Supporting Information

A catalyst− and solvent−free multicomponent synthesis and docking study of some new antiproliferative N_5-allyl-quinolylpyrido[2,3-b][1,4] benzodiazepinone precursors

Hitesh A. Barad,[a] Tushar R. Sutariya,[a] Gaurangkumar C. Brahmbhatt,[a] Narsidas J. Parmar,[a*] Irene Lagunes,[b] José M. Padrón,[b] Prashant Murumkar,[c] Mayank Kumar Sharma,[c] Mange Ram Yadav[c]

[a.] *Department of Chemistry, Sardar Patel University, Vallabh Vidyanagar-388120. Dist. Anand, Gujarat, India*

[b.] *BioLab, Instituto Universitario de Bio-Orgánica "Antonio González" (IUBO-AG), Centro de Investigaciones Biomédicas de Canarias (CIBICAN), Universidad de La Laguna, C/ Astrofísico Francisco Sánchez 2, 38206 La Laguna, Spain*

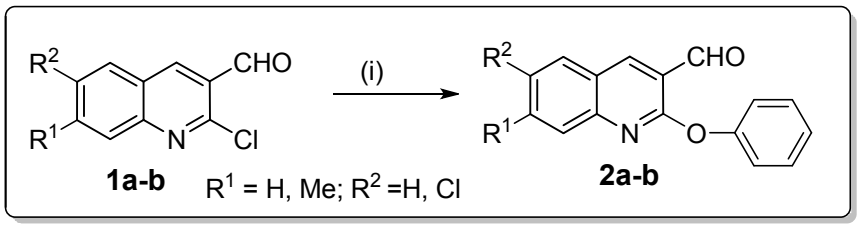
[c.] *Faculty of Pharmacy, The M.S. University of Baroda, Vadodara, Gujarat, India 390001*

1.1 General methods

All solvents and reagents were used as supplied from the commercial sources. Recorded all melting points are uncorrected. IR spectra were recorded on Shimadzu FT-IR 8401 spectrometer using KBr discs, and are expressed as wave numbers (cm^{-1}). ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 400 spectrometer operating at 400 MHz for ^1H NMR and 100 MHz for ^{13}C NMR as solutions in DMSO, unless and otherwise indicated. Chemical shifts are expressed in parts per million (ppm, δ) and referenced to the residual protic solvent. Coupling constants are expressed in Hertz (Hz). Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. The degree of substitution (C, CH, CH_2, and CH_3) was determined by the APT method. The ESI mass spectra were measured on Shimadzu LCMS-2010 spectrometer. TLC was performed on Merck 60 F254 pre-coated silica plates, and spots were detected either by means of UV (254 nm, 366 nm) or permanganate solution [$KMnO_4$ (3 g), K_2CO_3 (20 g), NaOH (5 mL, 5% in H_2O), H_2O (300 mL)] or 2,4 dinitro phenyl hydrazine solution [2,4-DNP (12 g), Conc. H_2SO_4 (6 mL), Water (8 mL), EtOH (20 mL)].

1.2 General procedure for the synthesis of aldehydes (2-4)

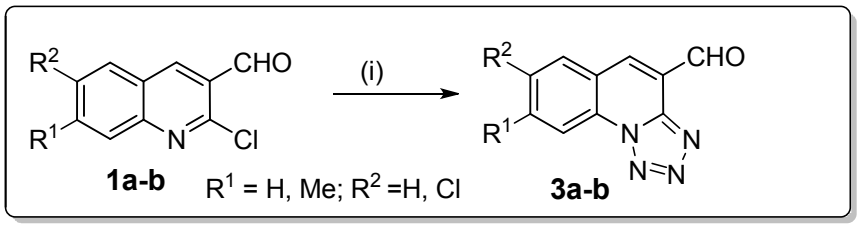
1.2.1 Synthesis of 2–phenoxyquinoline–3–carbaldehydes 2a-b.



Scheme 1 The reagents and conditions (i) Phenol, K_2CO_3, DMF, reflux, 3.5 h

A mixture containing 2-chloroquinoline–3–carbaldehyde **1a-b** (0.01 mol), phenol (0.01 mol) and K_2CO_3 (0.02 mol) taken in 10 mL DMF, in a 100 mL round bottom flask fitted with a reflux condenser, was heated under reflux and monitored by the TLC. It showed about 3.5 h as time to complete the reaction. The reaction mass was poured into ice species after cooling to room temperature with constant stirring. A 1.5 N HCl solution was used to bring pH of resulted content to 7. The solid mass precipitated out was filtered, washed well with water, dried and re-crystallized from ethyl acetate. It gave phenoxyquinoline–3–carbaldehyde in 85 % yields.

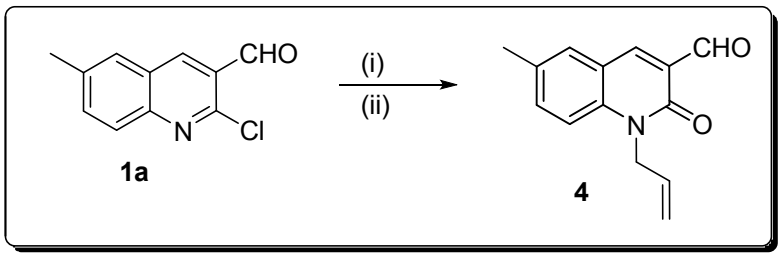
1.2.2 Synthesis of tetrazolo[1,5–*a*]quinoline–4–carbaldehydes, 3a-b.



Scheme 2: The reagents and conditions (i) NaN_3, TBA–HS, DMSO, 45—50 °C.

A mixture containing 2–chloroquinoline–3–carbaldehyde **1a-b** (0.01 mol) and sodium azide (0.02 mol) in 10 mL DMSO was heated at 50 °C in the presence of TBA–HS (0.0012 mol) for about 2 h to complete the reaction which was confirmed by TLC. The solid mass appeared isolated was filtered, washed with ethanol and purified using a 10:10 chloroform—methanol mixture as leaching solution. Solid tetrazolo[1,5–*a*] quinoline–4–carbaldehyde was obtained in 84 % yields.

1.2.3 Synthesis of 1-allyl-6-methyl-2-oxo-1,2-dihydroquinoline-3-carbaldehyde 4.



Scheme 3: Reagents and condition (i) 70% Acetic acid, reflux (ii) allyl bromide, K_2CO_3, DMF, rt, 12h

A suspension of 1 mmol of aldehyde **1a** with 10 mL, 70 % acetic acid was heated under reflux for 4-6 h and monitored by TLC to confirm the completion of quinolone formation. It was then allowed to cool normally to room temperature. A solid mass precipitated out was filtered, washed well with plenty of water portions and dried. It was then purified by re-crystallization using DMF as solvent. To 1 mmol of quinolone, which was added in suspension of 1.5 equiv. potassium carbonate with 5 mL DMF, was added 1.5 equiv. allyl bromide drop-wise within 2-3 h at room temperature. Progress of the reaction was monitored by the TLC. Confirming complete combination of reactants into product, the reaction mass was poured into ice-cooled water (25 ml). A solid precipitated out was filtered, washed well with water and dried. Final purification of the solid by aqueous ethanol as re-crystallizing solvent gave pure product.

1.3 General procedure for synthesis of quinolylpyrido[2,3-*b*][1,4] benzodiazepin-7-ones, 7a-j.

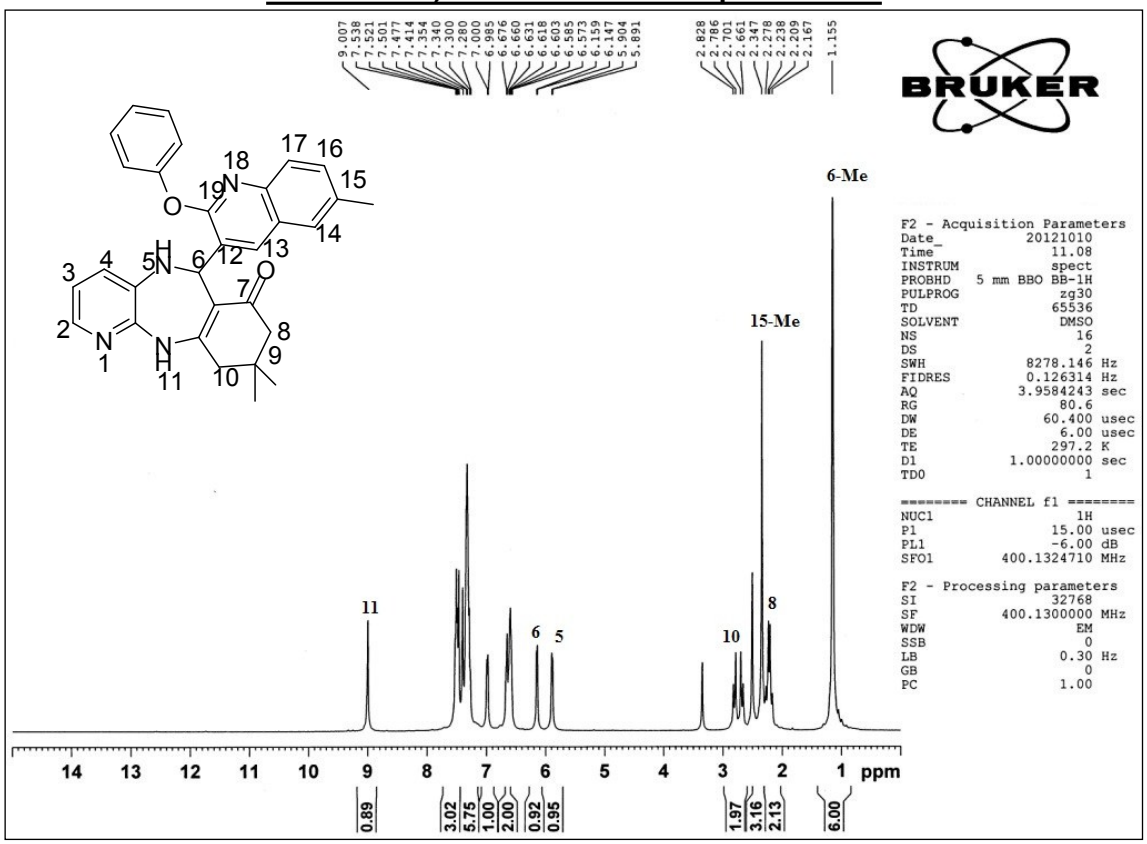
A mixture containing 2,3-diaminopyridine **5**, 1,3-cyclohexadione **6a-b** and quinoline-carbaldehyde **2-4** in equimolar amount (2 mmol) was heated at 120 ˚C under solvent-free condition. The progress of the reaction was monitored by the TLC and found that reaction finished entirely in 2.5-3.5 h. The solid product dropped out of the reaction was washed with ethanol and dried at room temperature. The entire products **7a-j** were received quantitatively with an excellent purity.

