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Two-step synthesis of indeno[1,2-*b*]furazanopyrazines through combination of the S_N^H and Heck reactions

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Table of Contents

General Information.

All reagents and solvents were obtained from commercial sources and dried by using standard procedures before use. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-400 and AVANCE-500 instruments using Me_4Si as an internal standard. The complete assignment of ^{1}H and ^{13}C signals was based on 2D ^{1}H-^{1}H NOESY, ^{1}H-^{13}C HSQC / HMBC experiments. Elemental analysis was carried on a Eurovector EA 3000 automated analyzer. High resolution mass spectrometry was performed using a Bruker maXis Impact HD spectrometer. Melting points were determined on Boetius combined heating stages and were not corrected.

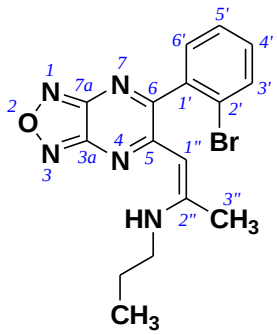
Flash-column chromatography was carried out using Alfa Aesar silica gel 0.040-0.063 mm (230–400 mesh), eluting with ethyl acetate-hexane. The progress of reactions and the purity of compounds were checked by TLC on Sorbfil plates (Russia), in which the spots were visualized with UV light (λ 254 or 365 nm).

X-ray diffraction analysis was performed on an automated X-ray diffractometer "Xcalibur E" on standard procedure. CCDC 2282840 (for **3a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via *www.ccdc.cam.ac.uk/data_request/cif*.

Synthesis

General procedure for the synthesis of S_N^H-products 3a-d. To a stirred 5-(2-bromophenyl)-[1,2,5]oxadiazolo[3,4-*b*]pyrazine **1** (277 mg, 1.0 mmol) in acetone (5 ml) was added the appropriate amine **2a-d** (1.2 mmol). The reaction mixture was stirred in air at 50 °C for 12 h. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatography (hexane/CH_2Cl_2, 1:1) to afford the desired S_N^H-products **3a-d**.

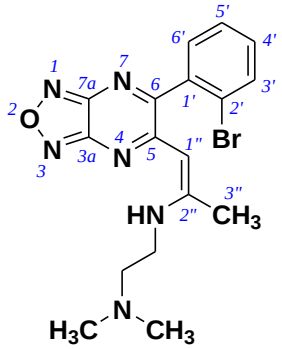
(*Z*)-1-6-(2-Bromophenyl)[1,2,5]oxadiazolo[3,4-*b*]pyrazin-5-yl]-*N*-propylprop-1-en-2-amine (3a). Yield 262 mg, 70%, dark red solid, mp 164-165 °C.



^{1}H NMR (500 MHz, DMSO-d_6) δ 12.03 (br.t, 1H, *J* 6.1 Hz, NH), 7.81 (d, 1H, *J* = 8.0 Hz, H-3'), 7.61-7.50 (m, 3H, H-5', H-6', H-4'), 4.80 (s, 1H, H-1''), 3.49 (q, 2H, *J* 6.5 Hz, NCH_2), 2.08 (s, 3H, H-3''), 1.68 (sex, 2H, *J* 7.1 Hz, CH_2), 1.03 (t, 3H, *J* 7.3 Hz, CH_3). ^{13}C NMR (126 MHz, DMSO-d_6) δ 167.4 (C-6''), 166.6 (C-2''), 155.0 (C-5), 151.4 (C-3a), 149.8 (C-7a), 138.0 (C-1'),

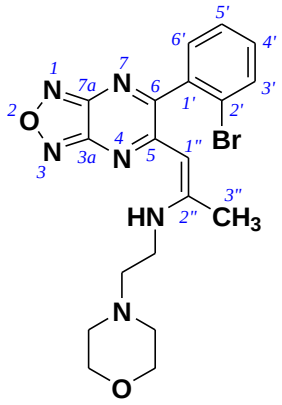
132.6 (C-3'), 131.4 (C-4'), 130.0 (C-6'), 128.0 (C-5'), 120.5 (C-2'), 95.1 (C-1''), 45.4 (NCH_2), 22.3 (CH_2), 20.0 (C-3''), 11.2 (CH_3). Calcd. for $C_{16}H_{16}BrN_5O$ (374.25): C, 51.35; H, 4.31; N, 18.71. Found: C, 51.27; H, 4.32; N, 18.74.

(*Z*)-*N*^{1}-{1-[6-(2-Bromophenyl)[1,2,5]oxadiazolo[3,4-*b*]pyrazin-5-yl]prop-1-en-2-yl}-*N*^{2},*N*^{2}-dimethylethane-1,2-diamine (3b). Yield 210 mg (52%), dark red solid, mp 165-166 °C.



^{1}H NMR (500 MHz, DMSO-d_6) δ 12.09 (br.t, 1H, *J* 5.6 Hz, NH), 7.81 (br.d, 1H, *J* 7.6 Hz, H-3'), 7.59 (td, 1H, *J* 7.6, 0.9 Hz, H-5'), 7.54 (dd, 1H, *J* 7.6, 1.8 Hz, H-6'), 7.51 (td, 1H, *J* 7.6, 1.8 Hz, H-4'), 4.76 (s, 1H, H-1''), 3.61-3.51 (m, 2H, NHC$\underline{H}_2$), 2.59-2.51 (m, 2H, NCH_2), 2.28 (s, 6H, NMe_2), 2.07 (s, 3H, H-3''). ^{13}C NMR (126 MHz, DMSO-d_6) δ 167.2 (C-6), 165.9 (C-2''), 154.9 (C-5), 151.4 (C-3a), 149.7 (C-7a), 138.0 (C-1'), 132.6 (C-3'), 131.3 (C-4'), 129.9 (C-6'), 127.9 (C-5'), 120.4 (C-2'), 94.9 (C-1''), 57.2 (NHC$\underline{H}_2$), 44.9 (NMe_2), 41.8 (NC$\underline{H}_2$), 20.2 (C-3''). Calcd. for $C_{17}H_{19}BrN_6O$ (403.28): C, 50.63; H, 4.75; N, 20.84. Found: C, 50.77; H, 4.74; N, 20.69.

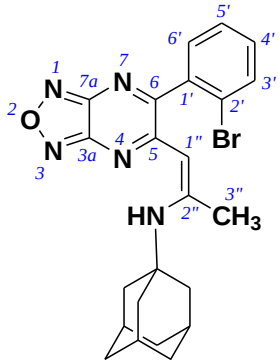
(*Z*)-1-[6-(2-Bromophenyl)[1,2,5]oxadiazolo[3,4-*b*]pyrazin-5-yl]-*N*-(2-morpholino-ethyl)prop-1-en-2-amine (3c). Yield 305 mg (69%), dark red solid, mp 169-170 °C.



