piperazin-1-yl)-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxylic acid* (7a-7g)**

A 150 mL conical flask was charged with 1-(1-aryl-1*H*-tetrazol-5-yl)-2-(piperazin-1-yl)ethanone (1 mmol), 10-chloro-9-fluoro-3,7-dihydro-3-methyl-7-oxo-2*H*-[1,4]oxazino[2,3,4-*ij*]quinoline-6-carboxylic acid (**6**) (1.2 mmol) and triethylamine (0.1 mmol) in acetonitrile (25 mL). The reaction mixture was stirred for 6 hrs at room temperature. The reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was quenched with crushed ice and the solid was filtered, washed with water and dried under vacuum to get novel 9-fluoro-3,7-dihydro-3-methyl-7-oxo-10-(4-(2-oxo-2-(1-phenyl-1H-tetrazol-5-yl)ethyl)piperazin-1-yl)-2*H*-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxylic acid. Finally the crude product was purified through the column chromatography.

Synthetic procedure and spectral data for new compounds

The compounds **5a-5g** was already reported and as a continuous research work, a mixture of 1-(1-aryl-1*H*-tetrazol-5-yl)-2-(piperazin-1-yl)ethanone (1mmol) (**5a-5g**) derivatives and 10-chloro-9-fluoro-3,7-dihydro-3-methyl-7-oxo-2*H*-[1,4]oxazino[2,3,4-*ij*]quinoline-6-carboxylic acid (**6**) in acetonitrile (25 ml) was stirred at room temperature for a 5-6 hours. The progress of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was quenched with crushed ice and the solid was filtered, washed with water and dried under vacuum to get novel 9-fluoro-3,7-dihydro-3-methyl-7-oxo-10-(4-(2-oxo-2-(1-aryl-1*H*-tetrazol-5-yl)ethyl)pip-erazin-1-yl)-2*H*-[1,4]oxazino[2,3,4-*ij*]quinoline-6-carboxylicacid (**7a-7g**). Finally the crude product was purified through column chromatography. Thus tetrazole containing hybrid levofloxacin derivatives (**7a-7g**) are synthesized with excellent yields.