1.4 General Procedure for synthesis of 5-allylquinolylpyrido[2,3-*b*][1,4] benzodiazepin-7-ones, 8a-j

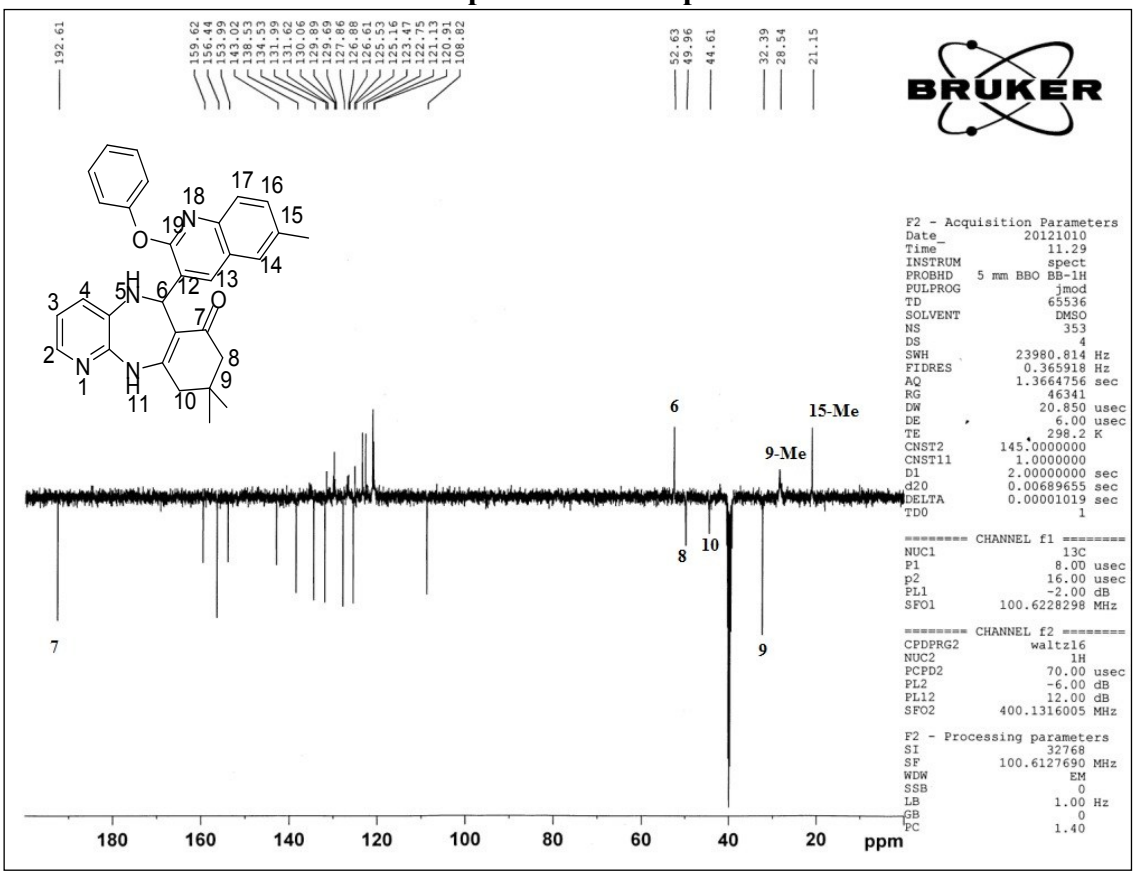
A respective quinolylpyrido[2,3-b][1,4]benzodiazepine-7-one **7a-j** crude product left above in the flask was mixed thoroughly with 15 mL K_2CO_3 (3 mmol) suspended in DMF, and added drop-wise 5 mL of allyl bromide (2 mmol) solution in DMF. Resulted end mass was then stirred at room temperature to complete the reaction, confirmed by the TLC (10–12 h). The end product was poured into crushed ice species with constant stirring. The solid portion separated out was filtered, washed with three 10 mL cold water portions and dried. Further purification by aqueous ethanol as re-crystallizing solvent, it gave pure product. All products **8a–j** were obtained quantitatively with an excellent purity.

1.5 Analytical data for compounds

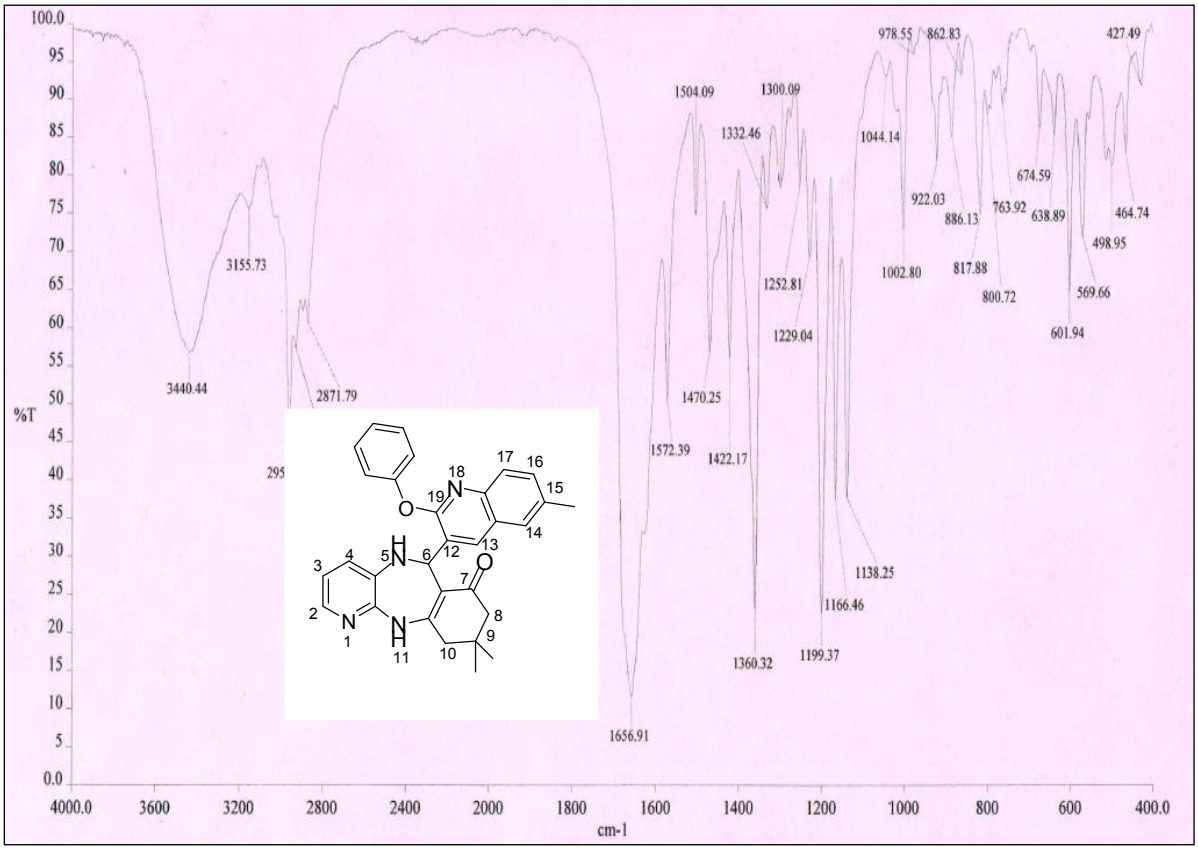
1.6 ^{1}H NMR, ^{13}C NMR and Mass Spectral Data