^{1}H NMR (500 MHz, DMSO-d_6) δ 12.05 (br.t, 1H, *J* 5.4 Hz, NH), 7.81 (br.d, 1H, *J* 7.9 Hz, H-3'), 7.59 (br.t, 1H, *J* 7.7 Hz, H-5'), 7.54 (dd, 1H, *J* 7.7, 1.9 Hz, H-6'), 7.51 (td, 1H, *J* 7.8, 1.9 Hz, H-4'), 4.77 (s, 1H, H-1''), 3.80-3.73 (m, 4H, $O(CH_2)_2$), 3.65-3.55 (m, 2H, NHC$\underline{H}_2$), 2.66-2.56 (m, 2H, NCH_2), 2.54-2.41 (m, 4H, $N(CH_2)_2$, overlaped by DMSO), 2.07 (s, 3H, H-3''). ^{13}C NMR (126 MHz, DMSO-d_6) δ 167.2 (C-6), 165.6 (C-2''), 155.0 (C-5), 151.6 (C-3a), 149.7 (C-7a), 138.1 (C-1'), 132.6 (C-3'), 131.3 (C-4'), 127.9 (C-5'), 120.4 (C-2'), 95.0 (C-1''), 66.1 ($O(CH_2)_2$),

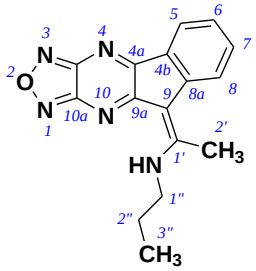
55.7 (NCH_2), 52.9 ($N(CH_2)_2$), 40.5 ($NHCH_2$), 20.5 (C-3''). Calcd. for $C_{19}H_{21}BrN_6O_2$ (445.32): C, 51.25; H, 4.75; N, 18.87. Found: C, 51.33; H, 4.72; N, 18.94.

(3*s*,5*s*,7*s*)-*N*-{(*Z*)-1-[6-(2-Bromophenyl)-[1,2,5]oxadiazolo[3,4-*b*]pyrazin-5-yl]prop-1-en-2-yl}adamantan-1-amine (3d). Yield 290 mg (62%), dark red solid, mp 250-251 °C.



^{1}H NMR (500 MHz, DMSO-d_6) δ 12.43 (br.s, 1H, NH), 7.68 (dd, 1H, *J* 8.1, 0.9 Hz, H-3'), 7.46 (td, 1H, *J* 7.5, 0.9 Hz, H-5'), 7.37 (td, *J* 7.8, 1.7 Hz, H-4'), 7.33 (dd, 1H, *J* 7.6, 1.7 Hz, H-6'), 4.75 (s, 1H, H-1''), 2.21-2.17 (m, 6H, H-3'', 3*CH-Ad), 2.13-2.11 (m, 6H, 3*CH_2-Ad), 1.77-1.69 11 (m, 6H, 3*CH_2-Ad). ^{13}C NMR (126 MHz, DMSO-d_6) δ 166.9 (C-6), 164.4 (C-2''), 155.0 (C-5), 151.3 (C-3a), 150.0 (C-7a), 138.6 (C-1'), 133.0 (C-3'), 130.8 (C-4'), 129.8 (C-6'), 127.5 (C-5'), 121.5 (C-2'), 96.7 (C-1''), 55.6 (NC-Ad), 42.9 (3*CH_2-Ad), 35.9 (3*CH_2-Ad), 29.4 (3*CH-Ad), 22.4 (C-3''). Calcd. for $C_{23}H_{24}BrN_5O$ (466.38): C, 59.23; H, 5.19; N, 15.02. Found: C, 59.24; H, 5.27; N, 15.09.

(*Z*)-*N*-{1-(9*H*-Indeno[1,2-*b*][1,2,5]oxadiazolo[3,4-*e*]pyrazin-9-ylidene)ethyl]propan-1-amine (4). A stirred mixture of (*Z*)-1-[6-(2-bromophenyl)[1,2,5]oxadiazolo[3,4-*b*]pyrazin-5-yl]-*N*-propylprop-1-en-2-amine **3a** (125 mg, 0.3 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (46 mg, 20 mol%), $Pd(OAc)_2$ (7 mg, 10 mol%) and K_3PO_4 (159 mg, 0.75 mmol) in deaerated toluene (5 ml) was heated at reflux under nitrogen for 18 h in a Schlenk tube. The reaction mixture was cooled, filtered, and dissolved with a mixture of CH_2Cl_2 and water 1:1 (50 ml), and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2×25 ml). The combined organic extracts were dried with $MgSO_4$ and the solvents evaporated. The residue was purified by flash column chromatography (hexane/ CH_2Cl_2, 1:1) to afford the desired cross-coupling product (**4**). In addition, starting compound **3a** was isolated in 59% yield. Product **4**: yield 11 mg, 13%, dark blue solid, mp 180-182 °C.



^{1}H NMR (500 MHz, $CDCl_3$) δ 10.98 (br.s, 1H, NH), 8.14 (d, 1H, *J* = 7.5 Hz, H-5), 7.51 (ddd, 1H, *J* 8.0, 7.0, 1.2 Hz, H-7), 7.47 (br.d, 1H, *J* 7.5, H-8), 7.18 (td, 1H, *J* 7.3, 1.1 Hz, H-6), 3.51 (td, 1H, *J* = 7.0, 5.8 Hz, H-1''), 2.55 (s, 3H, H-2'), 1.83 (sex, 1H, *J* 7.3 Hz, H-2''), 1.13 (t, 3H *J* = 7.4 Hz, H-3''). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.33 and 161.27 (C-1', C-4a), 157.3 (C-9a), 151.4 and 151.3 (C-3a, C-10a), 146.3 (C-8a), 134.2 (C-7), 127.4 (C-4b), 124.7 (C-5), 123.2 (C-6), 120.0 (C-8), 99.4 (C-9), 45.6 (C-1''), 23.3 (C-2''), 16.5 (C-2'), 11.4 (C-3''). Calcd. for $C_{16}H_{15}N_5O$ (293.33): C, 65.52; H, 5.15; N, 23.88. Found: C, 65.44; H, 5.12; N, 23.94.

Antimycobacterial assay.

The study of the tuberculostatic activity of the compounds was carried out on the basis of the REMA procedure.[S1,S2]

Preparation of MBT suspension.