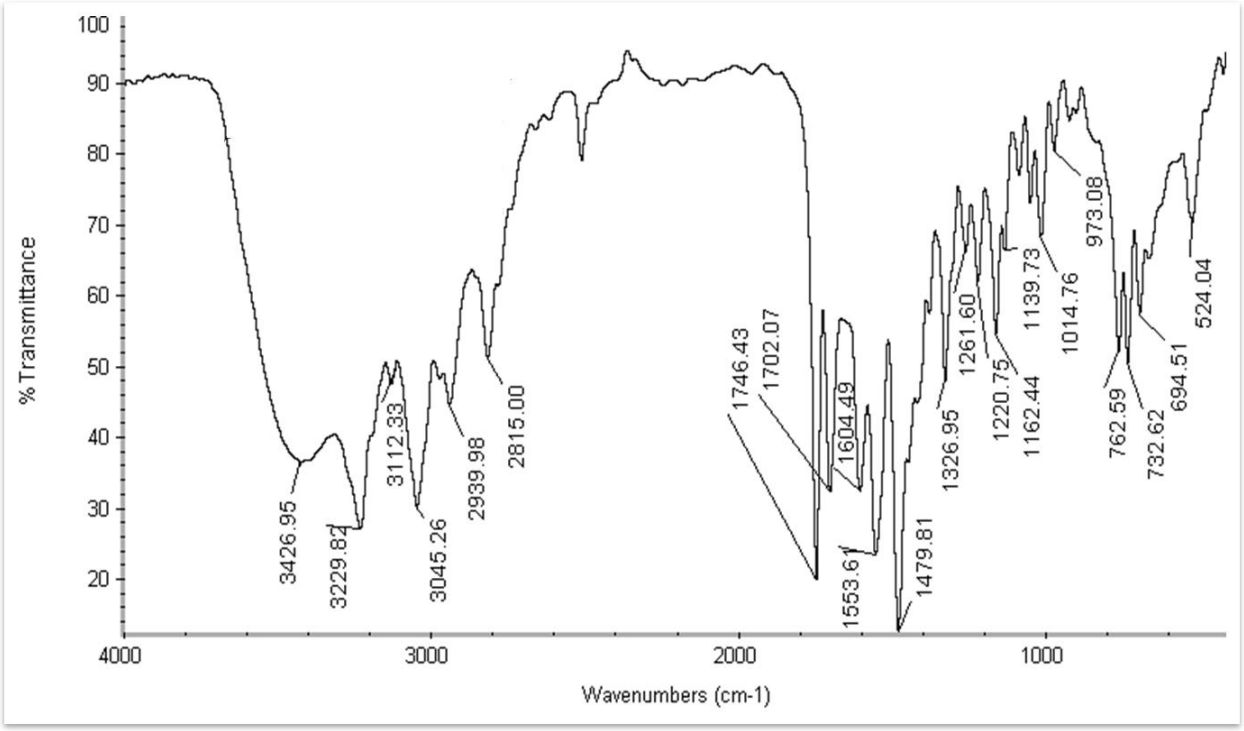


Fig. S1. IR spectrum of compound **7a**

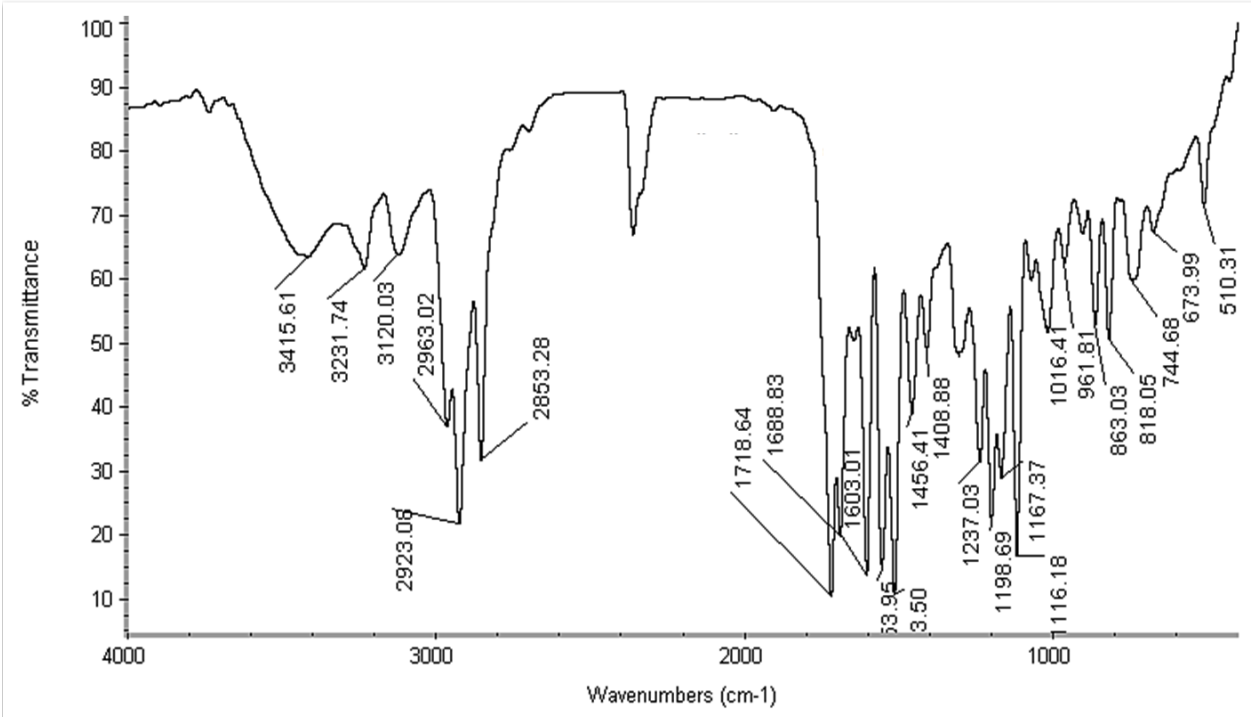


Fig. S2. IR spectrum of compound **7b**

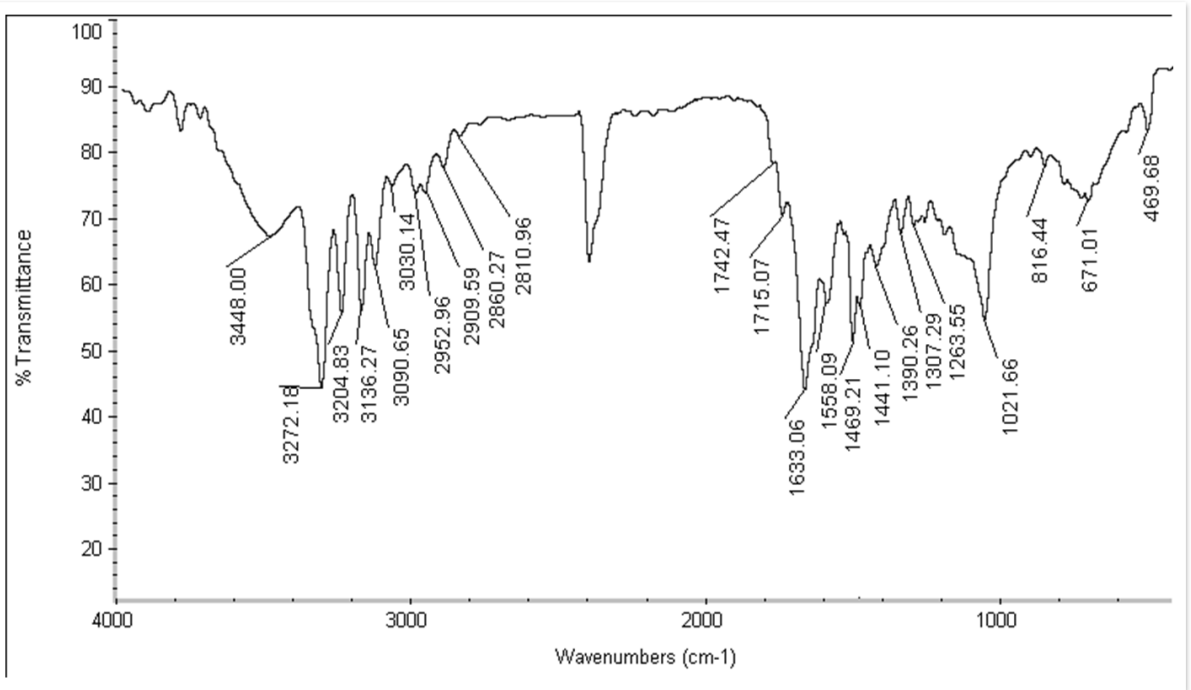


Fig. S3. IR spectrum of compound **7c**

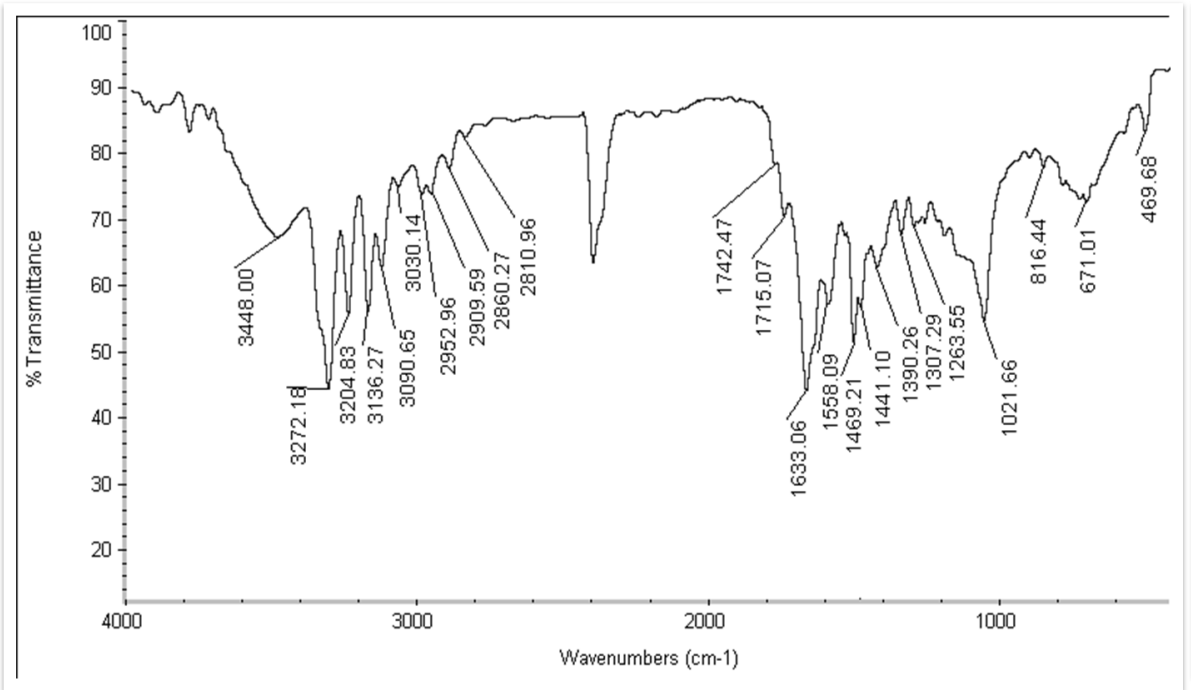


Fig. S4. IR spectrum of compound **7d**

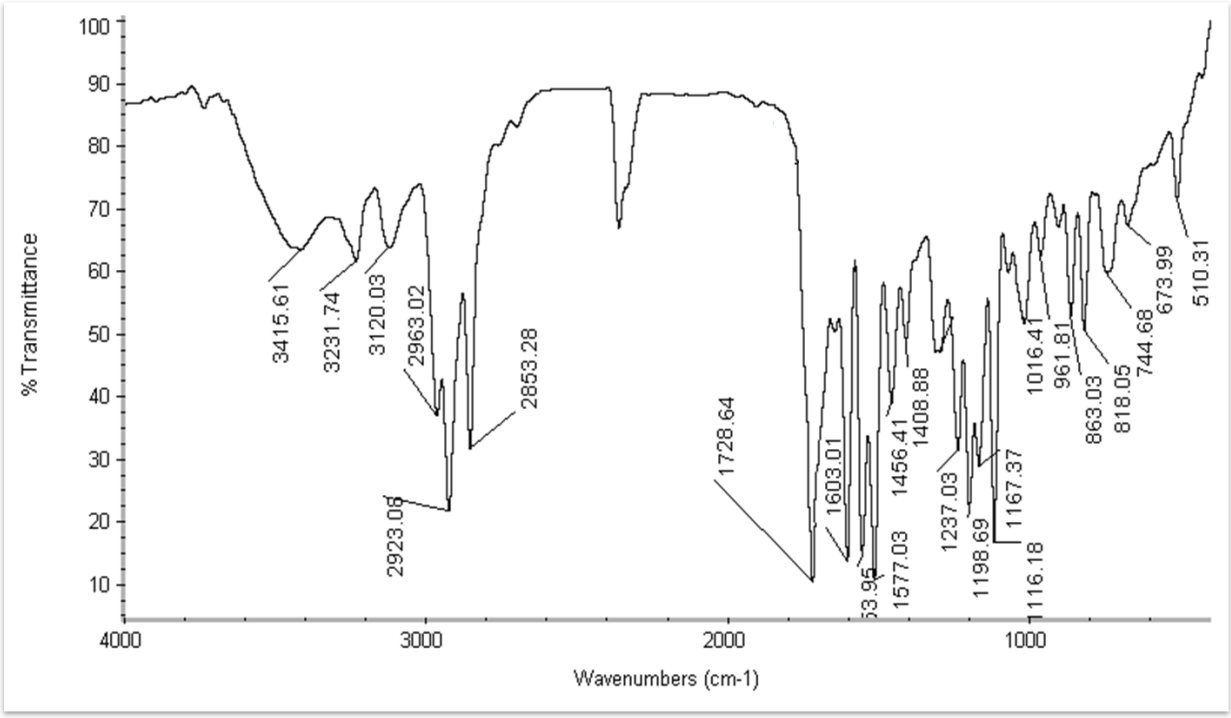


Fig. S5. IR spectrum of compound **7e**

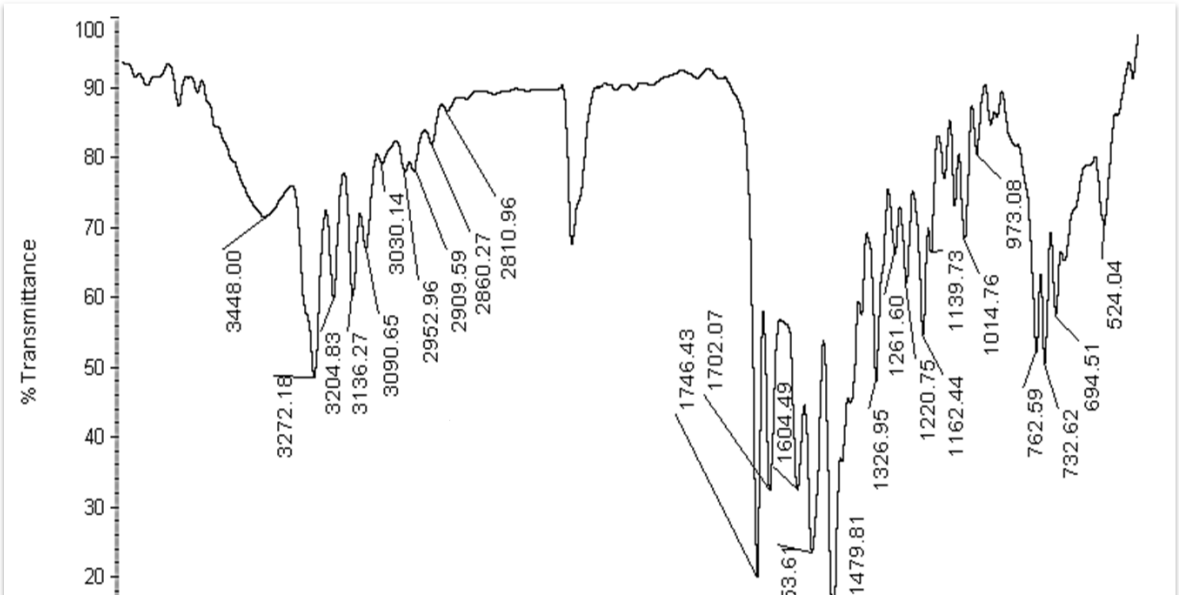
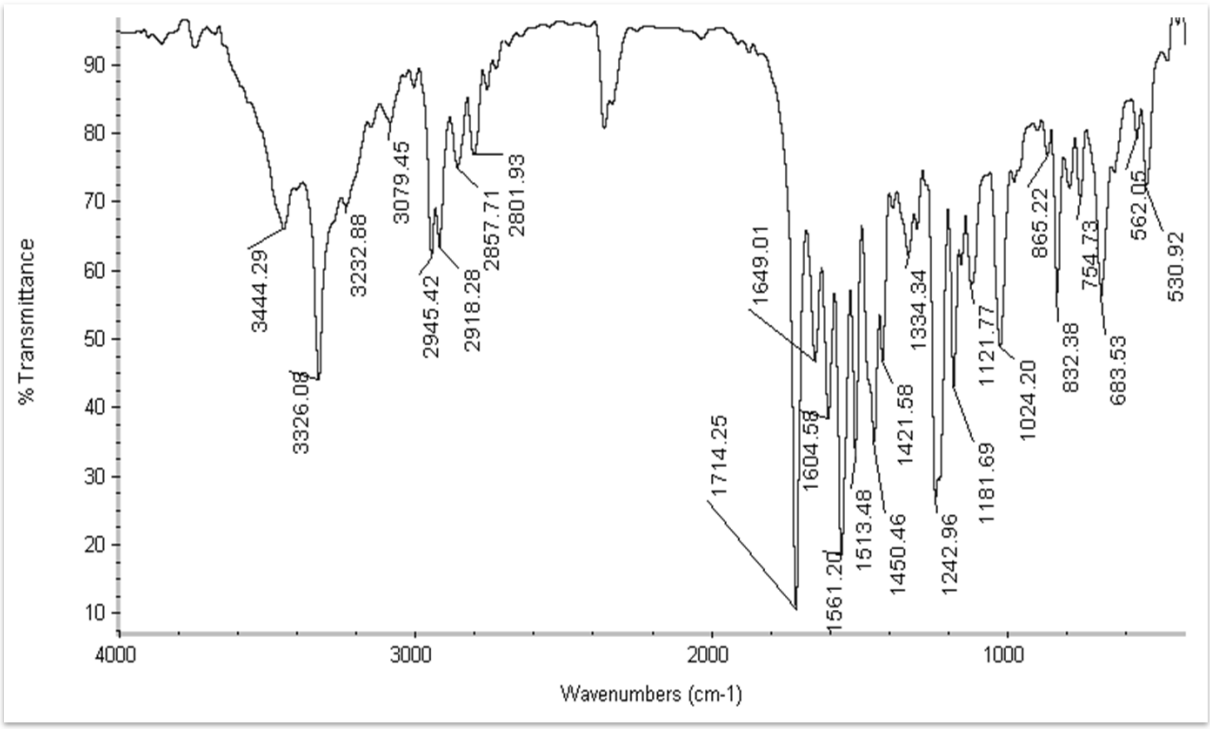


