A Metal-free 1,3-Dipolar Cycloaddition Approach towards Regioselective Synthesis of β-Carboline and Isoxazole Based Molecular Hybrids

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Supporting Information

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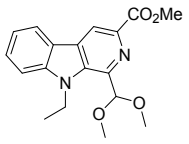
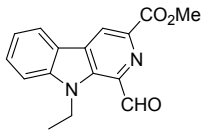
Procedure for preparation of methyl 1-(dimethoxymethyl)-9-ethyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (9b): To a stirred solution of **5** (6.00 g, 20.00 mmol) in dry DMF (60 mL), Cs_2CO_3 (9.78 g, 30.0 mmol) was added and stirred the reaction mixture at room temperature for 15 min. Thereafter ethyl bromide (2.25 mL, 30.00 mmol) was added drop-wise and the reaction mixture was stirred for additional 1 h at room temperature. On completion of the reaction, as monitored by TLC, the contents were poured into ice cold water (100 mL) under stirring. The solid product was filtered through sintered funnel which was washed twice with cold water. The product was further air dried under vacuum and finally washed with hexane to yield the yellow solid product, **9b** (6.40 g, 97%, R_f = 0.50 (hexane/EtOAc, 70:30, v/v) which was analytically pure and utilized for the next step as such.



Methyl 1-(dimethoxymethyl)-9-ethyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (9b). Yield: 97% (6.40 g from 6.00 g) as a light brown solid; m.p. 108-109 ^oC; R_f = 0.50 (hexane/EtOAc, 70:30, v/v); IR (KBr): ν_{max} = 1710 (CO_2CH_3); ^1H NMR (400 MHz, $CDCl_3$) δ = 1.42 (t, *J* = 6.8 Hz, 3 H), 3.55 (s, 6 H), 4.04 (s, 3 H), 4.91 (q, *J* = 6.8 Hz, 2 H), 5.76 (s, 1 H), 7.35 (s, 1 H), 7.56 (d, *J* = 7.2 Hz, 1 H), 7.63 (d, *J* = 6.8 Hz, 1 H), 8.19 (d, *J* = 7.2 Hz, 1 H), 8.89 (s, 1 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.1, 41.0, 52.8, 55.8, 110.3, 110.9, 118.5, 120.7, 121.4, 121.8, 128.9, 131.0, 135.0, 135.2, 140.9, 142.0 ppm; MS (ES): *m*/*z* (%) = 329.2 (100) $[M+1]^+$; $C_{18}H_{20}N_2O_4$ (328.1423): calcd. for C 65.84, H 6.14, N 8.53; found C 65.97, H 6.18, N 8.61.

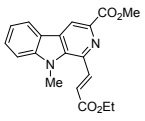
Procedure for preparation of methyl 9-ethyl-1-formyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (10b): To a stirred solution of **9b** (6.0 g, 18.27 mmol) in glacial AcOH (24 mL); water (36 mL) was added and heated the content at 100 ^oC for 45 min. During this period, yellow solid precipitated out from the reaction mixture and the content was diluted with ice cold water (100 mL). The solid product was filtered through sintered under suction, washed with 10% aqueous $NaHCO_3$ solution (50 mL) and further air dried. The product was triturated with 5% ethyl acetate: hexane (v/v, 10 mL) to yield the analytically pure yellow solid product, **10b** (4.60 g, 89%). It deserves attention here that if during deprotection of acetal heating is performed at 100 ^oC for longer duration (>1 h), it results in change in color of compound from yellow to dark brown solid and decrease in yield.



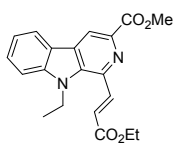
Methyl 9-ethyl-1-formyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (10b). Yield: 89% (4.60 g from 6.00 g) as a light brown solid; m.p. 121-122 ^oC; R_f = 0.55

(hexane/EtOAc, 70:30, v/v); IR (KBr): ν_{max} = 1709 (CO_2CH_3); ^{1}H NMR (400 MHz, DMSO-d_6) δ = 1.34 (t, *J* = 7.0 Hz, 3 H), 3.97 (s, 3 H), 4.87 (q, *J* = 7.0 Hz, 2 H), 7.45 (d, *J* = 7.4 Hz, 1 H), 7.75 (t, *J* = 7.6 Hz, 1 H), 7.87 (d, *J* = 8.4 Hz, 1 H), 8.54 (d, *J* = 7.7 Hz, 1 H), 9.19 (s, 1 H), 10.23 (s, 1 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 15.0, 42.3, 53.0, 110.9, 120.8, 121.3, 121.7, 121.8, 128.9, 130.0, 133.1, 135.8, 136.9, 137.0, 142.6 ppm; MS (ES): *m*/*z* (%) = 283.2 (100) $[M+1]^+$; $C_{16}H_{14}N_2O_3$ (282.1004): calcd. for C 68.07, H 5.00, N 9.92; found C 68.20, H 5.06, N 10.02.