Suspension of MBT with 1.0 McFarland turbidity was prepared (using saline) from a culture of *Mycobacterium tuberculosis* H_{37}Rv in the logarithmic phase of growth on the Löwenstein-Jensen medium. The resulting suspension (50 μl) was transferred into a tube with Middlebrook 7H9 nutrient broth and OADC growth supplement. In the wells of the plates, the resulting suspension (100 μl) was added. Preparation of dilutions of the test compounds. Dilutions of the test compounds were prepared using DMSO and sterile distilled water (Isoniazid was dissolved only in water). Weighed portions of testing compounds were dissolved in the calculated volume of DMSO in such a way as to obtain a stock solution with a concentration of 10000 μg ml^{-1}. Further, the dilution was carried out using pure DMSO.

Evaluating procedure:

For testing compounds, culture medium (97 μl) and solution of the test compounds (3 μl) prepared as described above were added to the wells of a 96-well plate. Then, MBT suspension (100 μl) was added to the wells of the plates. Thus, the required concentration of test compounds was obtained in the wells of the plate. The DMSO concentration in all wells is 1.5% (vol.). As a positive control, an MBT culture was used without adding compounds and with the addition of DMSO (final concentration 1.5%). Isoniazid was used as a reference drug. The plates were incubated at 37 ° C for 7 days. After the incubation time, 30 μl of Resazurin solution (with the addition of Tween 80) was added to the wells, and the incubation was continued at 37 °C. The result was taken into account after 24, 48, and 72 hours. The MIC was taken as the minimum concentration of the test compound that prevents the color change of Resazurin.

S1 J. Palomino, A. Martin, M. Camacho, H. Guerra, J. Swings, F. Portaels, Resazurin Microtiter Assay Plate: Simple and Inexpensive Method for Detection of Drug Resistance in *Mycobacterium tuberculosis* / // *Antimicrob. Agents Chemother*. - **2002**. - Vol. 46. N 8. - P. 2720–2722;

S2 N. Taneja, J. Tyagi, Resazurin reduction assays for screening of anti-tubercular compounds against dormant and actively growing *Mycobacterium tuberculosis*, *Mycobacterium bovis* BCG and *Mycobacterium smegmatis* / // *J. Antimicrob. Chemother*. - 2007. - Vol. 60. - P. 288-293.

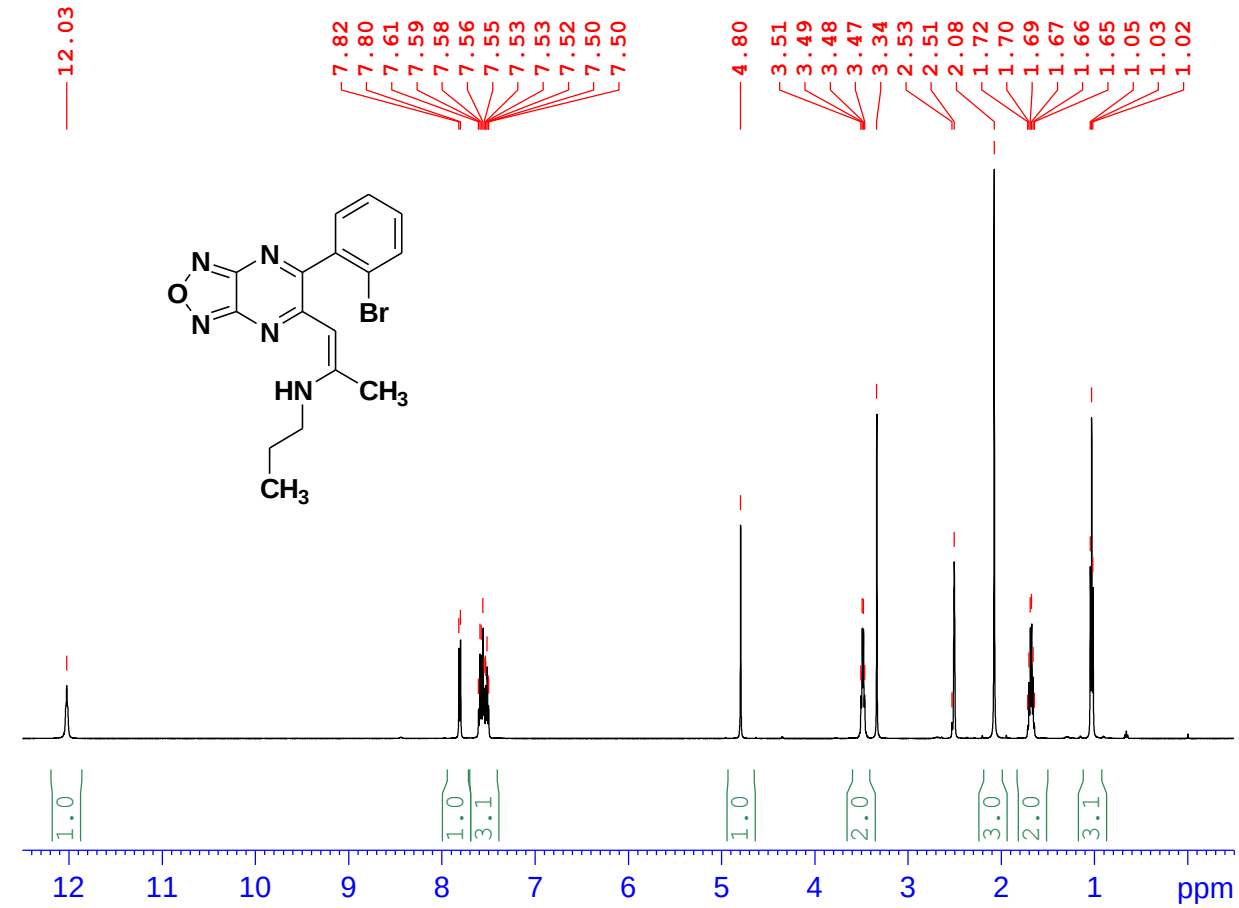


Figure S1. ^{1}H NMR (500 MHz, DMSO-d_6) spectrum of **3a**.