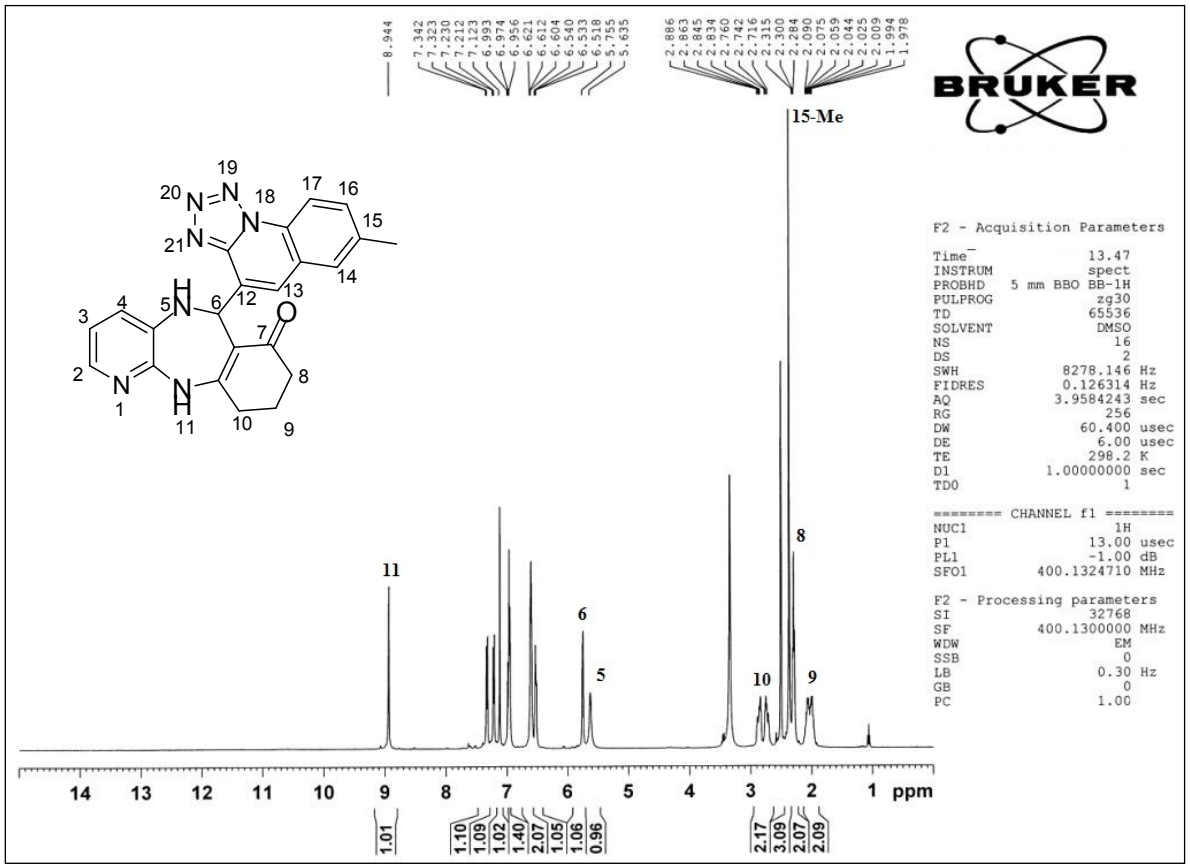
^{1}H NMR spectrum of compound 7a



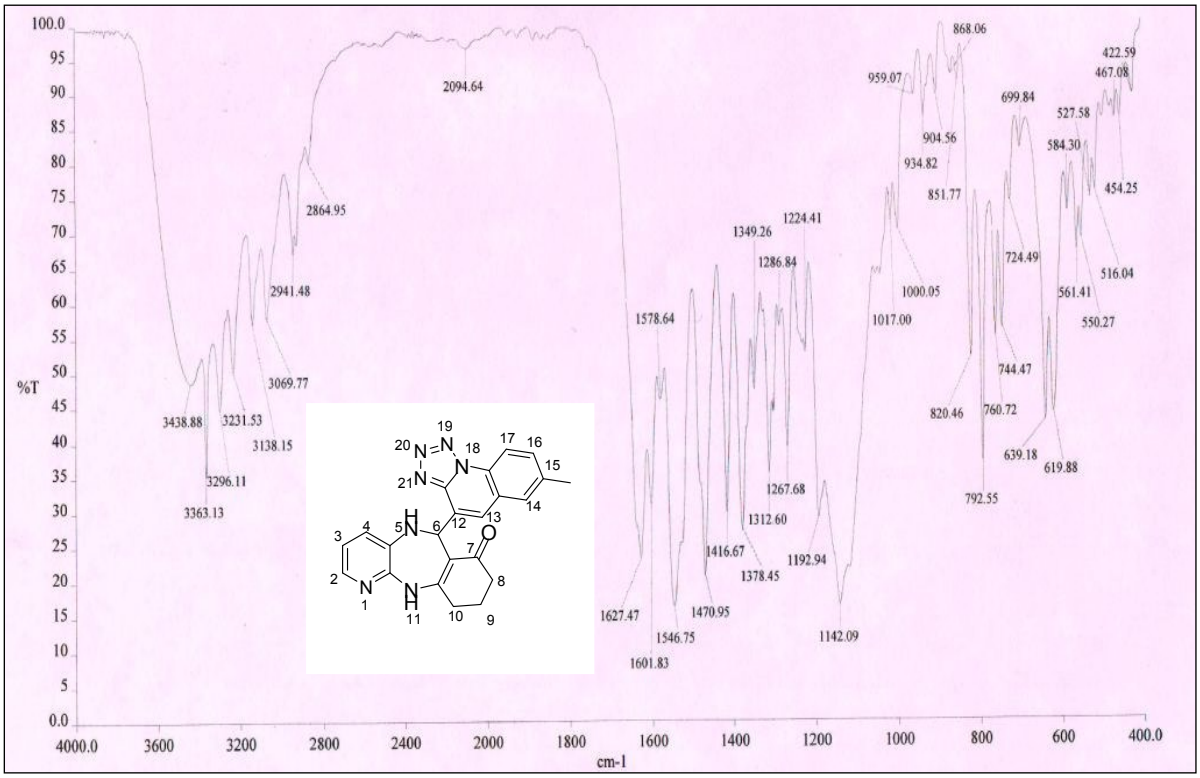
APT spectrum of compound 7a



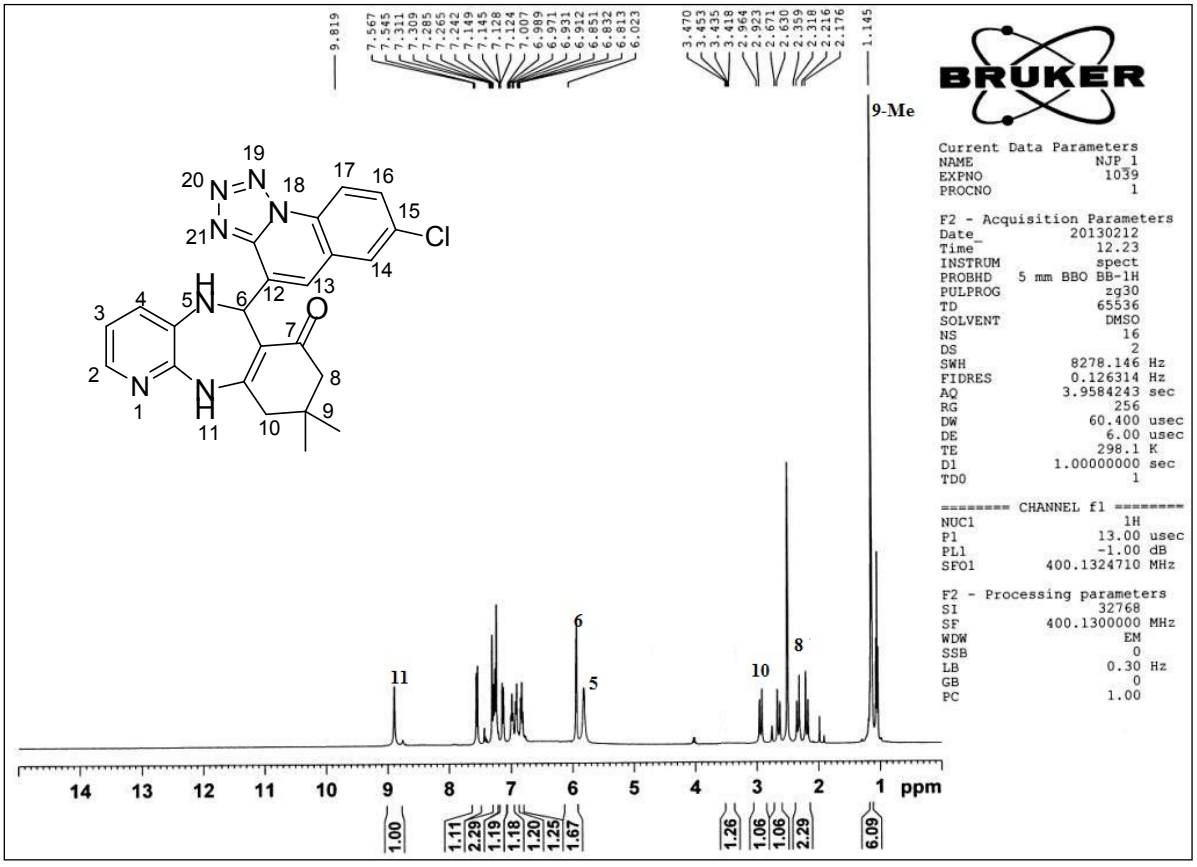
FT–IR spectrum of compound 7a



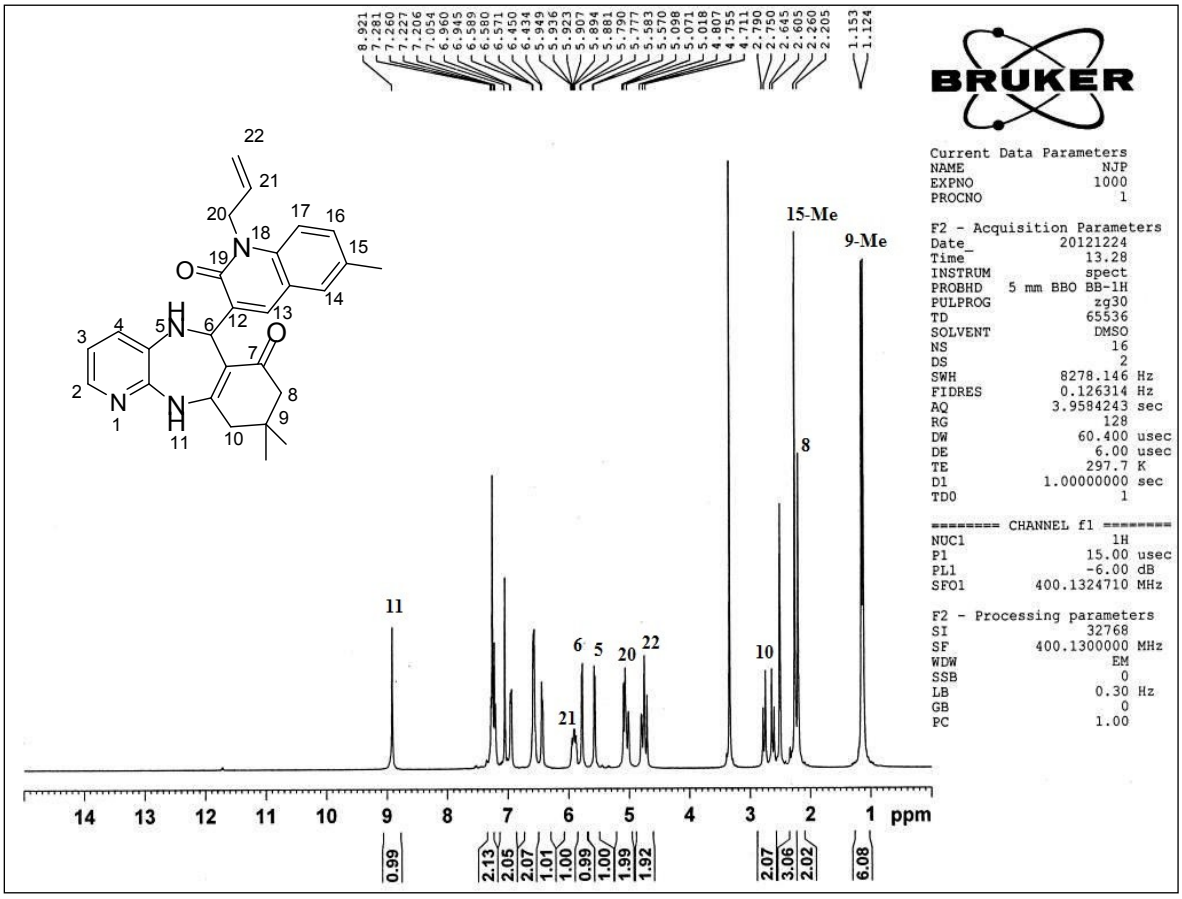
^{1}H NMR spectrum of compound 7f



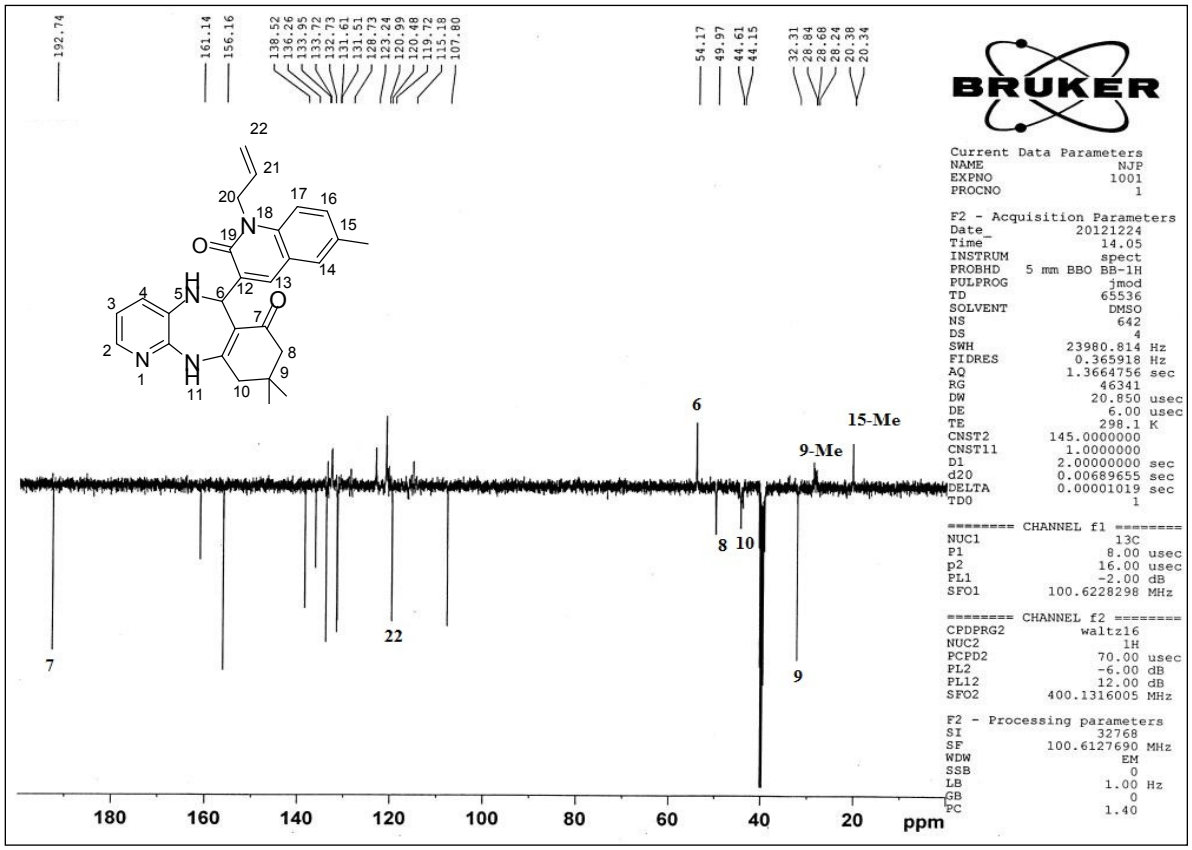
FT–IR spectrum of compound 7f