Fig. S6. IR spectrum of compound **7f**



+

Fig. S7. IR spectrum of compound **7g**

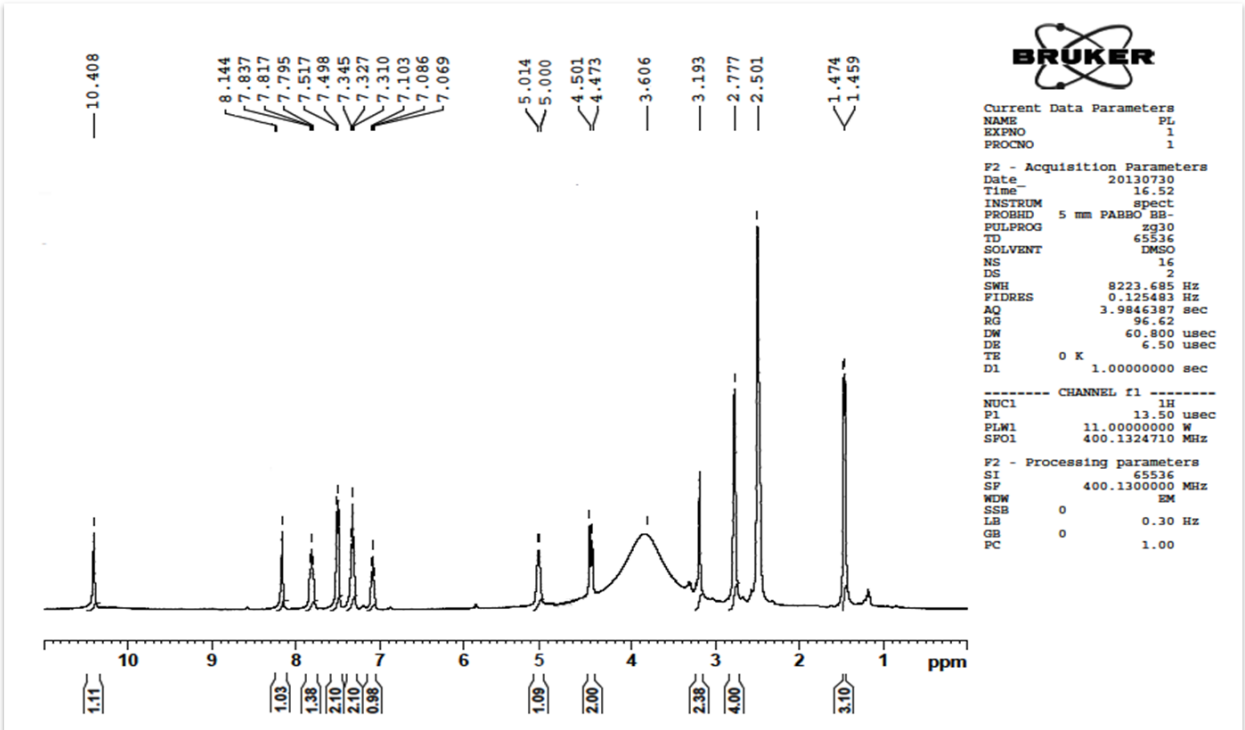


Fig. S8.[1]H NMR spectrum of compound **7a**

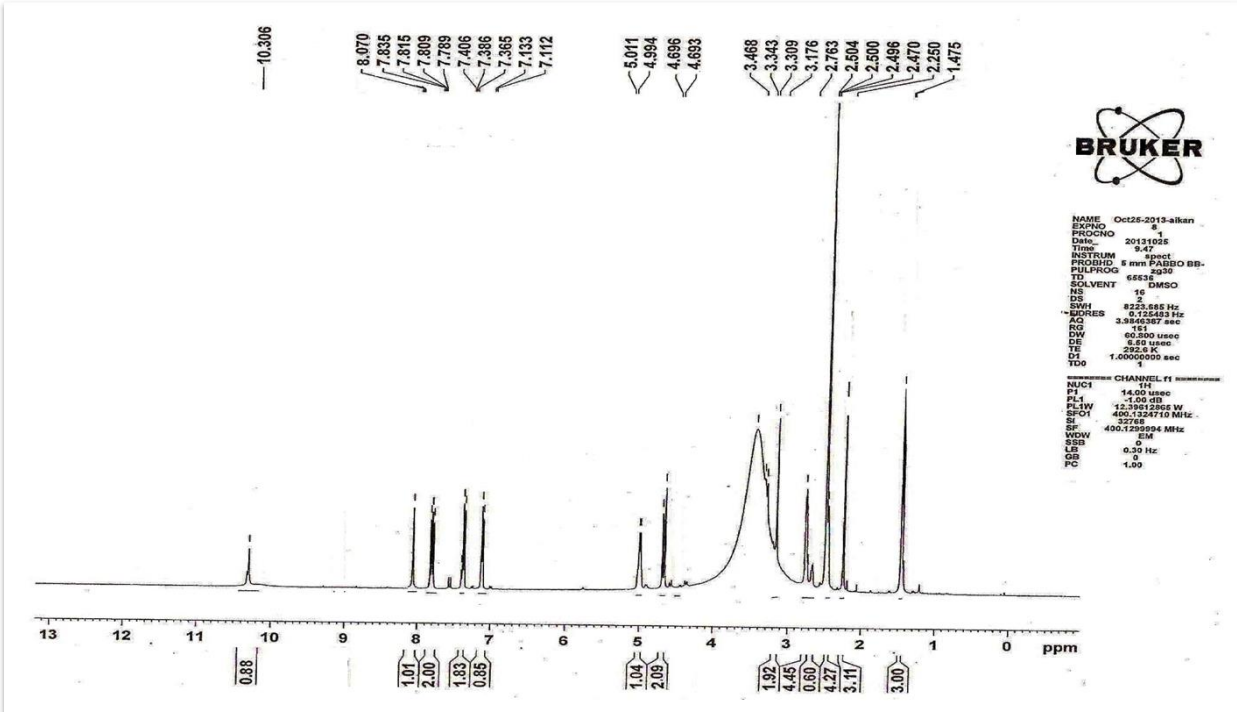


Fig. S9. [1]H NMR spectrum of compound **7b**

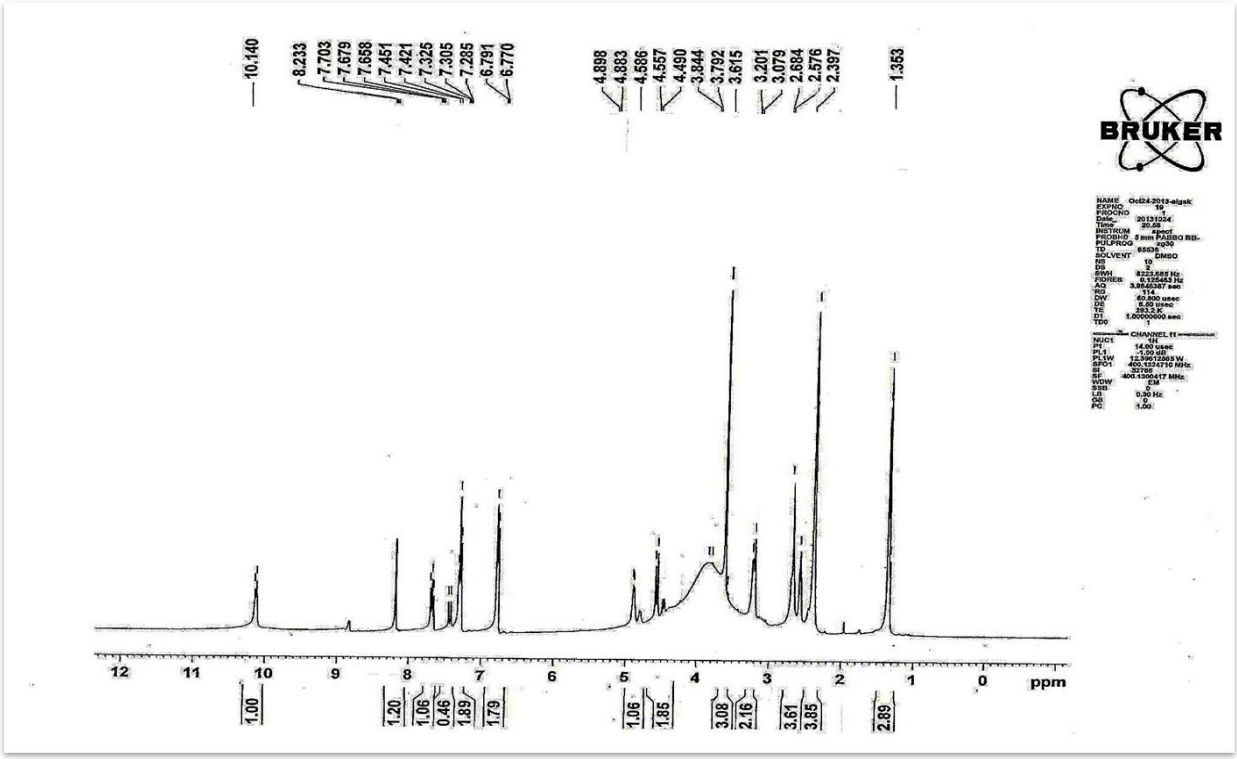


Fig. S10. [1]H NMR spectrum of compound **7c**

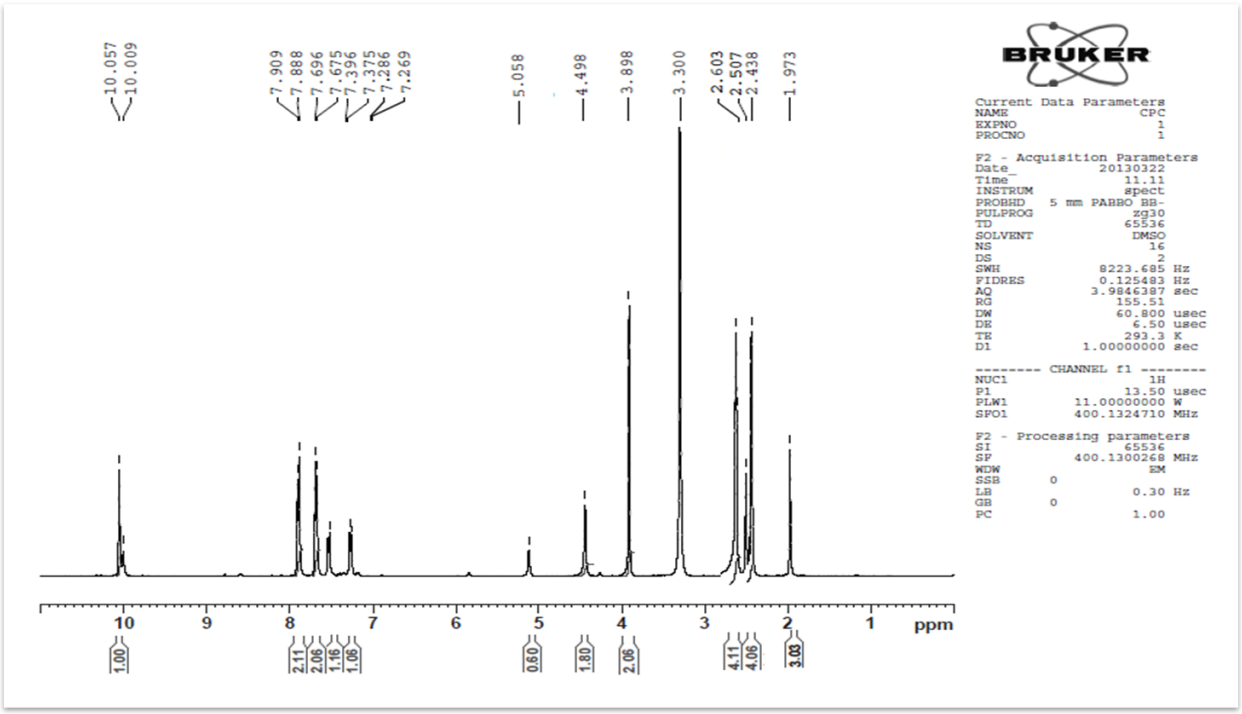


Fig. S11. ^{1}H NMR spectrum of compound **7d**

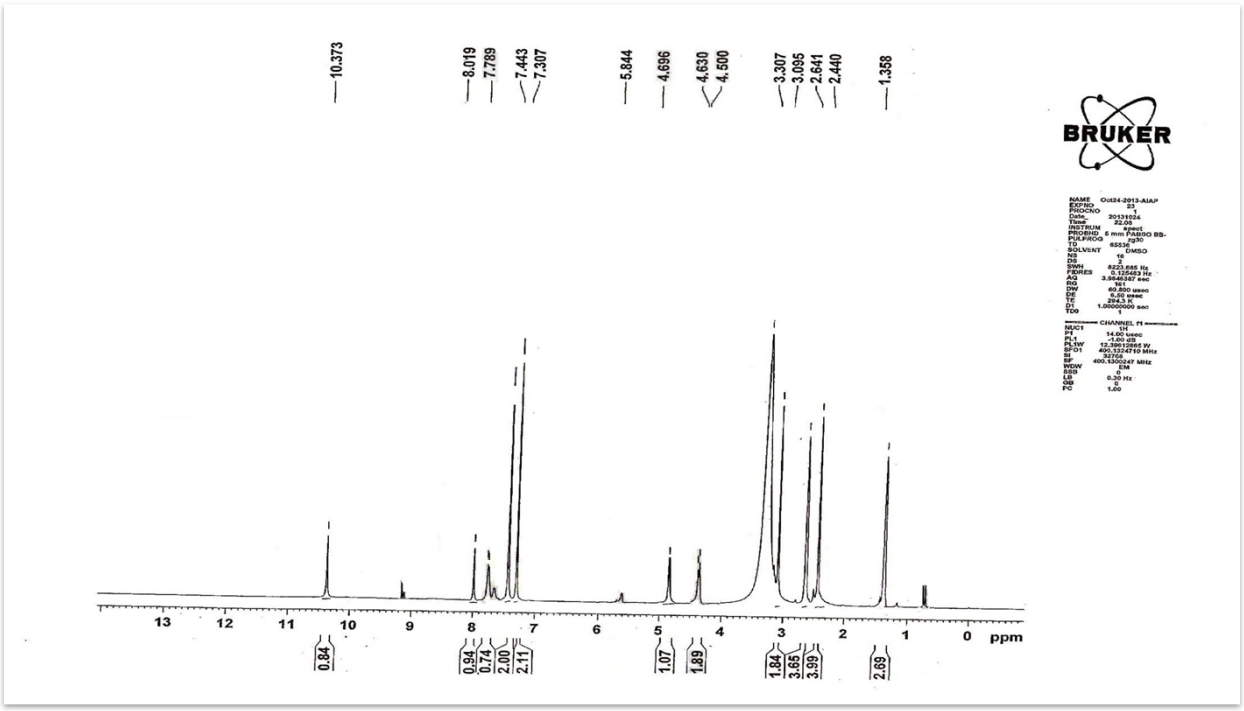