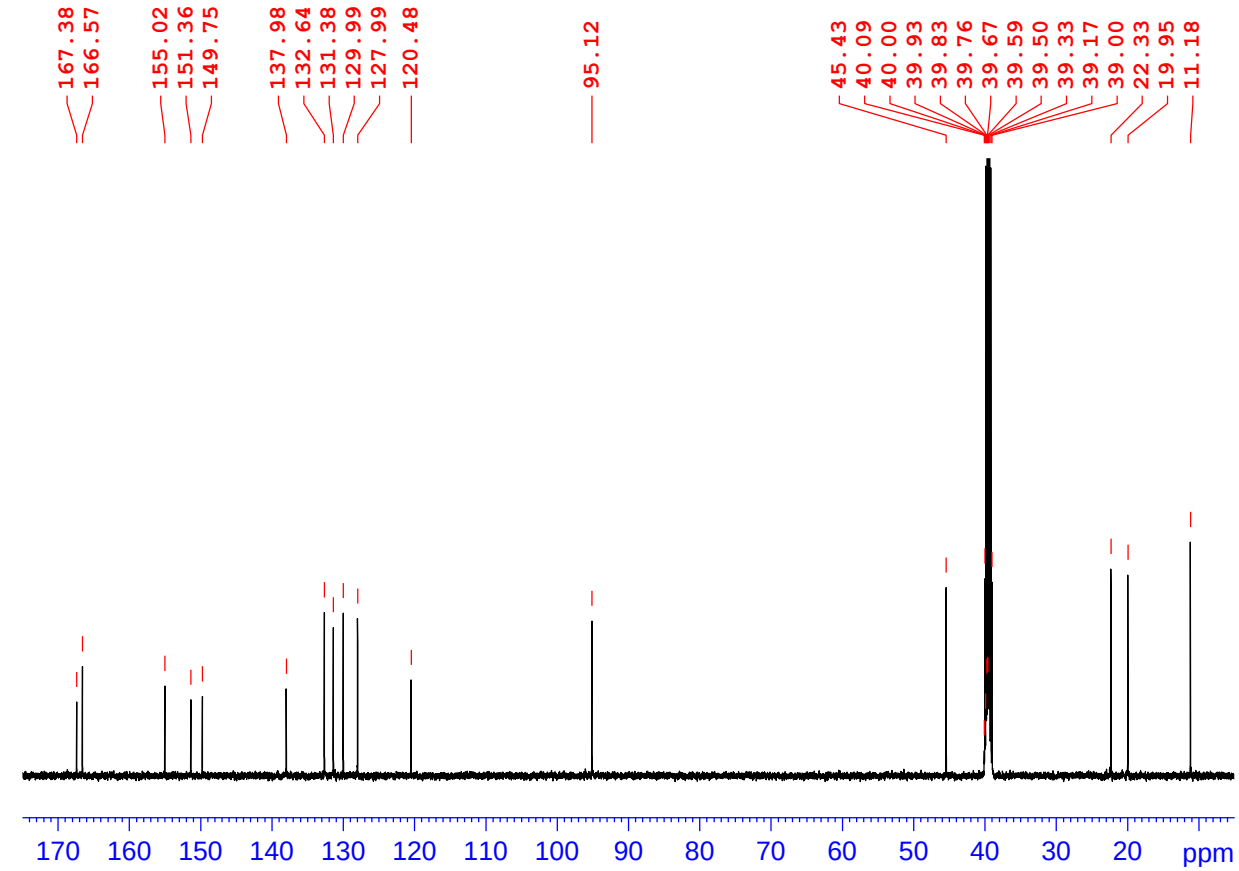


Figure S2. ^{13}C NMR (126 MHz, DMSO-d_6) spectrum of **3a**.

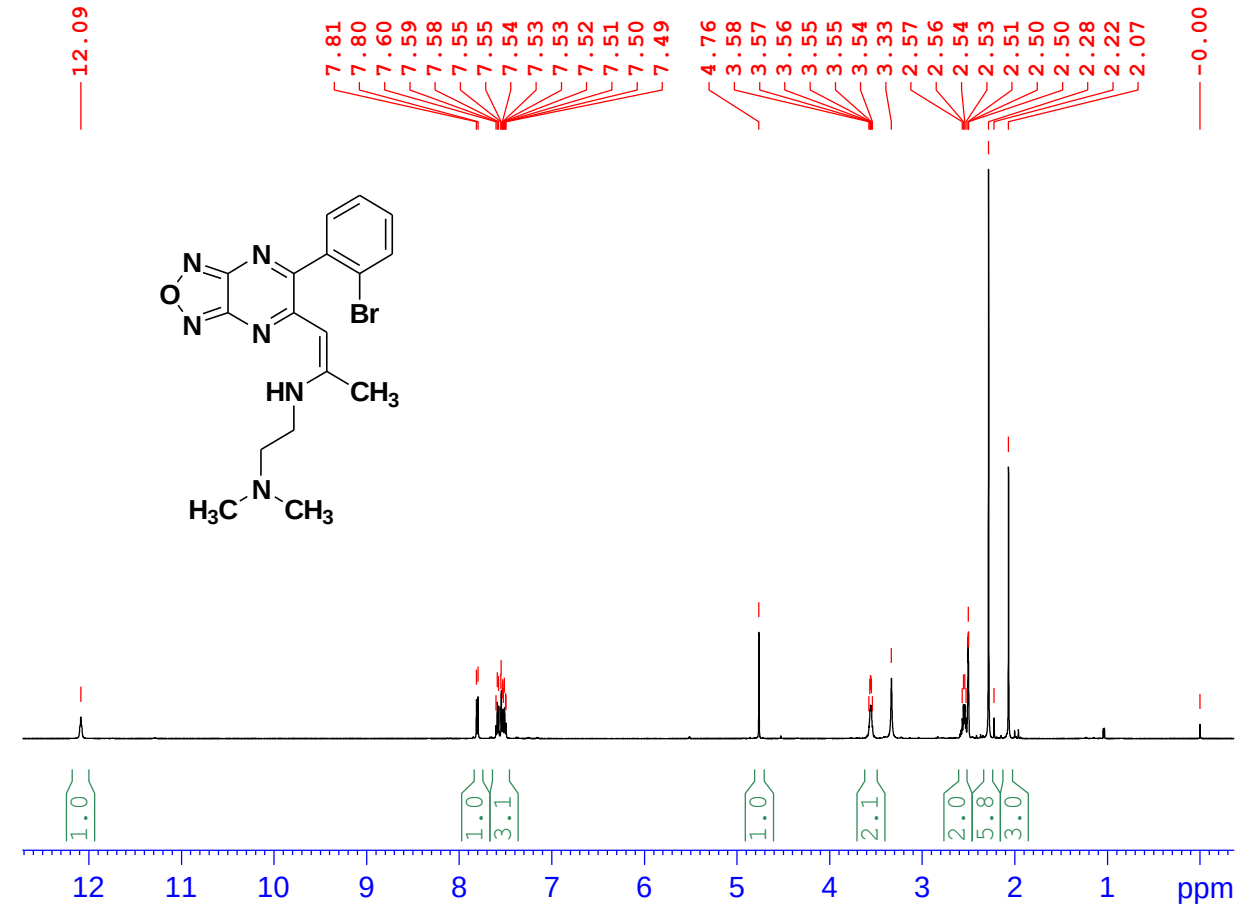


Figure S3. ^{1}H NMR (500 MHz, DMSO-d_6) spectrum of **3b**.