Procedure for the synthesis of (*E*)-methyl 1-(3-ethoxy-3-oxoprop-1-en-1-yl)-9-methyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate derivatives (11a-11d) as exemplified for compound 11a: To a cooled stirred suspension of NaH (0.54 g, 13.42 mmol) in dry THF (40 mL), triethyl phosphonoacetate (2.29 mL, 11.18 mmol) was added dropwise at 0 °C and stirred the content for 15 minutes at the same temperature. Thereafter **10a** (2.00 g, 7.46 mmol) was added portion-wise and the reaction mixture was allowed to stirr for additional 2 h at room temperature. On completion of the reaction as monitored by TLC, THF was evaporated under reduced pressure to yield the yellow solid product which was suspended in ice cold water (50 mL), filtered through sintered funnel, washed with hexane and dried under vacuum to obtain pure yellow solid product, **11a** (2.40 g, 95%, R_f = 0.55 (hexane/EtOAc, 70:30, v/v).



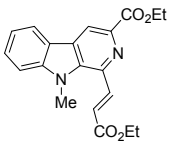
(*E*)-methyl 1-(3-ethoxy-3-oxoprop-1-en-1-yl)-9-methyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (11a). Yield: 95% (2.40 g from 2.00 g) as a yellow solid; m.p. 183-184 °C; R_f = 0.55 (hexane/EtOAc, 70:30, v/v); IR (KBr): ν_{max} = 1702 (CO_2CH_3 and $CO_2CH_2CH_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.37 (t, *J* = 7.1 Hz, 3 H), 4.05 (s, 3 H), 4.19 (s, 3 H), 4.33 (q, *J* = 6.8 Hz, 2 H), 7.24 (d, *J* = 12.8 Hz, 1 H), 7.37 (t, *J* = 7.6 Hz, 1 H), 7.50 (d, *J* = 8.0 Hz, 1 H), 7.67 (t, *J* = 7.6 Hz, 1 H), 8.17 (d, *J* = 8.0 Hz, 1 H), 8.52 (d, *J* = 15.6 Hz, 1 H), 8.82 (s, 1 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.4, 33.4, 52.8, 60.8, 110.0, 117.9, 121.1, 121.2, 121.8, 124.8, 129.4, 131.0, 136.5, 136.9, 137.5, 138.8, 142.8, 166.4, 166.9 ppm; MS (ES): *m*/*z* (%) = 339.1 (100) $[M+1]^+$; $C_{19}H_{18}N_2O_4$ (338.1267): calcd. for C 67.44, H 5.36, N 8.28; found C 67.57, H 5.41, N 8.35.



(*E*)-methyl 1-(3-ethoxy-3-oxoprop-1-en-1-yl)-9-ethyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (11b). Yield: 96% (2.40 g from 2.00 g) as a yellow solid; m.p. 132-133 °C; R_f = 0.60 (hexane/EtOAc, 70:30, v/v); IR (KBr): ν_{max} = 1708 (CO_2CH_3 and $CO_2CH_2CH_3$);

^{1}H NMR (400 MHz, DMSO-d_6) δ = 1.35 (t, J = 7.0 Hz, 3 H), 1.48 (t, J = 7.0 Hz, 3 H), 3.97 (s, 3 H), 4.26 (q, J = 7.0 Hz, 2 H), 4.67 (q, J = 7.0 Hz, 2 H), 7.06 (d, J = 14.8 Hz, 1 H), 7.39 (t, J = 7.4 Hz, 1 H), 7.71 (t, J = 7.8 Hz, 1 H), 7.84 (d, J = 8.4 Hz, 1 H), 8.37 (d, J = 14.9 Hz, 1 H), 8.46 (d, J = 7.8Hz, 1 H), 8.95 (s, 1 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.4, 15.0, 40.7, 52.8, 60.8, 109.9, 118.0, 121.2, 121.4, 121.9, 125.1, 129.5, 131.3, 136.1, 136.2, 137.5, 138.9, 142.0, 166.5, 166.9 ppm; MS (ES): m/z (%) = 353.2 (100) $[M+1]^+$; $C_{20}H_{20}N_2O_4$ (352.1423): calcd. for C 68.17, H 5.72, N 7.95; found C 68.30, H 5.78, N 8.01.