Fig. S12. ^{1}H NMR spectrum of compound **7e**

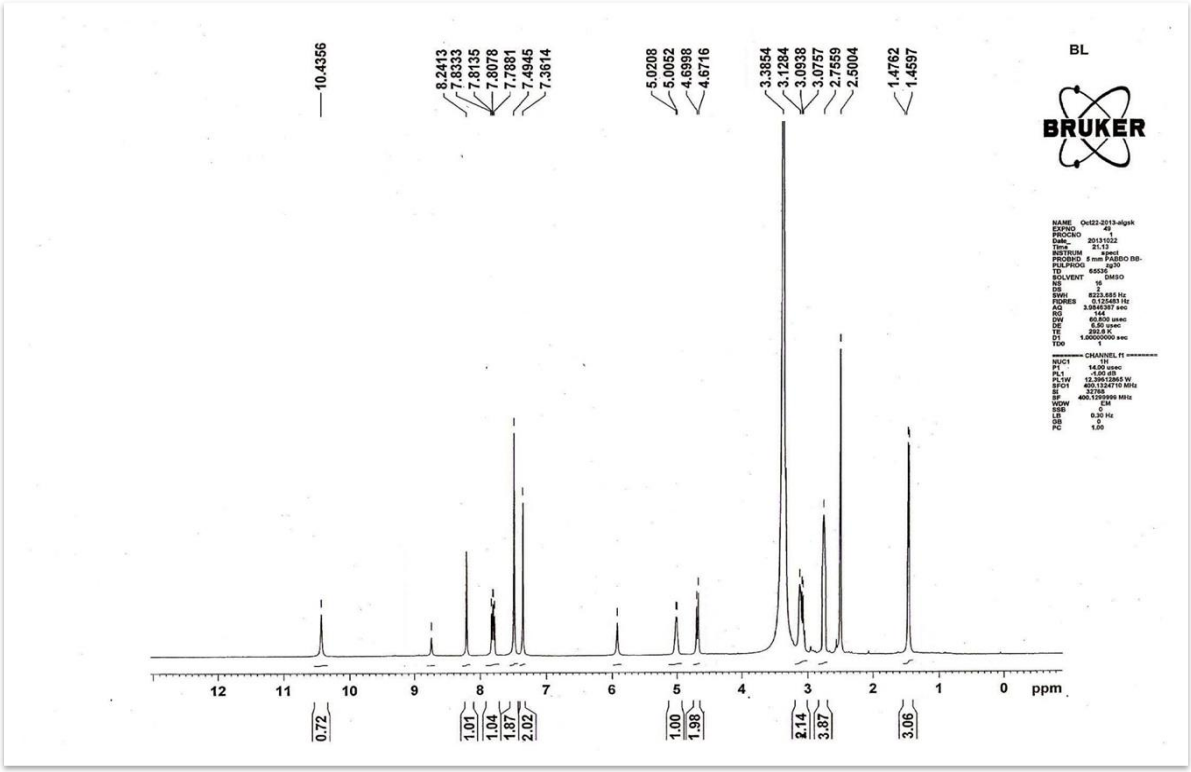


Fig. S13. ^{1}H NMR spectrum of compound **7f**

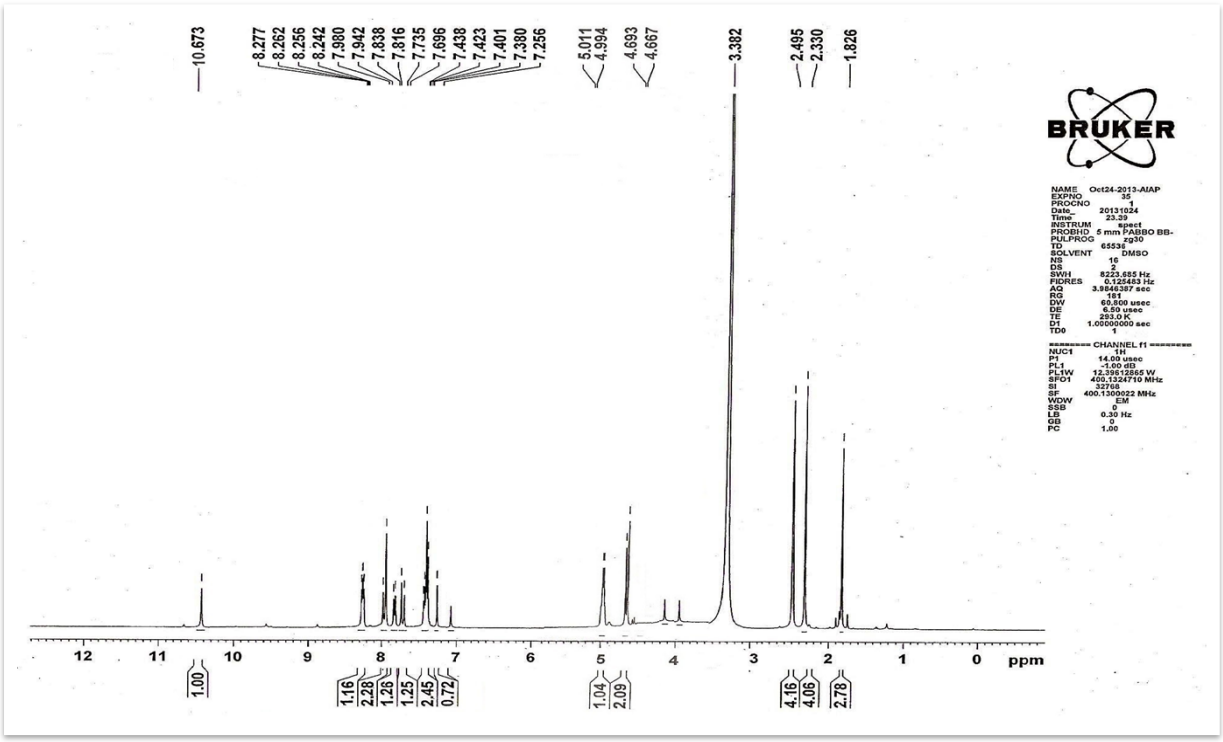


Fig. S14. ^{1}H NMR spectrum of compound **7g**

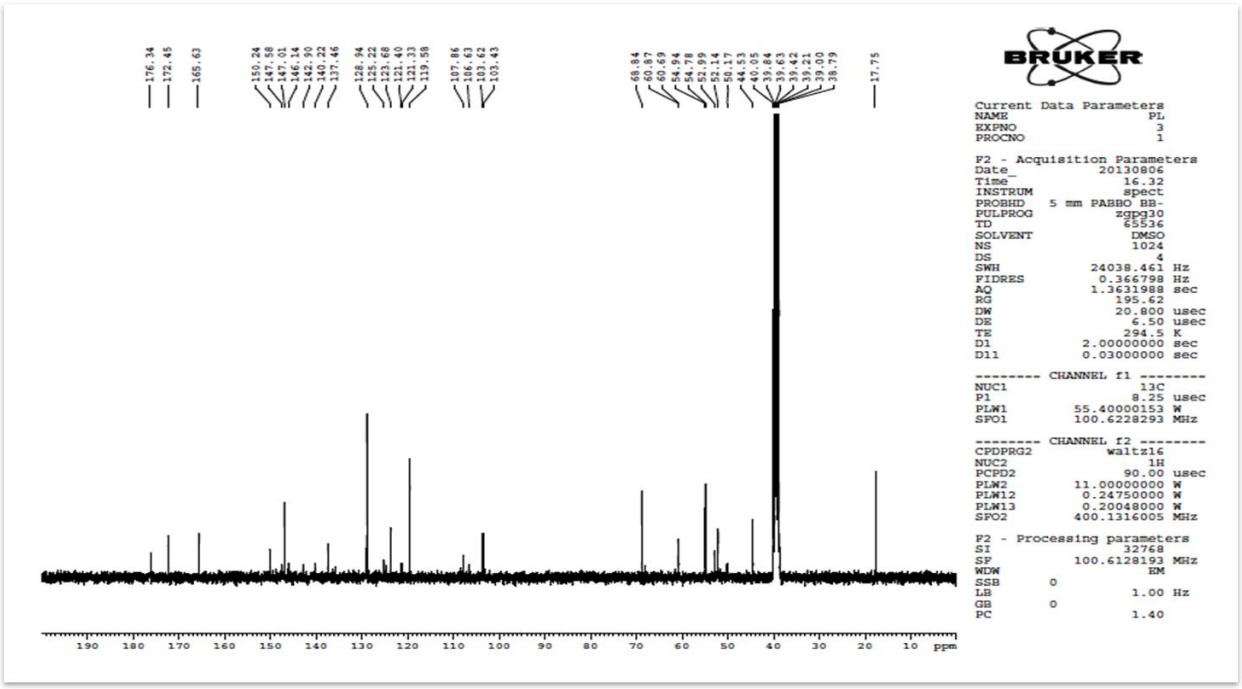


Fig. S15.[13]C NMR spectrum of compound **7a**

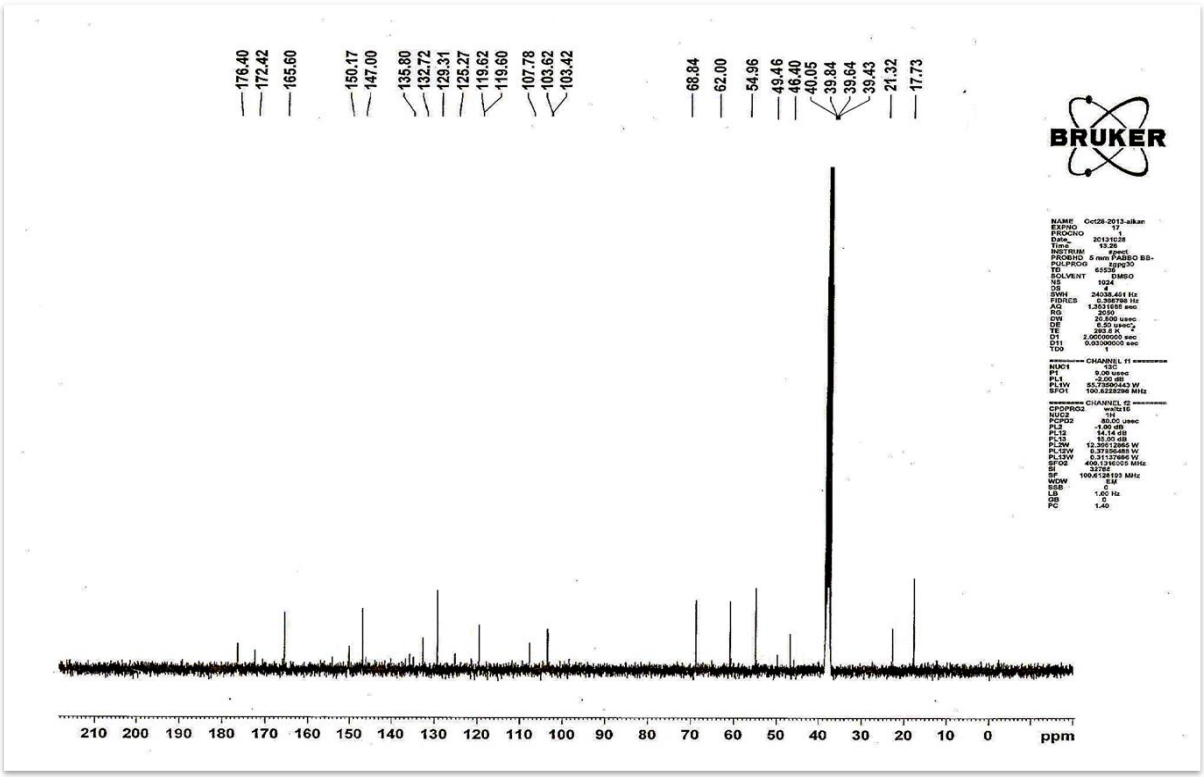


Fig. S16. [13]C NMR spectrum of compound **7b**

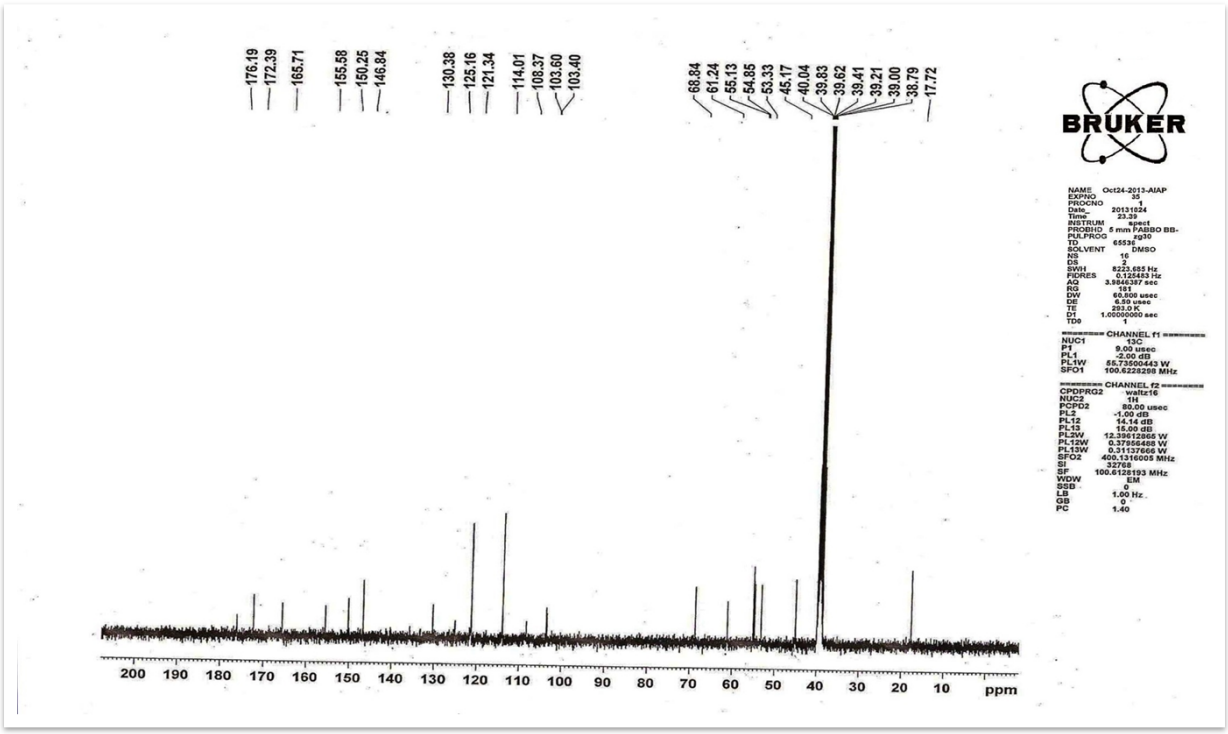


Fig. S17. ^{13}C NMR spectrum of compound **7c**