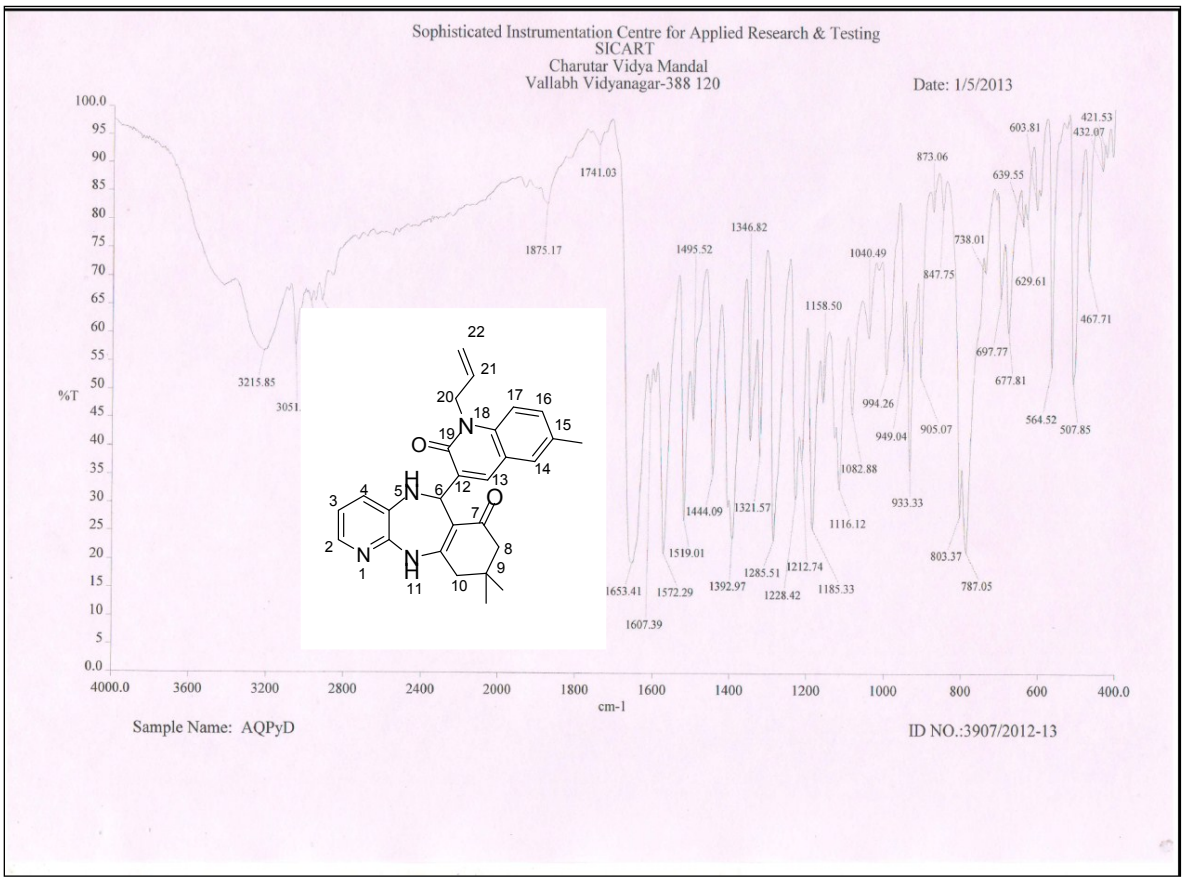
^{1}H NMR spectrum of compound 7g



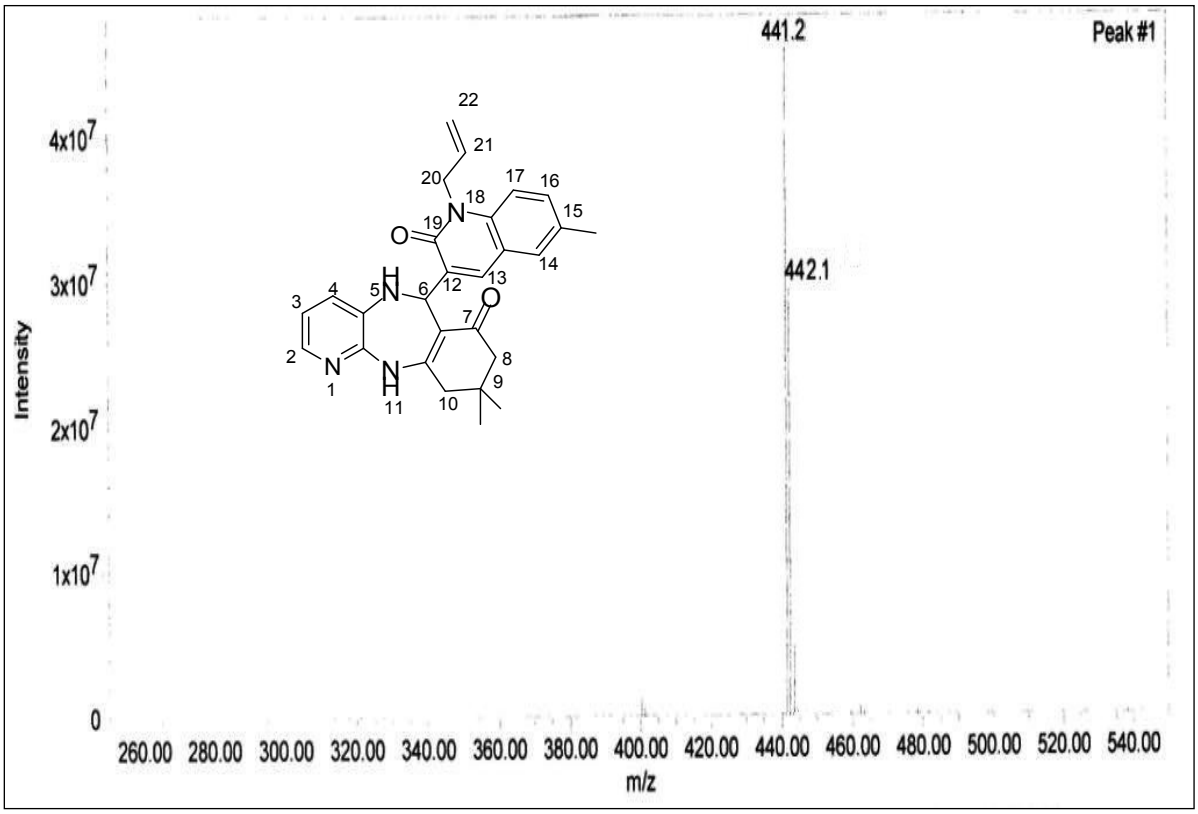
^{1}H NMR spectrum of compound 7i



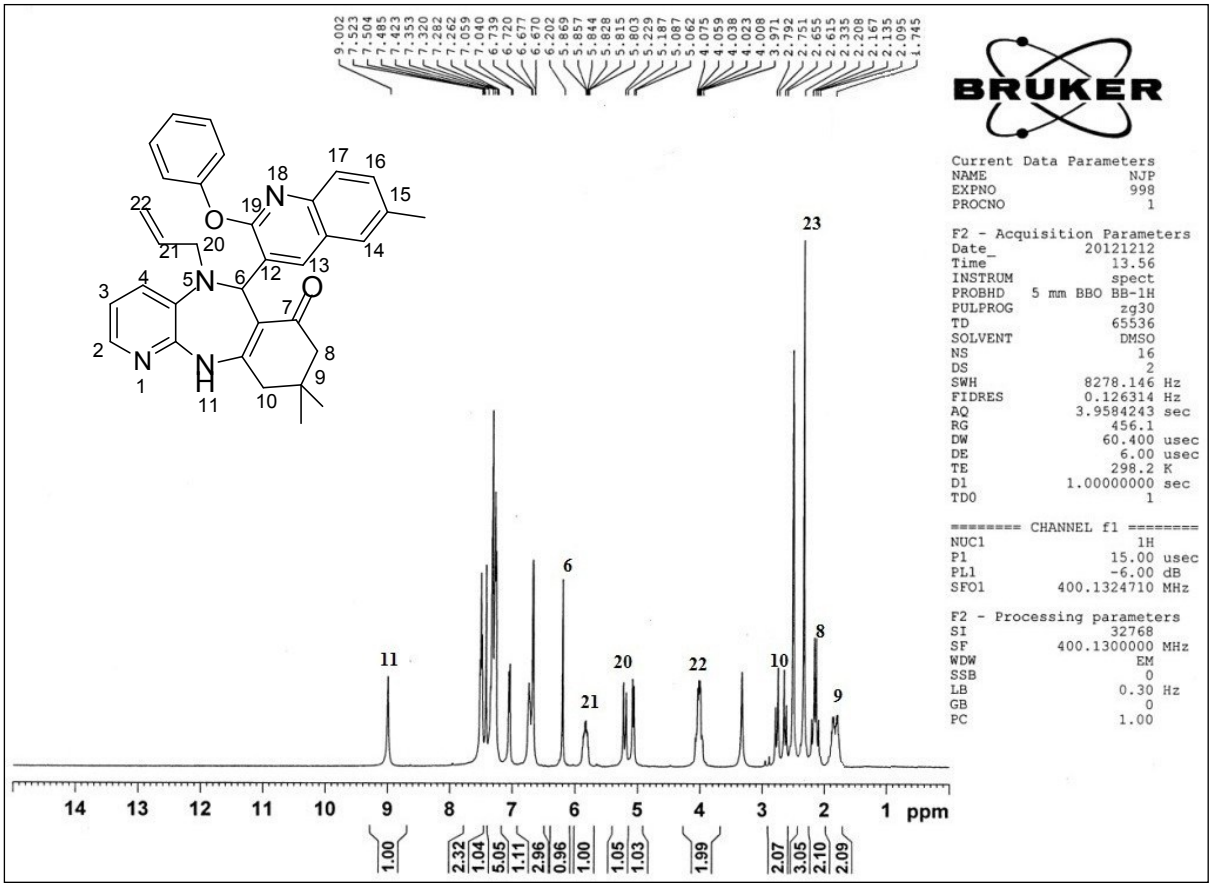
APT spectrum of compound 7i



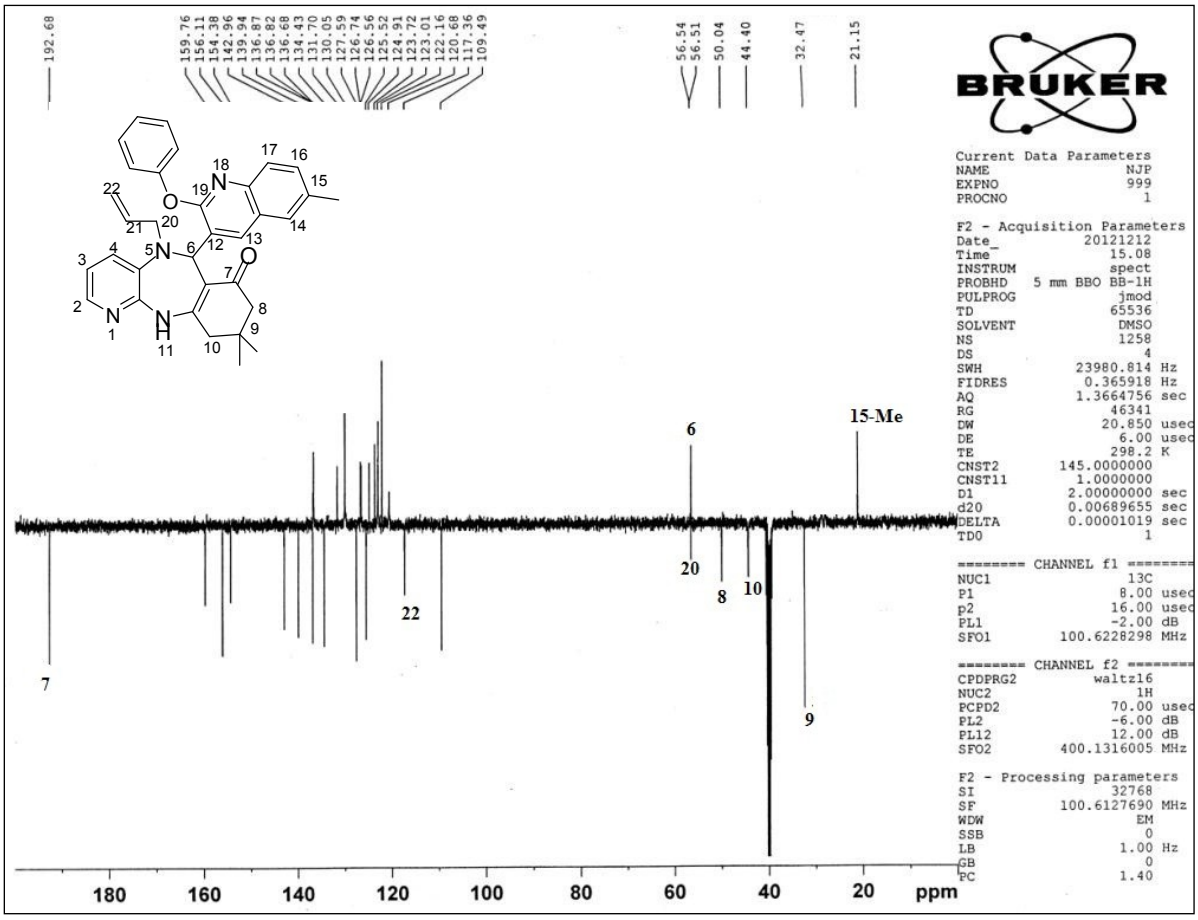
FT–IR spectrum of compound 7i



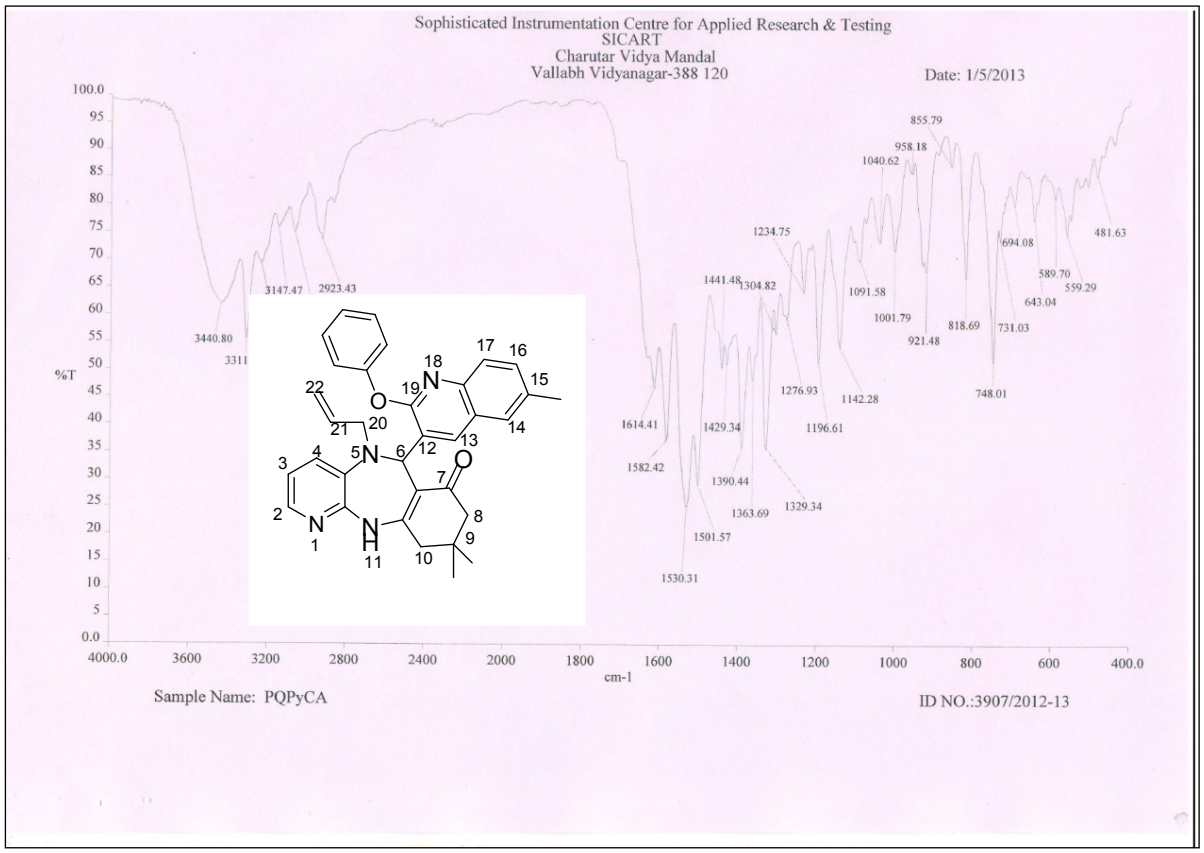
ESI-MS of compound 7i



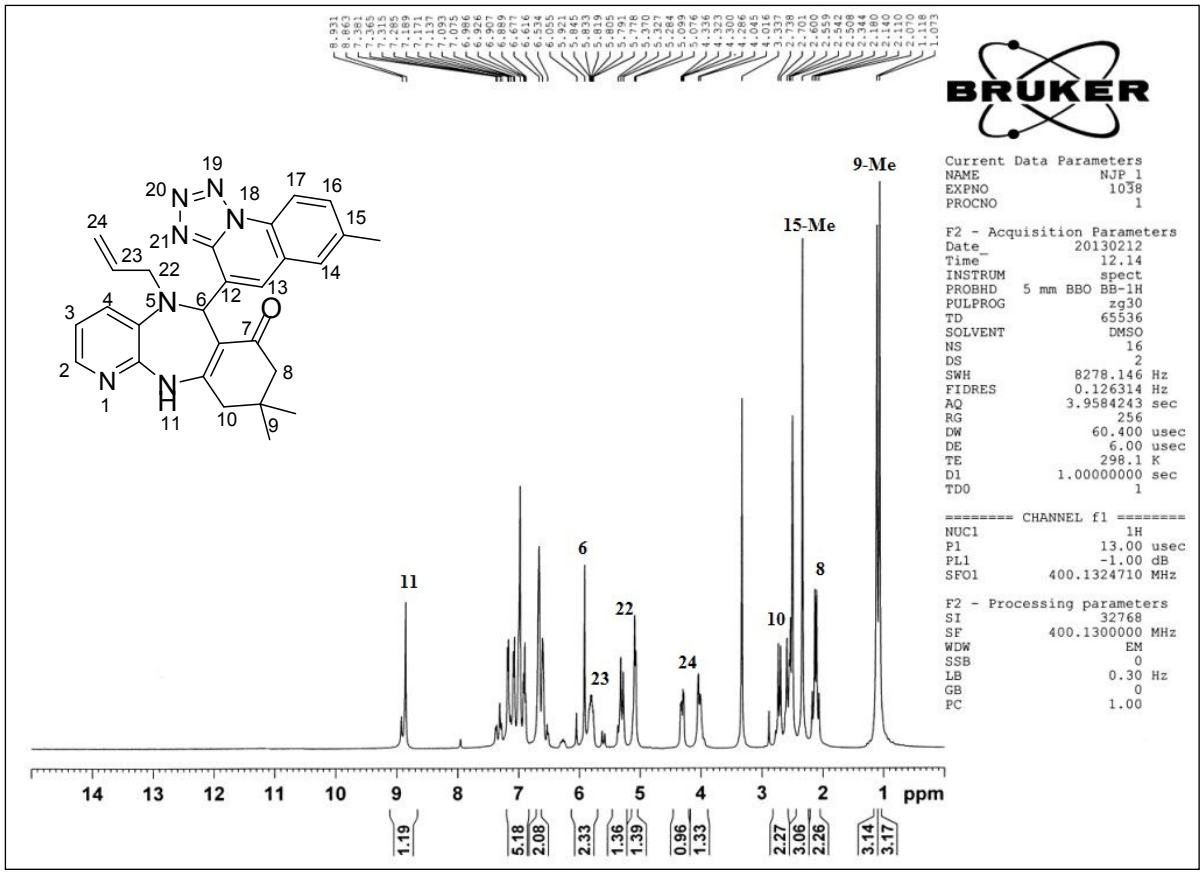