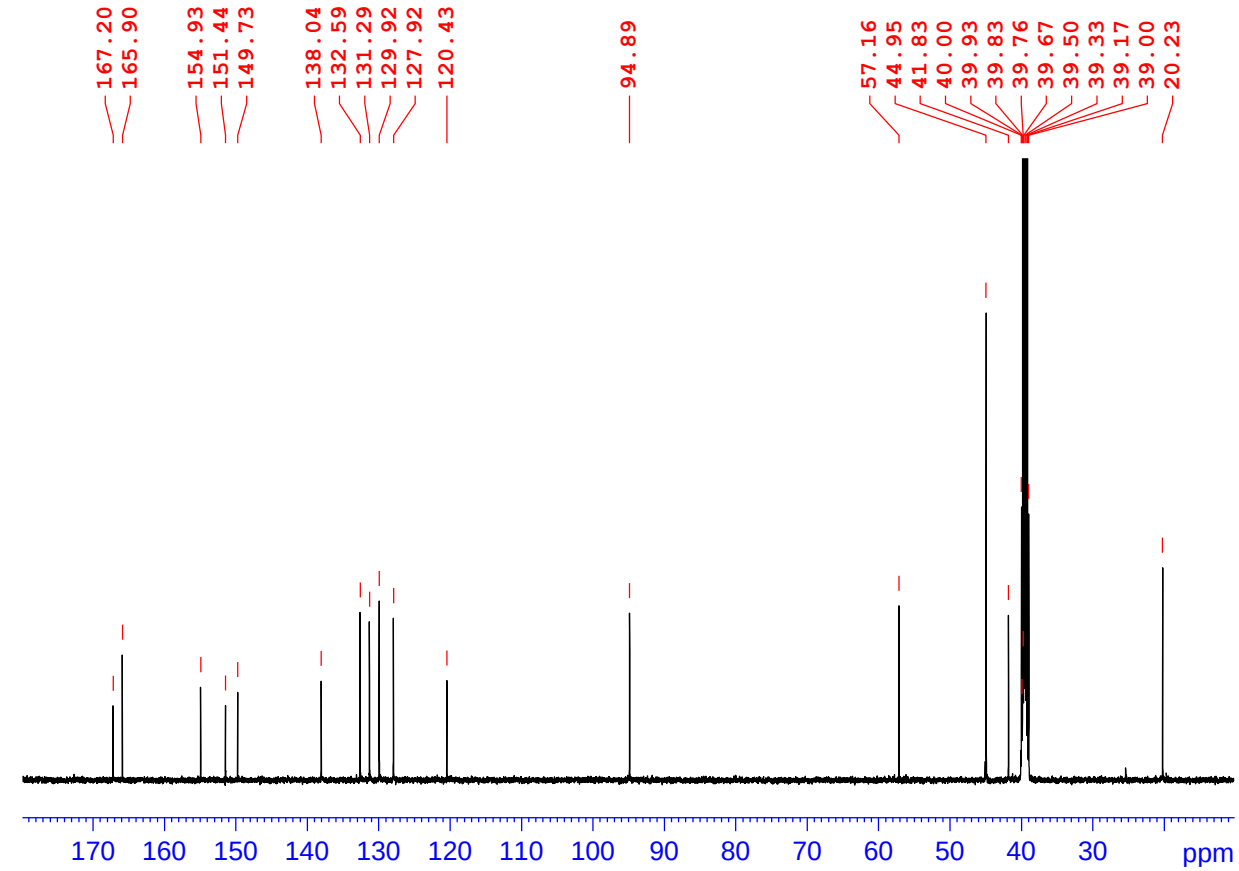


Figure S4. ^{13}C NMR (151 MHz, DMSO-d_6) spectrum of **3b**.