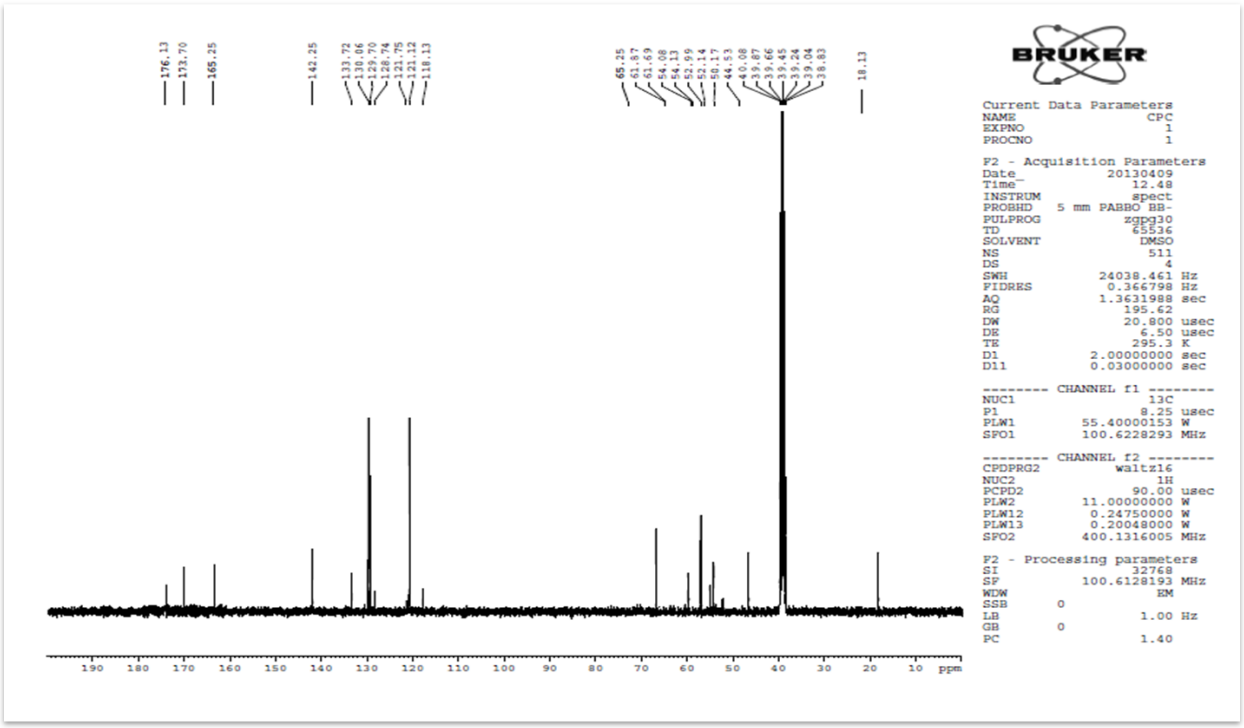


Fig. S18. ^{13}C NMR spectrum of compound **7d**

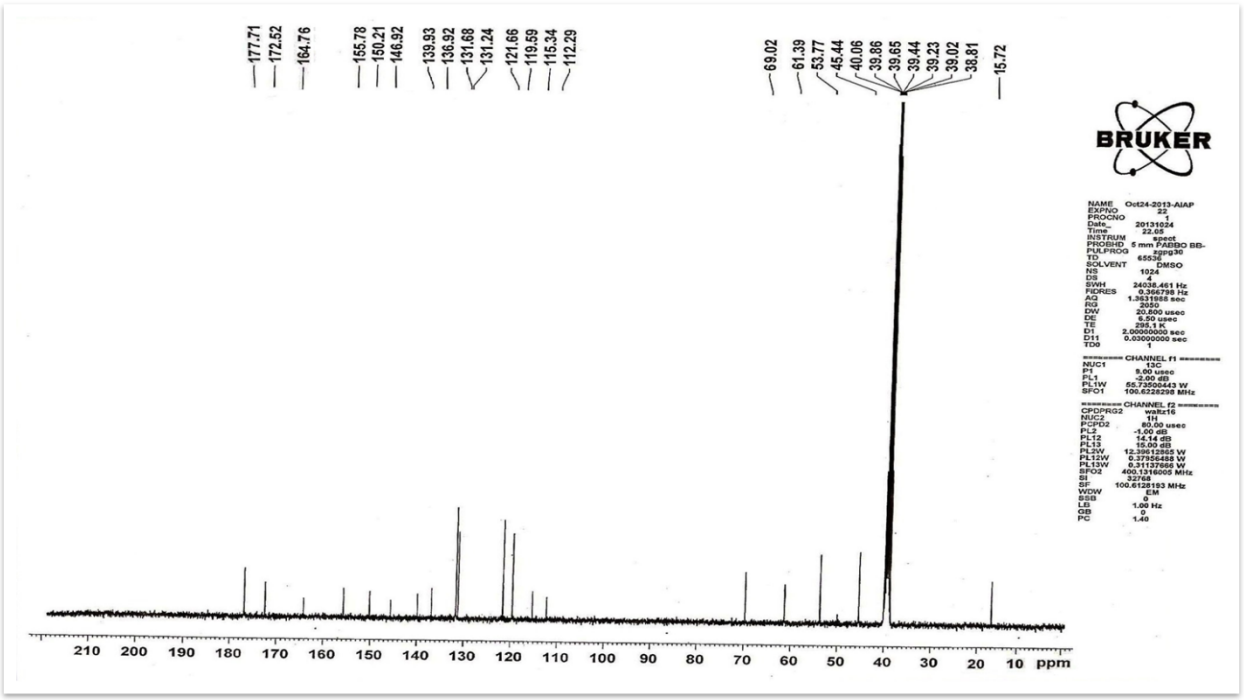


Fig. S19. ^{13}C NMR spectrum of compound **7e**

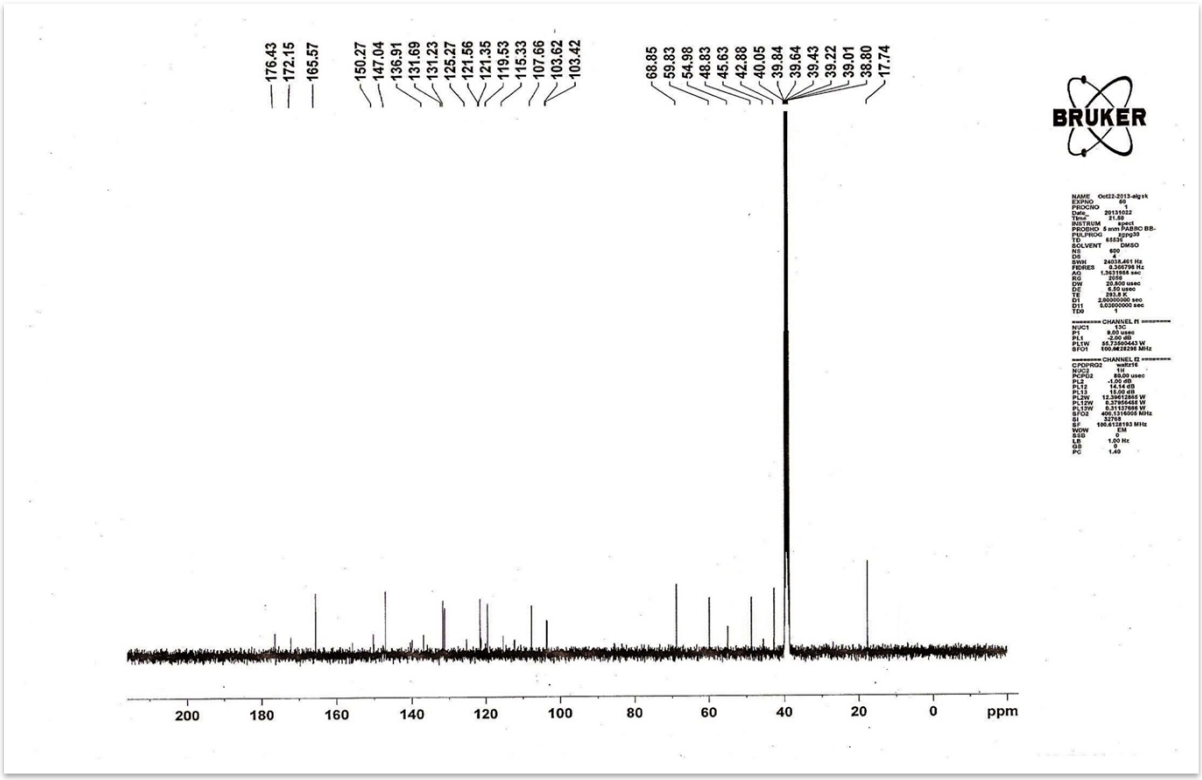


Fig. S20. ^{13}C NMR spectrum of compound **7f**

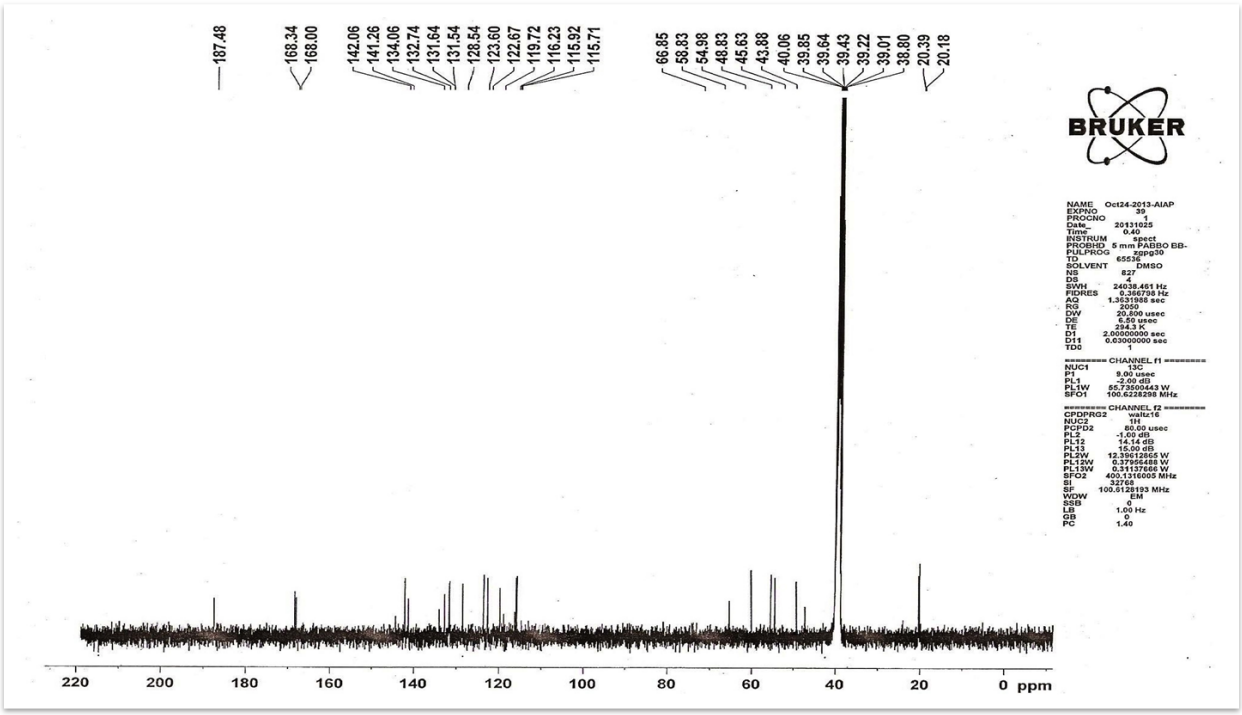


Fig. S21. ^{13}C NMR spectrum of compound **7g**

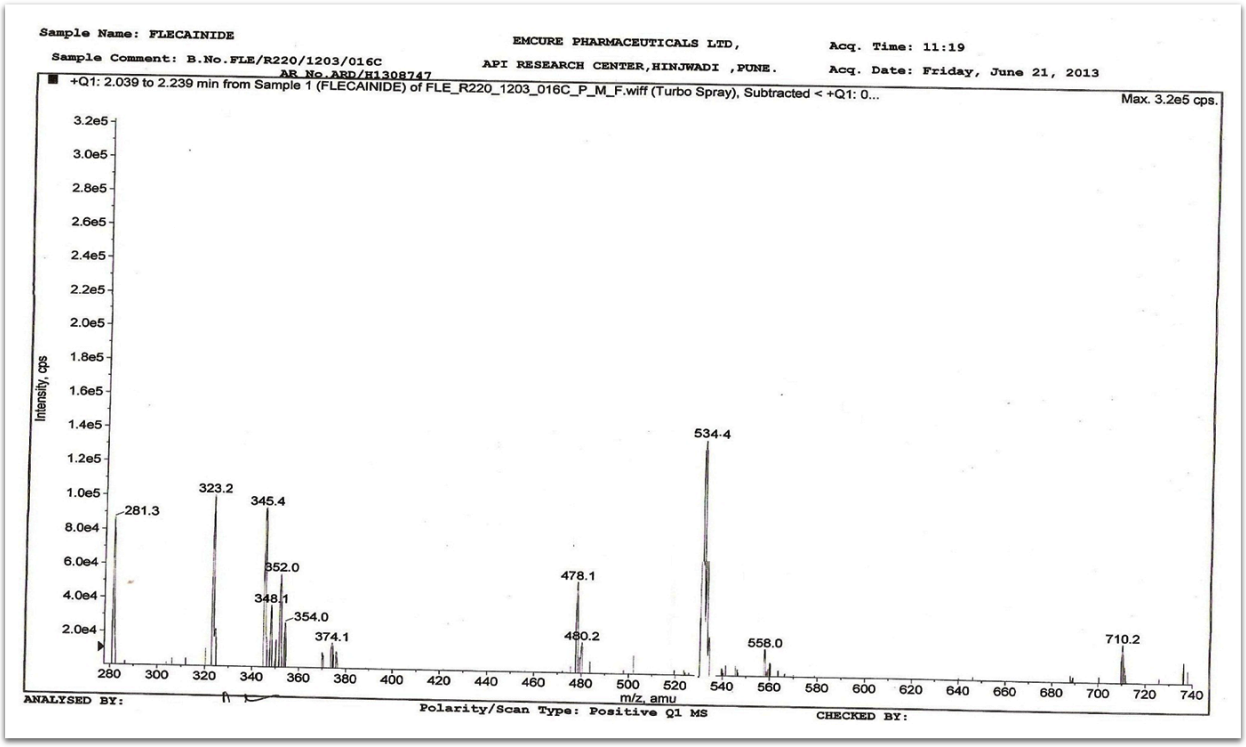


Fig. S22. Mass spectrum of compound **7a**