^{1}H NMR spectrum of compound 8b



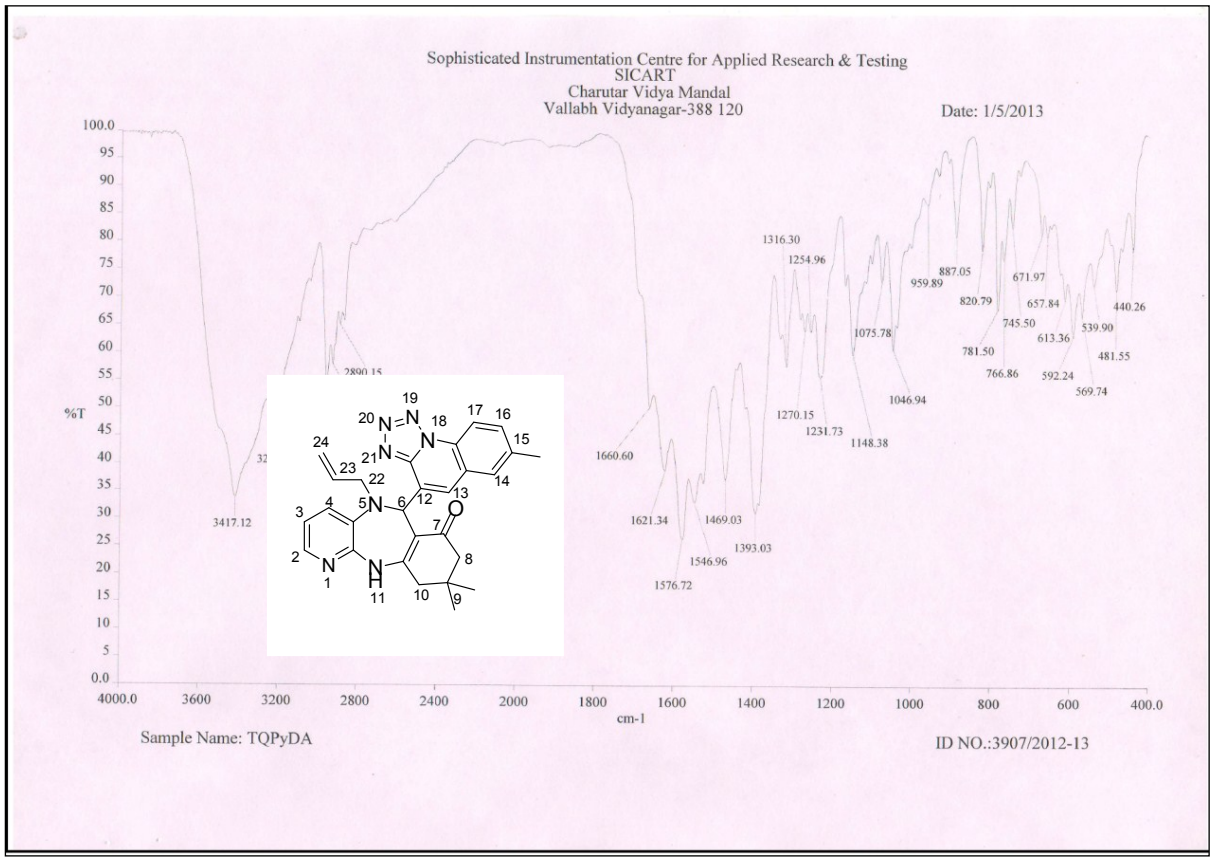
APT spectrum of compound 8b



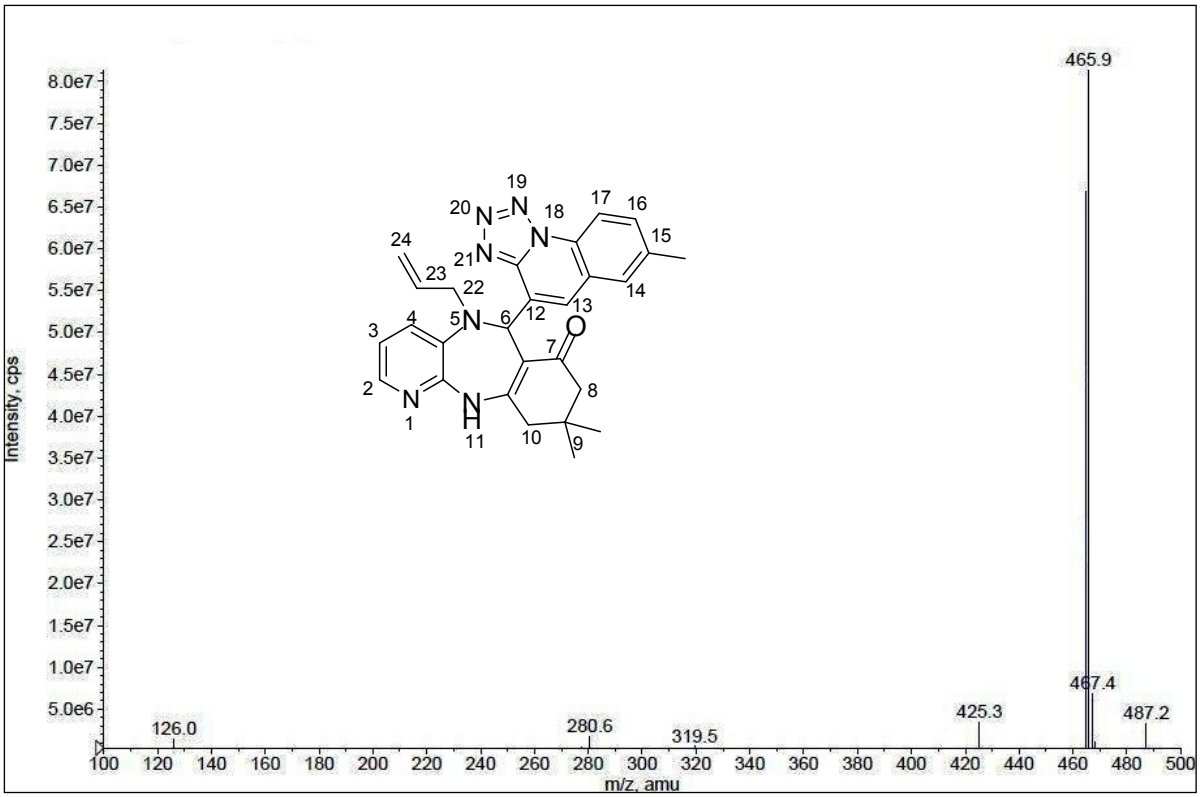
FT–IR spectrum of compound 8b



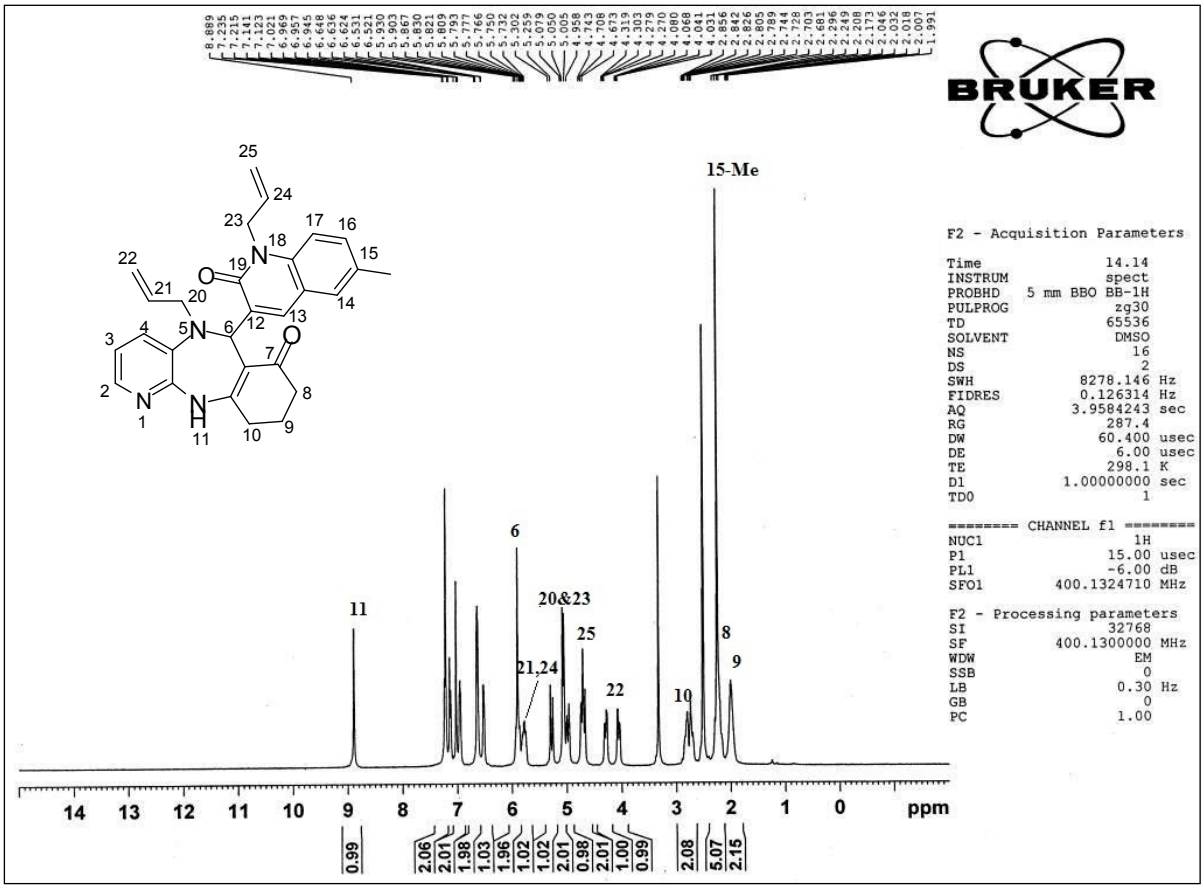
^{1}H NMR spectrum of compound 8e



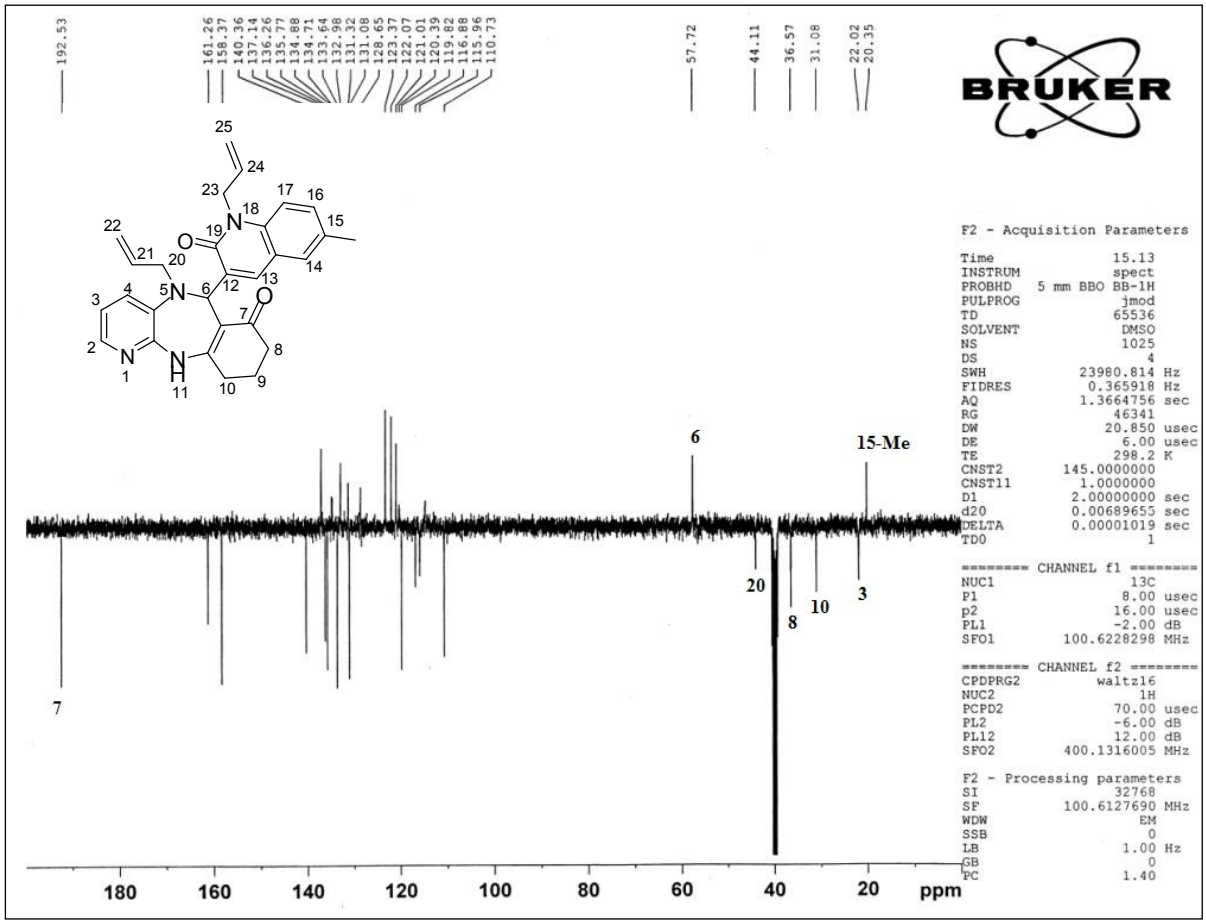
FT–IR spectrum of compound 8e



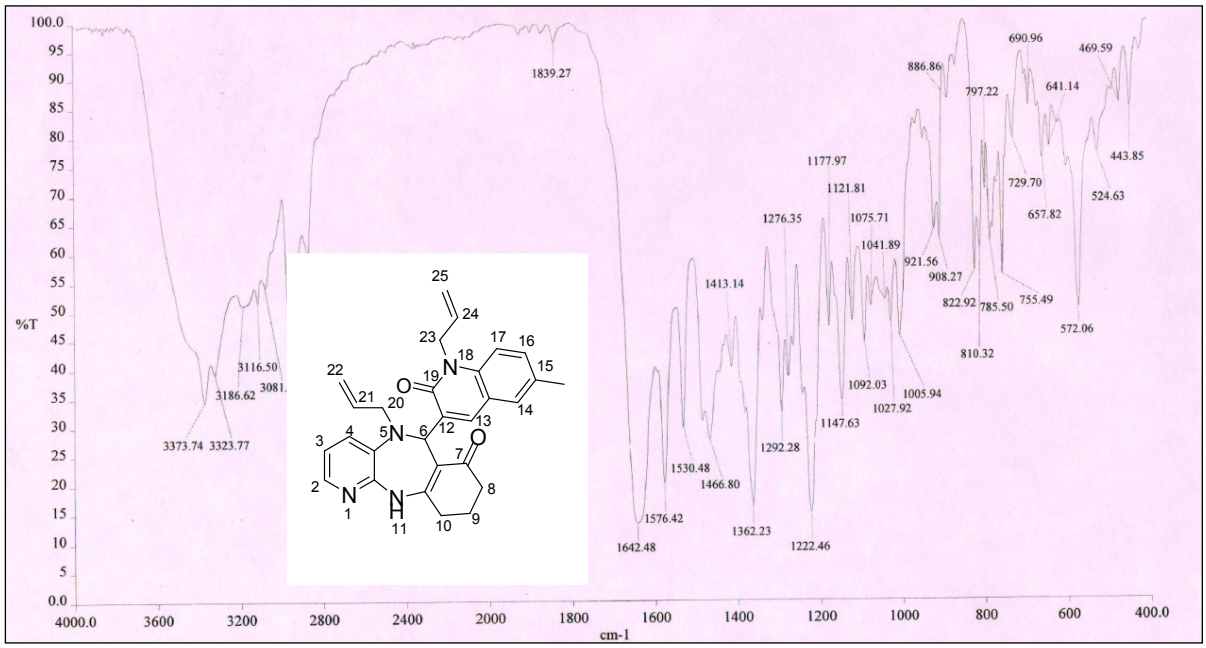
ESI-MS of compound 8e