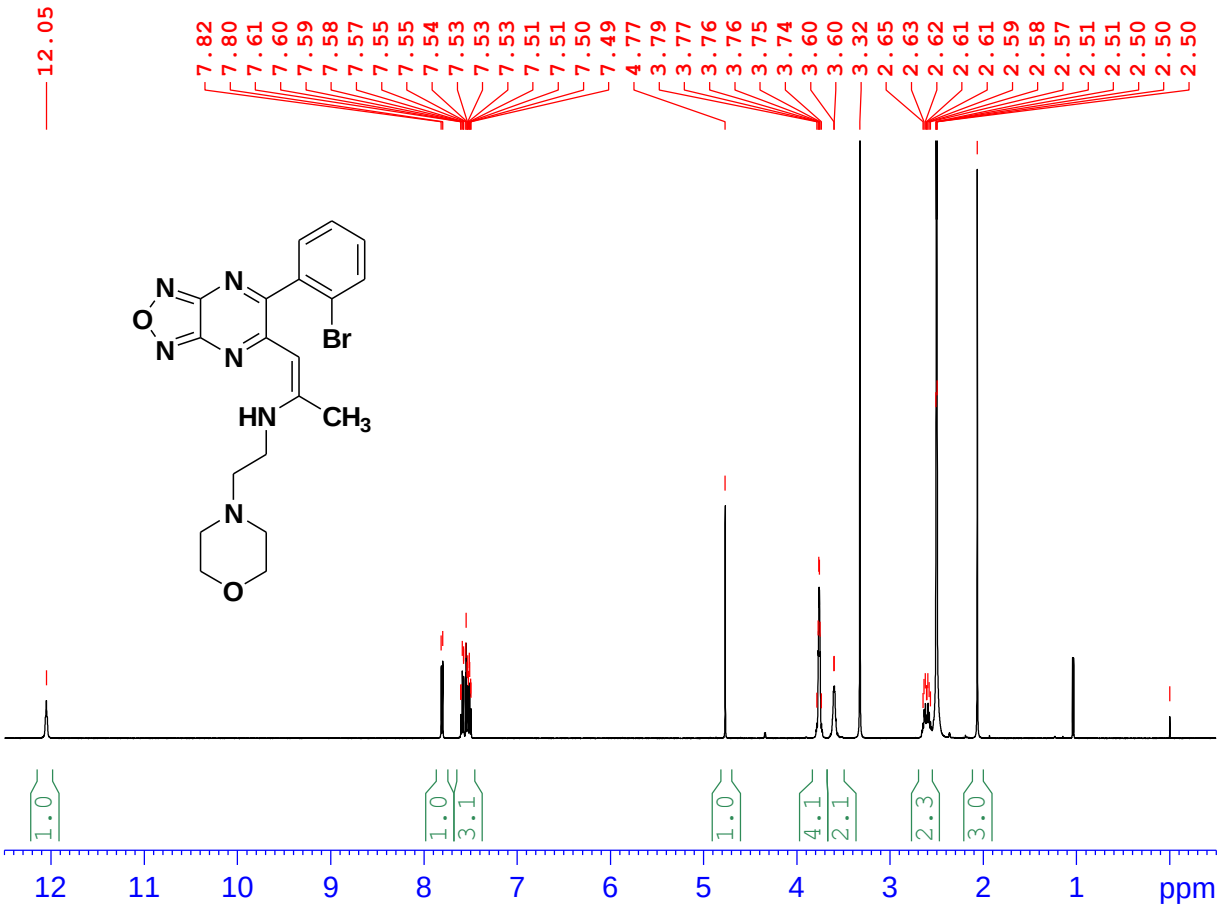


Figure S5. ^{1}H NMR (500 MHz, DMSO-d_6) spectrum of **3c**.

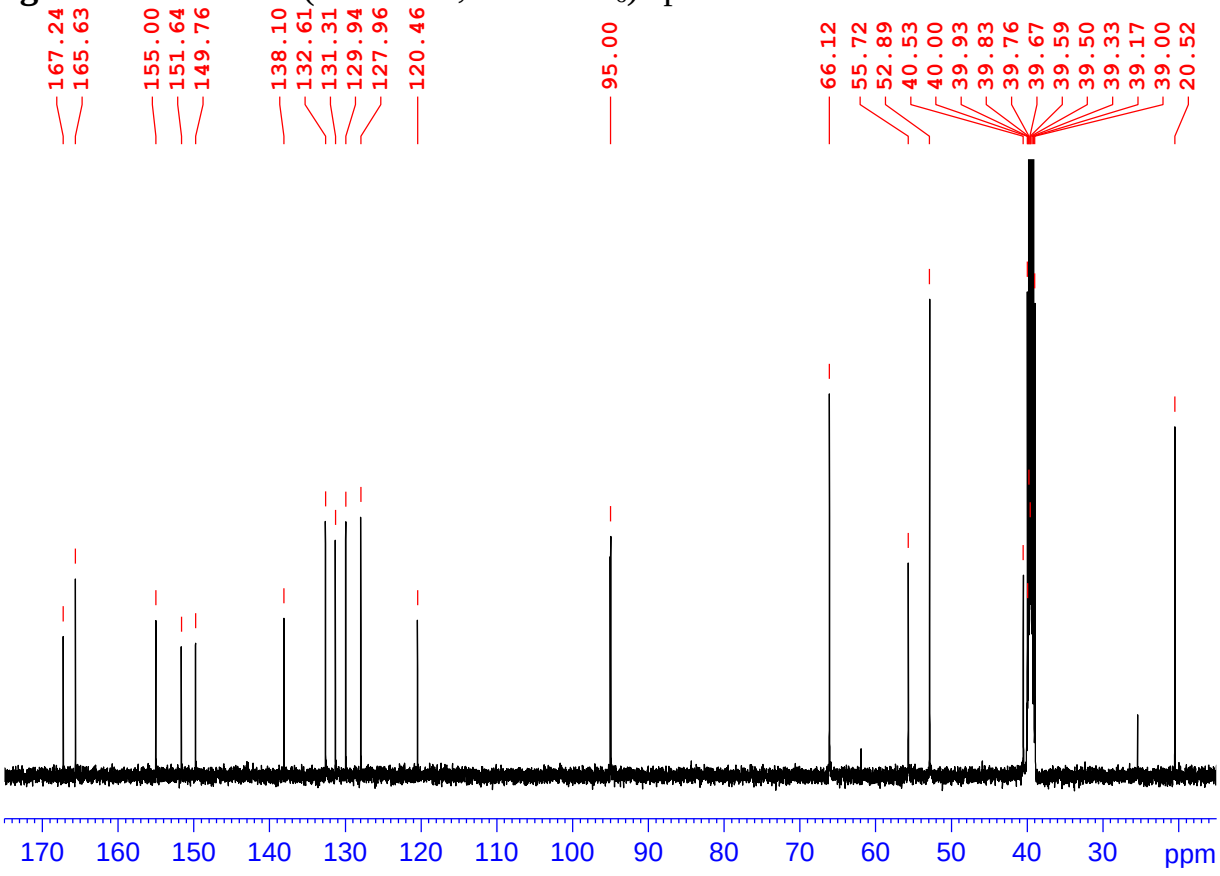


Figure S6. ^{13}C NMR (126 MHz, DMSO-d_6) spectrum of **3c**.