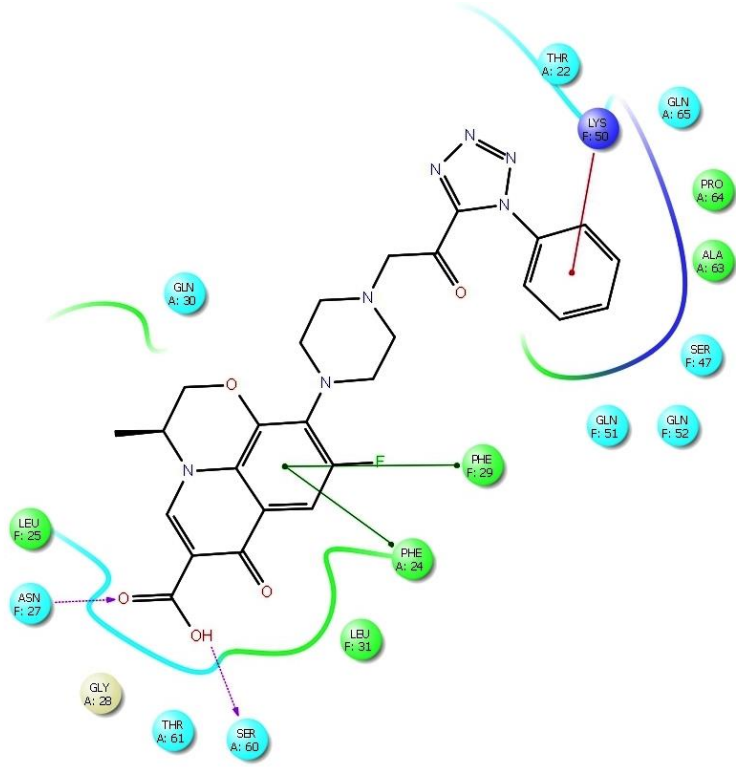


Fig. S23. Docking model of the compound with 3HSB **7a**

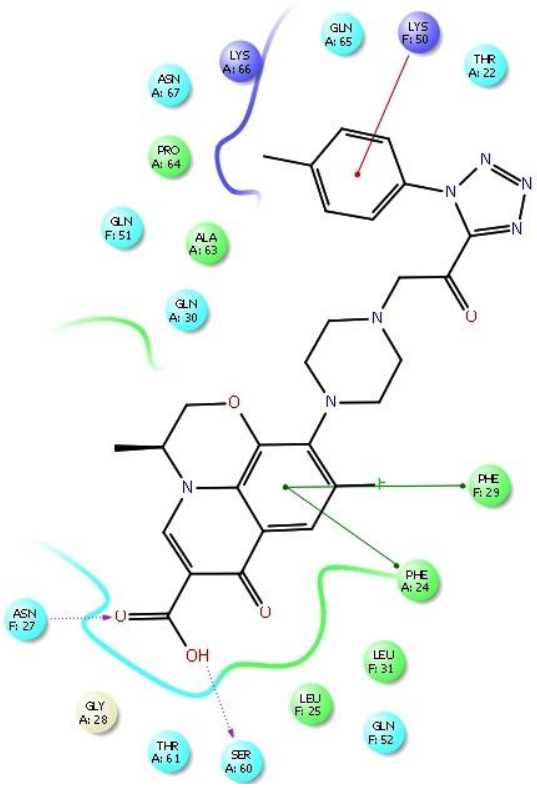


Fig. S24. Docking model of the compound with 3HSB **7b**

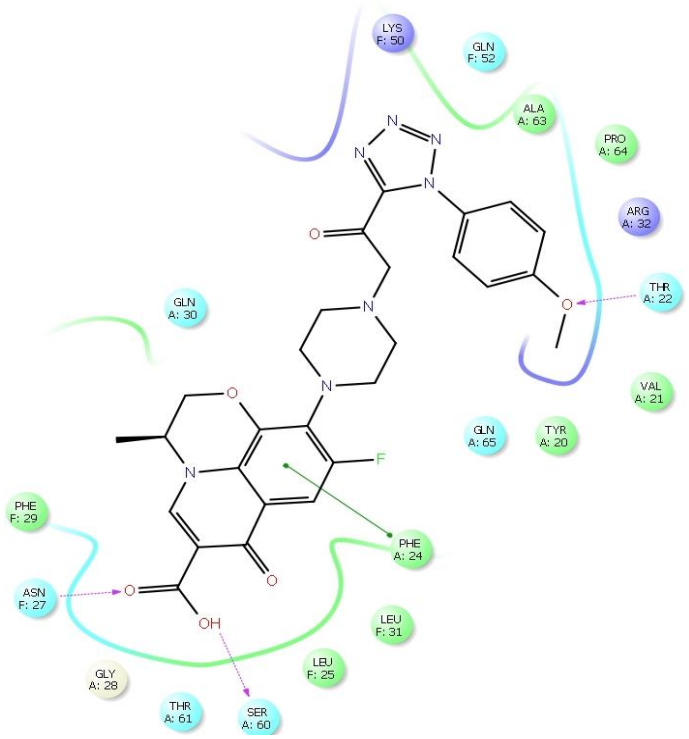


Fig. S25. Docking model of the compound with 3HSB **7c**

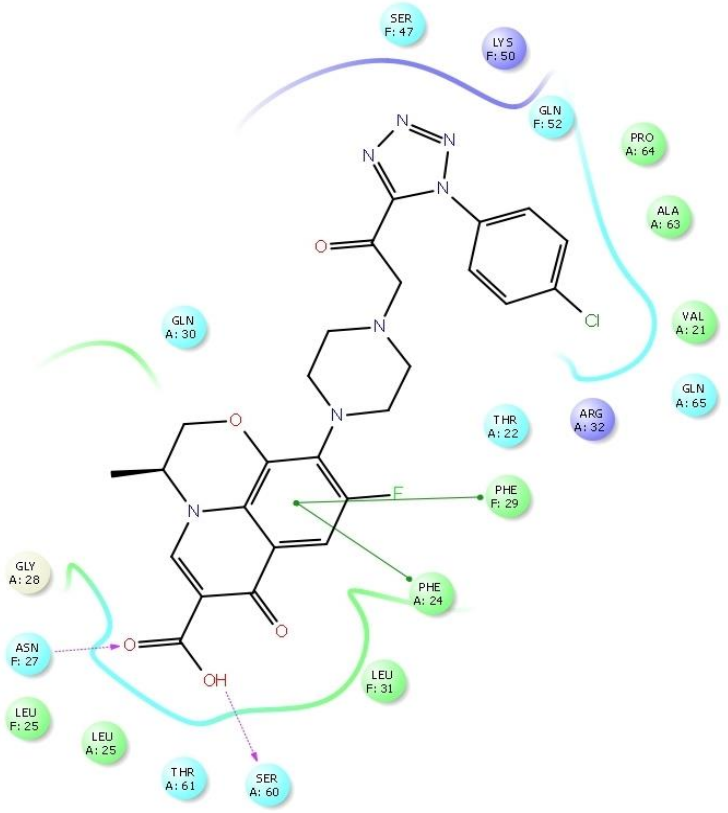


Fig. S26. Docking model of the compound with 3HSB **7d**

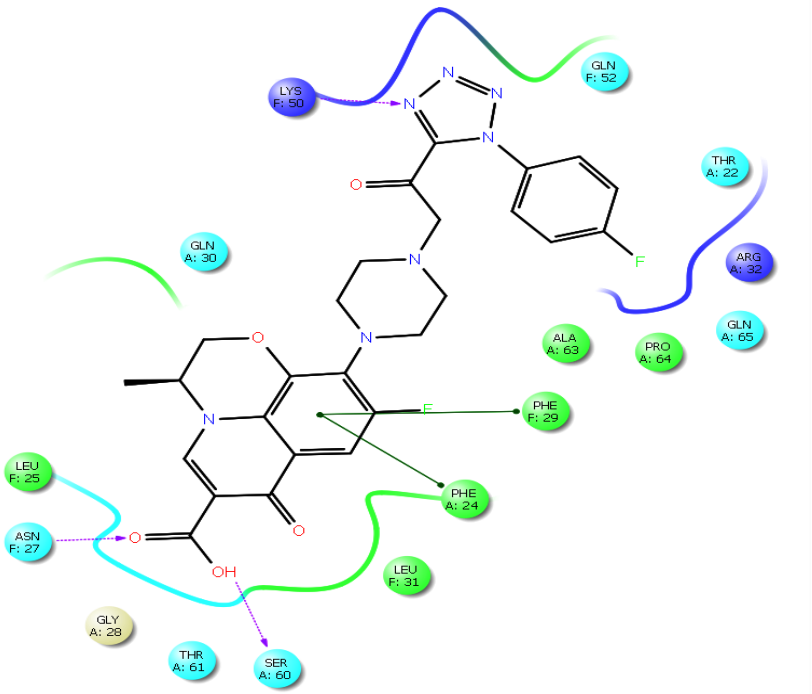


Fig. S27. Docking model of the compound with 3HSB **7e**