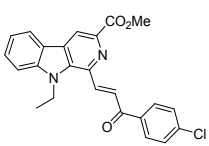
(*E*)-ethyl 1-(3-ethoxy-3-oxoprop-1-en-1-yl)-9-methyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate



(11c). Yield: 97% (1.20 g from 1.00 g) as a yellow solid; m.p. 156-157 ^{o}C; R_f = 0.50 (hexane/EtOAc, 70:30, v/v); IR (KBr): ν_{max} = 1693 ($CO_2CH_2CH_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.37 (t, J = 7.2 Hz, 3 H), 1.50 (t, J = 7.6 Hz, 3 H), 4.19 (s, 3 H), 4.32 (q, J = 7.2 Hz, 2 H), 4.52 (q, J = 7.6 Hz, 2 H), 7.26 (d, J = 15.2 Hz, 1 H), 7.37 (t, J = 7.6 Hz, 1 H), 7.50 (d, J = 8.4 Hz, 1 H), 7.66 (t, J = 8.0 Hz, 1 H), 8.18 (d, J = 7.6 Hz, 1 H), 8.52 (d, J = 14.8 Hz, 1 H), 8.80 (s, 1 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.4, 14.6, 33.4, 60.8, 61.7, 110.0, 117.8, 121.1, 121.2, 121.8, 124.6, 129.4, 131.1, 136.5, 136.9, 137.9, 138.8, 142.8, 165.9, 167.0 ppm; MS (ES): m/z (%) = 353.9 (100) $[M+1]^+$; $C_{20}H_{20}N_2O_4$ (352.1423): calcd. for C 68.17, H 5.72, N 7.95; found C 68.30, H 5.76, N 8.08.

General procedure for the synthesis of (*E*)-methyl 1-(3-(4-chlorophenyl)-3-oxoprop-1-en-1-yl)-9-ethyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate derivatives (16a-16c) as exemplified for compound 16b: To a stirred solution of KOH (0.22 g, 3.90 mmol) in dry MeOH (20 mL), 4-cholro acetopehnone (0.58 mL, 3.72 mmol) was added dropwise at room temperature and stirred the content for 15 minutes. Thereafter **10b** (1.00 g, 3.54 mmol) was added portion-wise and the reaction mixture was allowed to stirred for additional 1 h at room temperature. During this period, yellow solid precipitated out from the reaction mixture and the progress of reaction was monitored by TLC. The precipitate was filtered through sintered funnel, washed twice with MeOH and dried under vacuum to obtain pure yellow solid product, **15b** (2.40 g, 95%, R_f = 0.55 (hexane/EtOAc, 70:30, v/v).

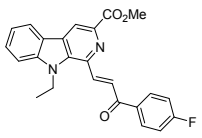
(*E*)-methyl 1-(3-(phenyl)-3-oxoprop-1-en-1-yl)-9-ethyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (16a). The compound **16a** was unstable and immediately used for cycloaddition reaction.



(*E*)-methyl 1-(3-(4-chlorophenyl)-3-oxoprop-1-en-1-yl)-9-ethyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (16b). Yield: 91% (1.35 g from 1.00 g) as a yellow solid;