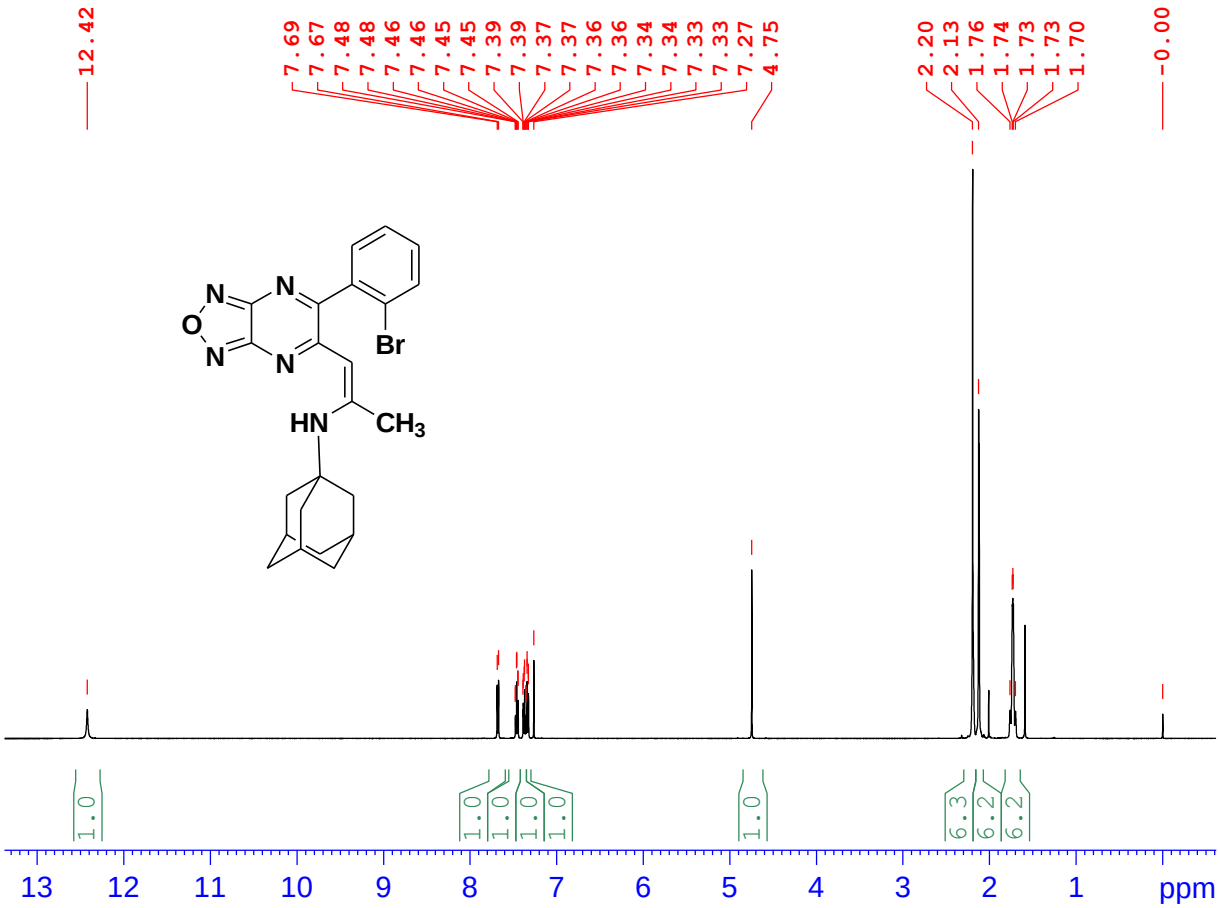


Figure S7. ^{1}H NMR (500 MHz, DMSO-d_6) spectrum of **3d**.

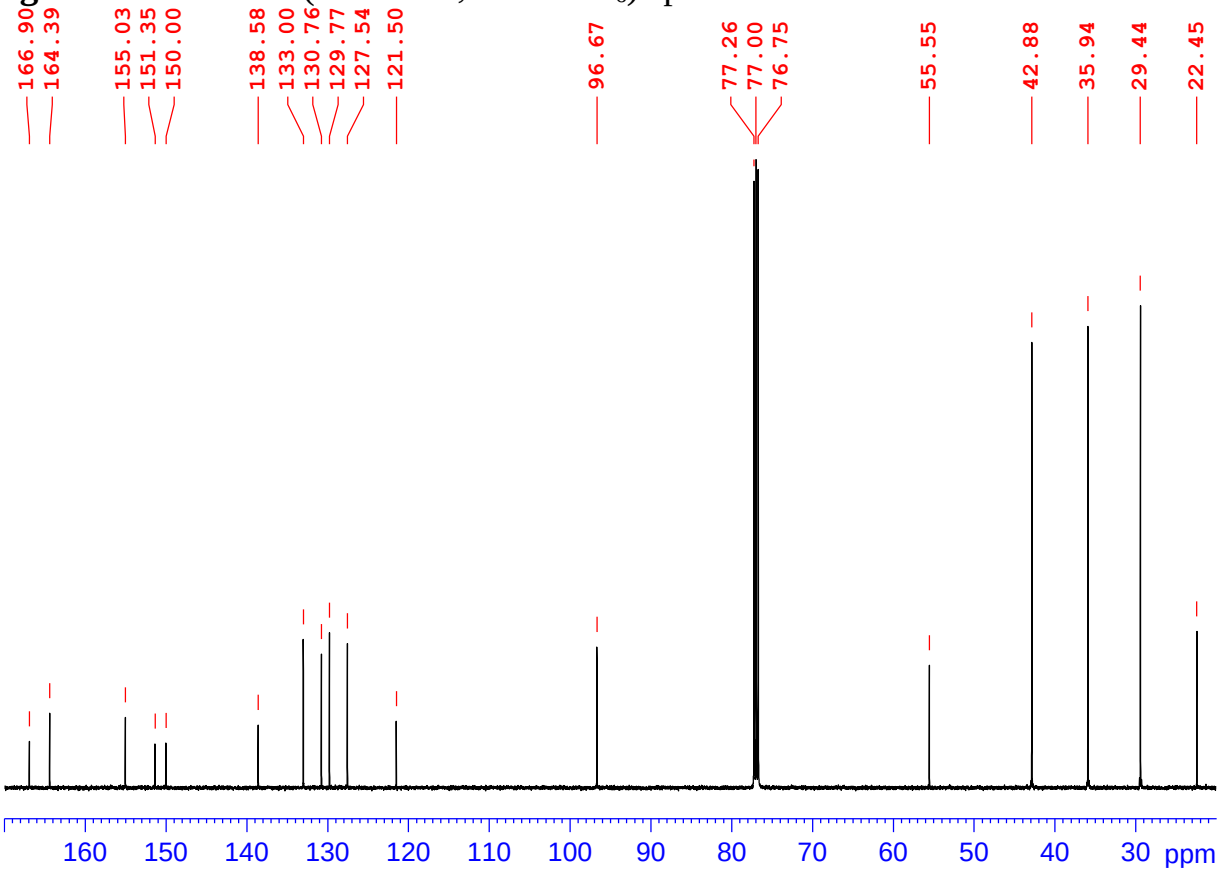


Figure S8. ^{13}C NMR (126 MHz, DMSO-d_6) spectrum of **3d**.