^{1}H NMR spectrum of compound 8j



APT spectrum of compound 8j



FT–IR spectrum of compound 8j

1.7 Antiproliferative activity:

Antiproliferative assays for antitumor activity were performed in 96-well plates using the National Cancer Institute (NCI) protocol.[1] As a model to study the anticancer activity of the synthetic compounds, we used six human solid tumor cell lines A549 (non-small cell lung), HBL-100 (breast), HeLa (cervix), SW1573 (non-small cell lung), T-47D (breast), and WiDr (colon). The *in vitro* antiproliferative activity was evaluated after 48 h of drug exposure using the sulforhodamine B (SRB)[2] According to NCI protocol; only compounds soluble in DMSO at 40 mM were tested. The results expressed as GI_{50} (50% growth inhibition).

1.8 Reference:

1) Monks, A.; Scudiero, D.; Skehan, P.; Shoemaker, R.; Paull, K.; Vistica, D.; Hose, C.; Langley, J.; Cronise, P.; Vaigro-Wolff, A.; Gray-Goodrich, M.; Campbell, H.; Mayo, J.; Boyd, M. J. Natl. Cancer Inst. 1991, 83, 757.

2) Skehan, P.; Storeng, P.; Scudeiro, D.; Monks, A.; McMahon, J.; Vistica, D.; Warren, J. T.; Bokesch, H.; Kenney, S.; Boyd, M. R. J. Natl. Cancer Inst. 1990, 82, 1107.