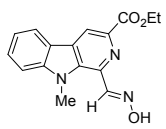
m.p. 141-142 °C; R_f = 0.50 (hexane/EtOAc, 70:30, v/v); IR (KBr): ν_{max} = 1719 (CO_2CH_3); ^{1}H NMR (400 MHz, DMSO-d_6) δ = 1.47 (t, *J* = 7.0 Hz, 3 H), 3.97 (s, 3 H), 4.70 (q, *J* = 7.0 Hz, 2 H), 7.41 (t, *J* = 7.4 Hz, 1 H), 7.70-7.74 (m, 3 H), 7.86 (d, *J* = 8.4 Hz, 1 H), 8.12 (d, *J* = 8.2 Hz, 2 H), 8.18 (d, *J* = 14.6 Hz, 1 H), 8.46 (d, *J* = 14.5 Hz, 1 H), 8.50 (d, *J* = 8.0 Hz, 1 H), 9.02 (s, 1 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 15.0, 40.9, 52.9, 110.0, 118.4, 121.4, 122.0, 126.9, 128.9, 129.1, 129.6, 130.1, 130.3, 131.5, 136.1, 136.4, 136.7, 137.4, 138.9, 139.8, 142.1, 166.4, 188.5 ppm; MS (ES): *m*/*z* (%) = 419.2 (100) $[M+1]^+$; $C_{24}H_{19}ClN_2O_3$ (418.1084): calcd. for C 68.82, H 4.57, N 6.69; found C 68.95, H 4.61, N 6.74.

(*E*)-methyl 9-ethyl-1-(3-(4-fluorophenyl)-3-oxoprop-1-en-1-yl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (16c). Yield: 87% (1.24 g from 1.00 g) as a yellow solid; m.p. 144-145 °C; R_f = 0.50 (hexane/EtOAc, 70:30, v/v); IR (KBr): ν_{max} = 1725 (CO_2CH_3); ^{1}H NMR (400 MHz, DMSO-d_6) δ = 1.47 (t, *J* = 6.8 Hz, 3 H), 3.97 (s, 3 H), 4.69 (q, *J* = 6.8 Hz, 2 H), 7.40 (t, *J* = 7.3 Hz, 1 H), 7.44 (t, *J* = 8.5 Hz, 2 H), 7.72 (t, *J* = 7.8 Hz, 1 H), 7.85 (d, *J* = 8.2 Hz, 1 H), 8.17-8.21 (m, 3 H), 8.44 (d, *J* = 14.6 Hz, 1 H), 8.48 (d, *J* = 7.6 Hz, 1 H), 8.99 (s, 1 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 15.0, 40.9, 52.9, 110.0, 115.8, 116.1, 118.3, 121.3, 121.4, 121.9, 127.1, 129.6, 131.4, 131.6, 134.2, 136.5, 136.6, 137.4, 138.7, 142.1, 164.7, 166.4, 167.2, 188.2 ppm; MS (ES): *m*/*z* (%) = 403.2 (100) $[M+1]^+$; $C_{24}H_{19}FN_2O_3$ (402.1380): calcd. for C 71.63, H 4.76, N 6.96; found C 71.76, H 4.79, N 7.02.



Experimental procedure for the synthesis of (*E*)-ethyl 1-((hydroxyimino)methyl)-9-methyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (19). The stirred solution of **10c** (1.00 g, 3.54 mmol), hydroxylamine hydrochloride (0.31 g, 4.43 mmol) and sodium acetate (0.36 g, 4.43 mmol) in dry MeOH (10 mL) was refluxed for 1 h. On completion of the reaction as monitored by TLC, MeOH was removed under reduced pressure to yield the pale yellow solid product which was suspended in cold water (50 mL), filtered through sintered funnel, washed with anhydrous diethyl ether and dried under high vacuum to obtain pure off white solid product, **19** (98%, 1.03 g, R_f = 0.10 (hexane/EtOAc, 70:30, v/v).

(*E*)-ethyl 1-((hydroxyimino)methyl)-9-methyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (19). Yield: 98% (1.03 g from 1.00 g) as a light brown solid; m.p. 179-180 °C; R_f = 0.10 (hexane/EtOAc, 70:30, v/v); IR (KBr): ν_{max} = 1699 ($CO_2CH_2CH_3$), 3451 (NOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.50 (t, *J* = 7.1 Hz, 3 H), 4.07 (s, 3 H), 4.25 (s, 1 H), 4.53 (q, *J* = 7.1 Hz, 2 H), 7.37 (t, *J* = 7.5 Hz, 1 H), 7.53 (d, *J* = 8.3 Hz, 1 H), 7.67 (t, *J* = 7.7 Hz, 1 H), 8.18