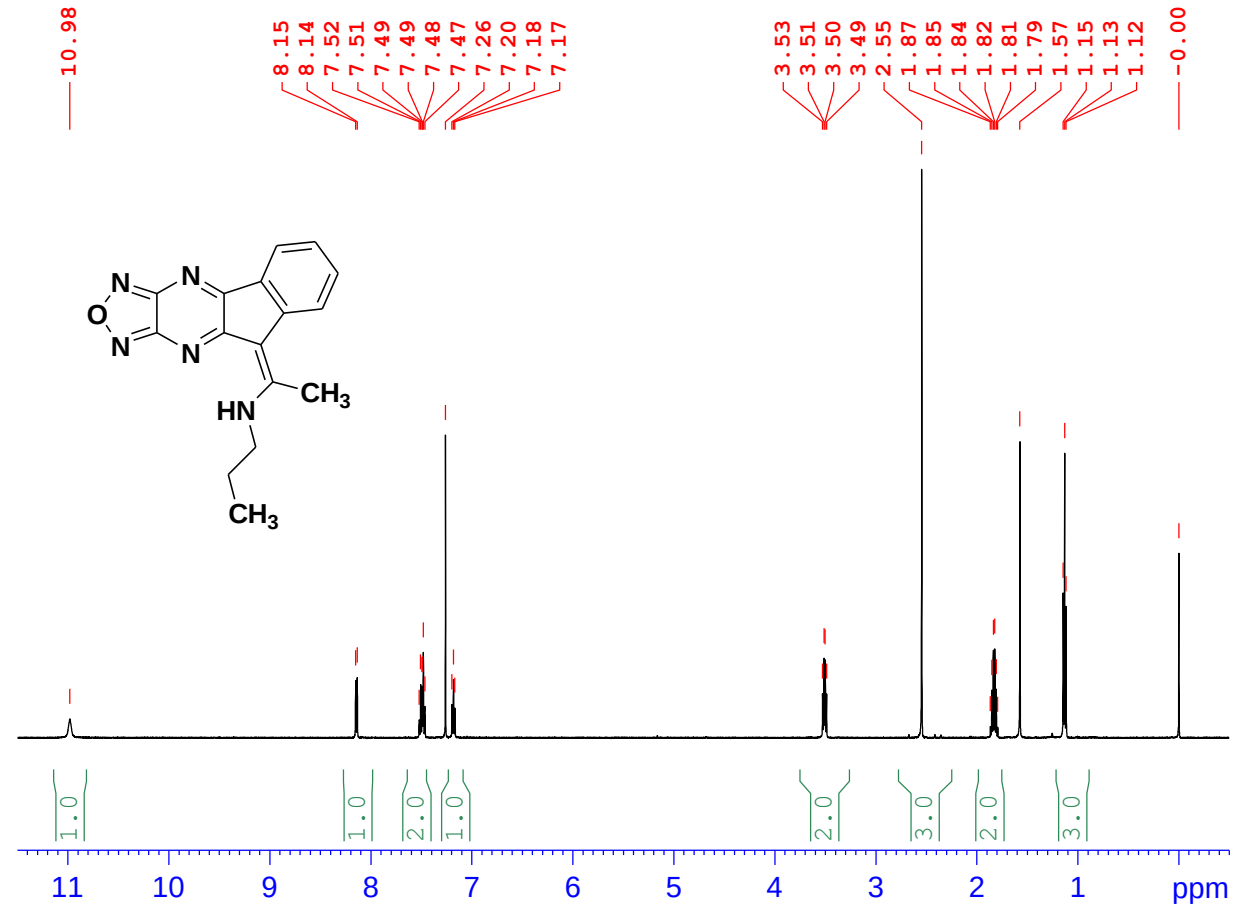


Figure S9. ^{1}H NMR (500 MHz, $CDCl_3$) spectrum of **4**.

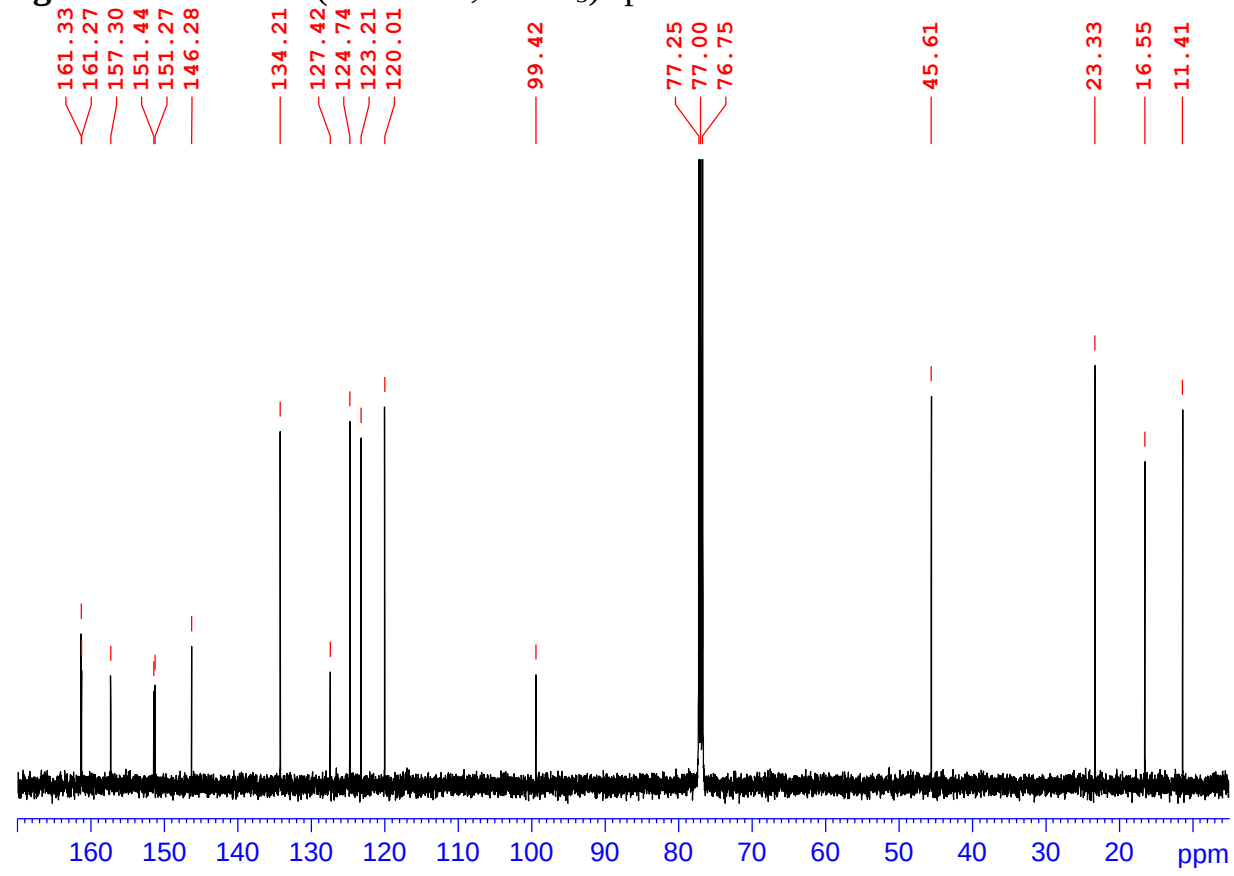


Figure S10. ^{13}C NMR (126 MHz, $CDCl_3$) spectrum of **4**.