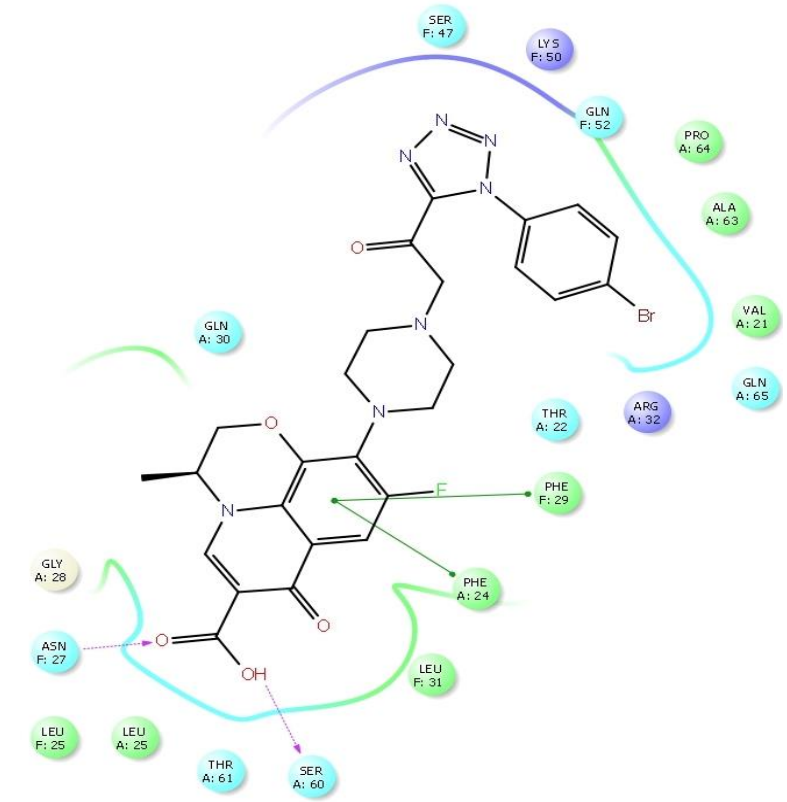


Fig. S28. Docking model of the compound with 3HSB **7f**

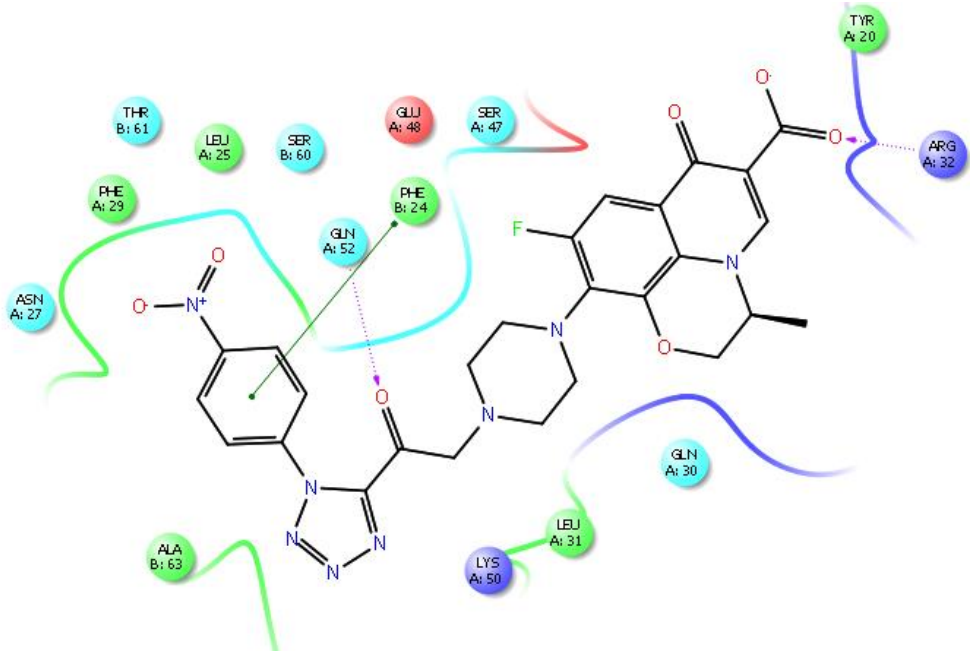


Fig. S29. Docking model of the compound with 3HSB **7g**

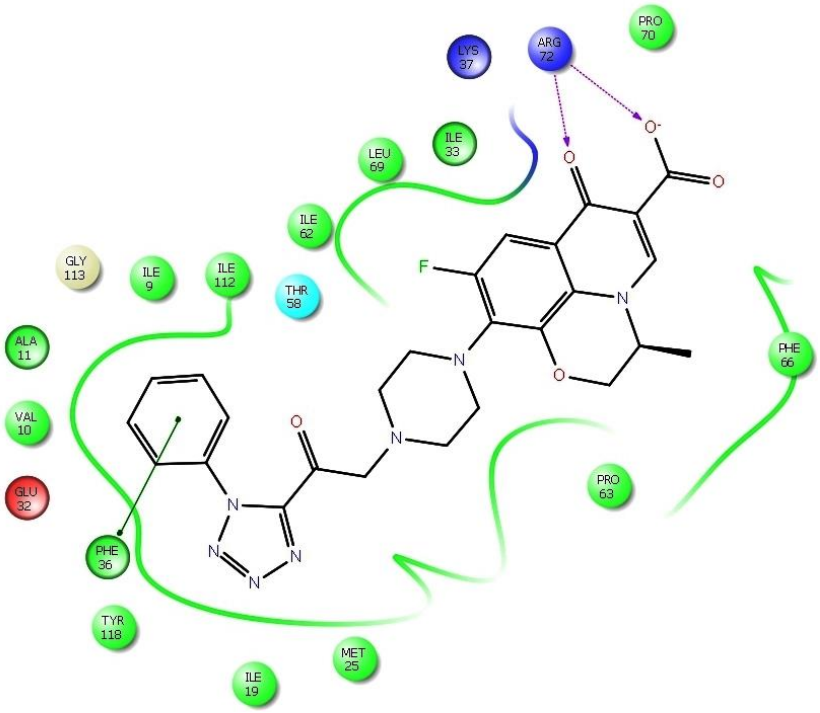


Fig. S29. Docking model of the compound with 1AI9 7a

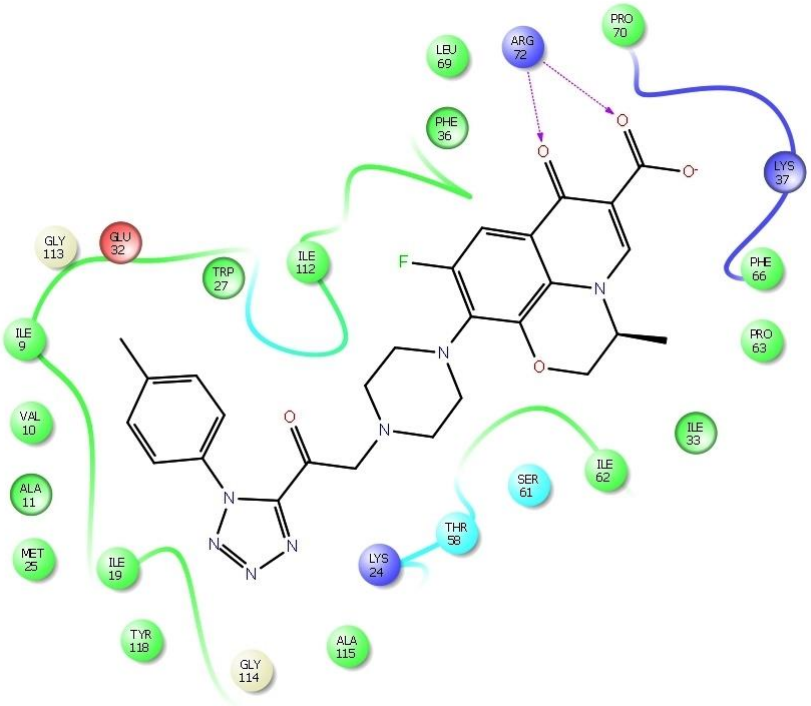


Fig. S30. Docking model of the compound with 1AI9 7b

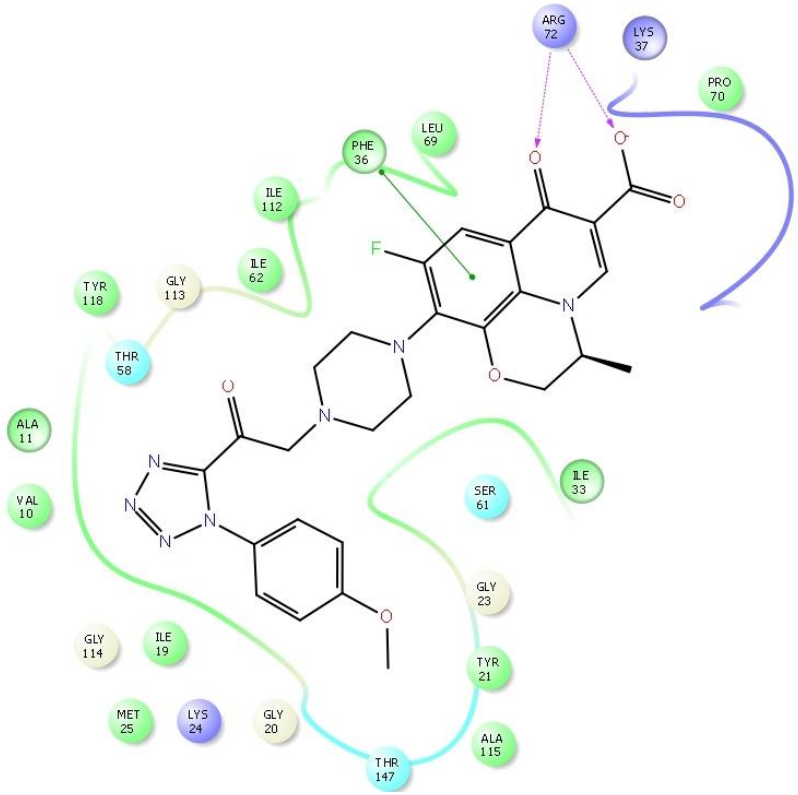


Fig. S31. Docking model of the compound with 1AI9 7c