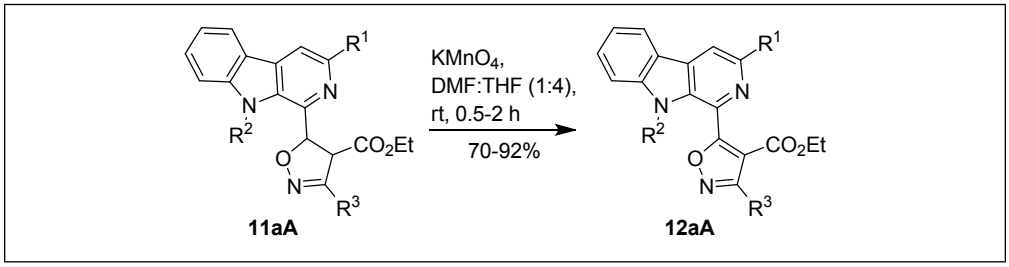


(d, *J* = 7.8 Hz, 1 H), 8.84 (s, 1 H), 8.85 (s, 1 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.5, 33.7, 62.1, 110.3, 118.6, 121.2, 121.9, 122.0, 130.2, 132.0, 133.8, 134.9, 137.6, 143.1, 148.6, 164.4 ppm; MS (ES): *m/z* (%) = 298.3 (100) $[M+1]^+$; $C_{16}H_{15}N_3O_3$ (297.1113): calcd. for C 64.64, H 5.09, N 14.13; found C 64.70, H 5.11, N 14.17.

Experimental procedure for the synthesis of (*Z*)-ethyl 1-(chloro(hydroxyimino)methyl)-9-methyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (20). The stirred solution of **19** (1.00 g, 3.37 mmol) in dry DMF (4 mL), *N*-chlorosuccinimide (0.67 g, 5.05 mmol) was added in small portions (As the reaction was exothermic) and stirred the content at room temperature for 1 h. On completion of the reaction as monitored by TLC, the content was poured into ice cold water and extracted with diethyl ether (3 x 25 mL). The organic layer was further washed with brine (20 mL) and concentrated in vacuuo at low temperature to obtain **20** (84%, 0.93 g, R_f = 0.11 (hexane/EtOAc, 70:30, v/v) as the yellow solid which was significantly pure and utilized for next without further purification.

General procedure for the synthesis of β-carboline-(C-4)isoxazoles based molecular hybrids (12 and 18) as exemplified for compound 12aA: To a stirred solution of **11aA** (0.20 g, 0.44 mmol) in anhydrous THF: DMF (4:1, v/v) (10 mL), $KMnO_4$ (0.60 g) was added portion-wise at room temperature and stirred the reaction mixture for additional 30 min at room temperature. On completion of the reaction as monitored by TLC, content was filtered through celite bed under vacuum and washed the bed three times with chloroform. The collected organic layer were combined and concentrated under vacuum to yield the dull white solid product which was washed twice with anhydrous diethyl ether and air dried under high vacuum to obtain the analytically pure white solid product, **12aA** (0.15 g, 75%, R_f = 0.30 (hexane/EtOAc, 80:20, v/v).

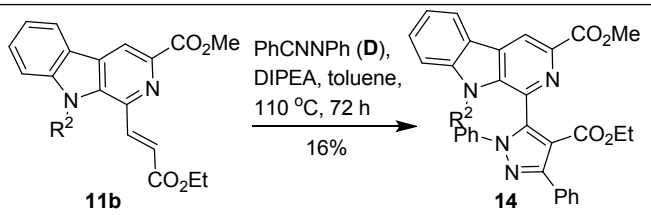
Table 1- **Standardization of oxidation process for the synthesis of β-carboline-isoxazole based molecular hybrids** (**12**)



Sr. No.	Oxidant	Solvent	Temp (°C)	Time	Yield (12aA)
1.	$KMnO_4$	Dry THF	80	6 h	80%
2.	$KMnO_4$	Dry DMF	70	25 min	84%
3.	$KMnO_4$	THF: DMF (4:1, v/v)	80	40 min	90%

Experimental procedure for the synthesis of β-carboline-pyrazole based molecular hybrid (14). The stirred solution of **11b** (0.20 g, 0.57 mmol), hydrazonyl chlorides,[22b] **D** (0.65 g, 2.84 mmol) and DIPEA (0.29 mL, 1.70 mmol) in dry toluene (10 mL) was heated at 110 °C for 72 h. After that the toluene was evaporated under vacuum and crude mass was extracted with ethyl acetate (3 x 10 mL). The organic layer was further washed with $NaHCO_3$ solution (10 mL) and brine (10 mL). Thereafter the crude product was purified through column chromatography silica gel (230-400 mesh) using ethylacetate and hexane as a eluent to yield the white solid product, **14** (0.05 g, 16%, R_f = 0.40 (hexane/EtOAc, 70:30, v/v). We wish to mention that even after 3 days the reaction was not complete and 5-6 products were visible in crude mixture on TLC analysis. We purified the major product from the reaction mixture which was analyzed as **14** (*in situ* oxidized product). The hydrazonyl chloride (**D**) was synthesized from corresponding phenyl hydrazone by using 1.05 equiv. of NCS in dry DMF.