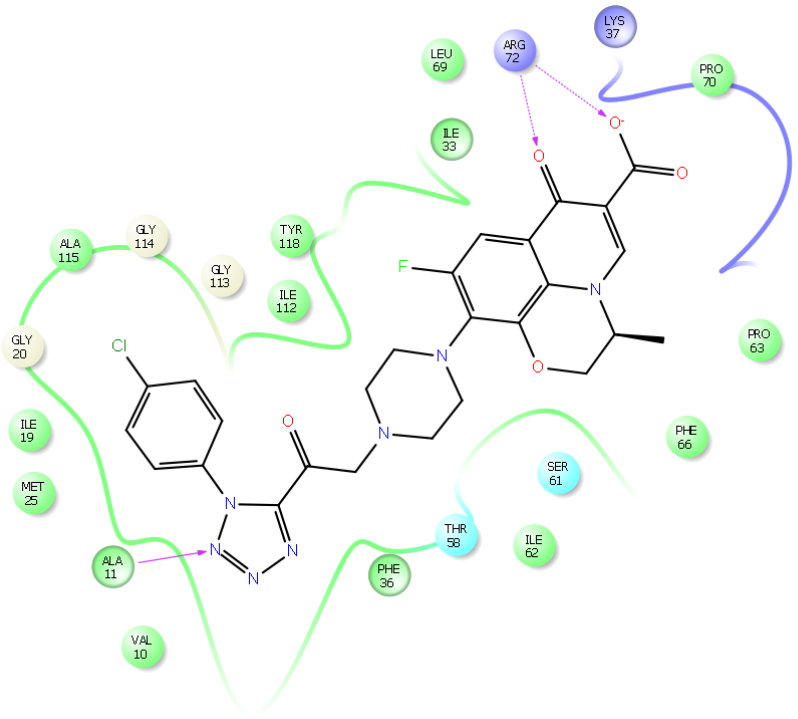


Fig. S32. Docking model of the compound with 1AI9 7d

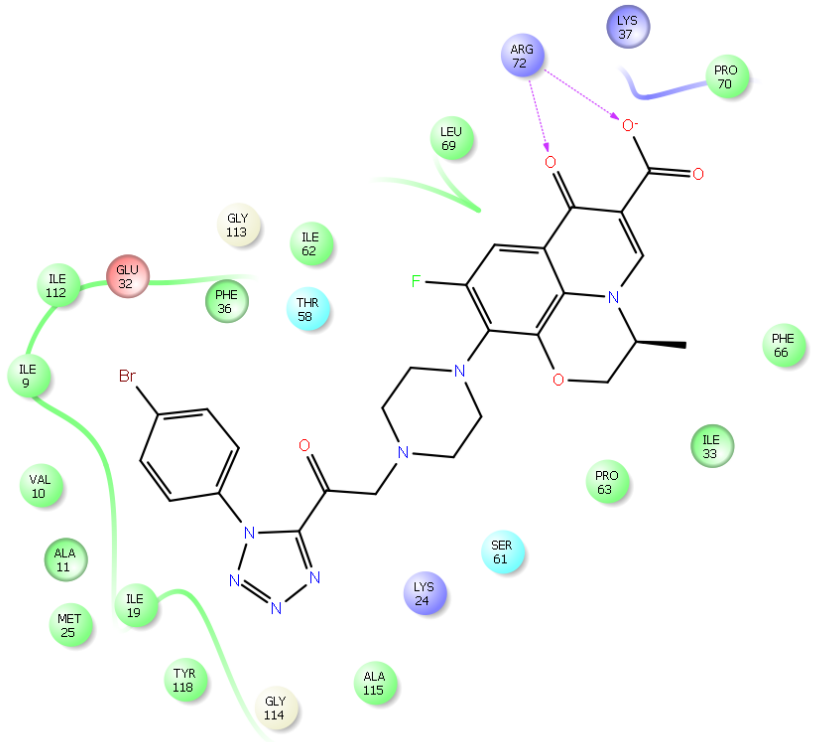


Fig. S33. Docking model of the compound with 1AI9 7e

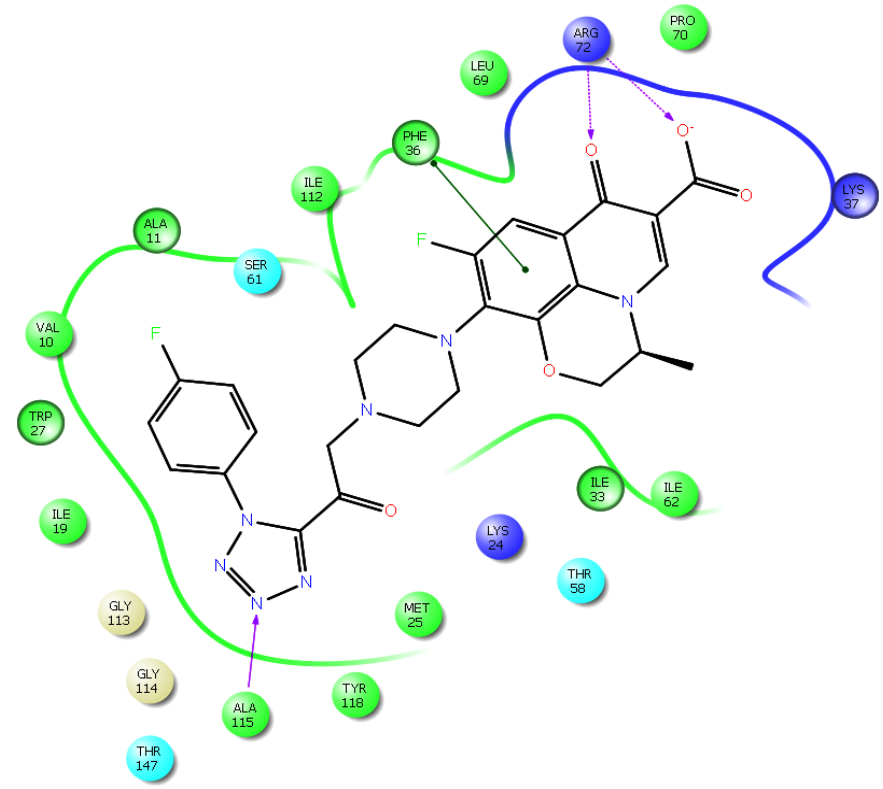


Fig. S34. Docking model of the compound with 1AI9 **7f**

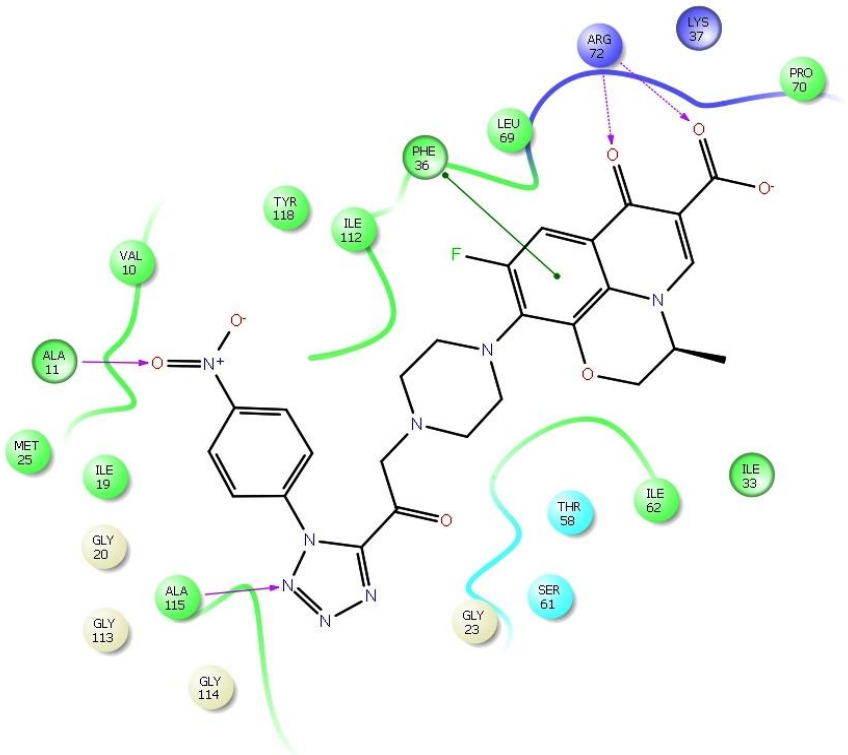


Fig. S35. Docking model of the compound with 1AI9 **7g**

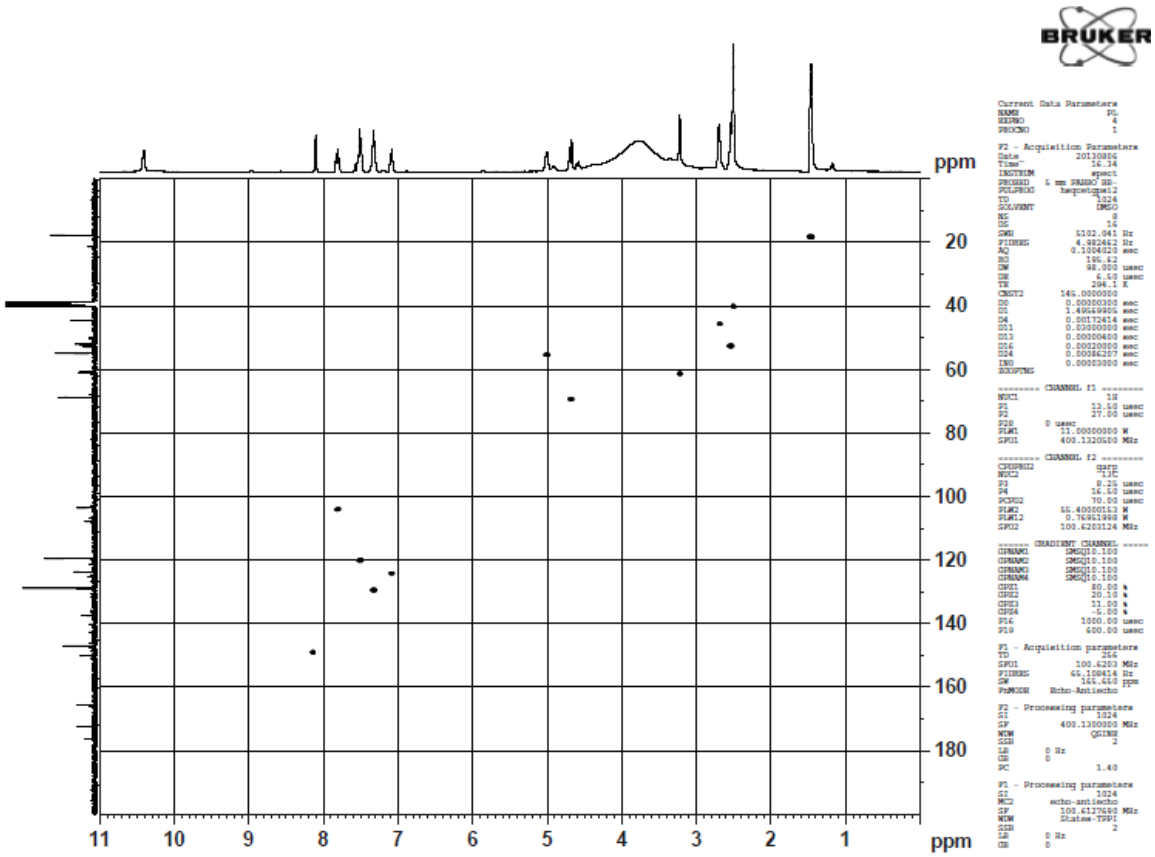


Fig. S36. HSQC spectrum of compound **7a**