Table 2- Standardization of reaction conditions for the synthesis of β-carboline-pyrazole based molecular hybrid (14)



Sr. No.	Base	Solvent	Temp (°C)	Time	Yield (14)
1.	Et_3N	Dry THF	80	72 h	Traces
2.	Et_3N	Dry DCM	70	72 h	No reaction
3.	DIPEA	Dry THF	80	72 h	7% + **11b**
4.	DIPEA	Dry Toluene	110	72 h	16% + **11b**

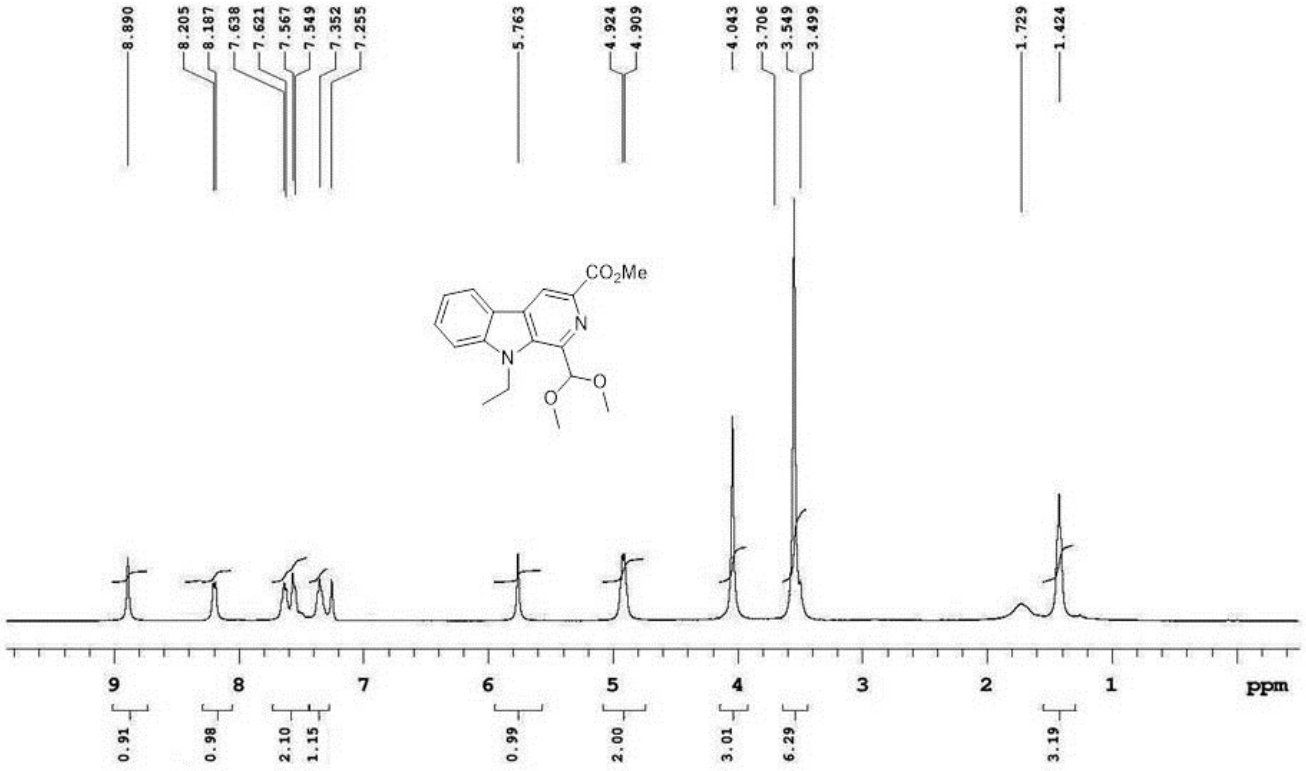


Figure S-1:- ^{1}H-NMR spectrum of methyl 1-(dimethoxymethyl)-9-ethyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(9b).**

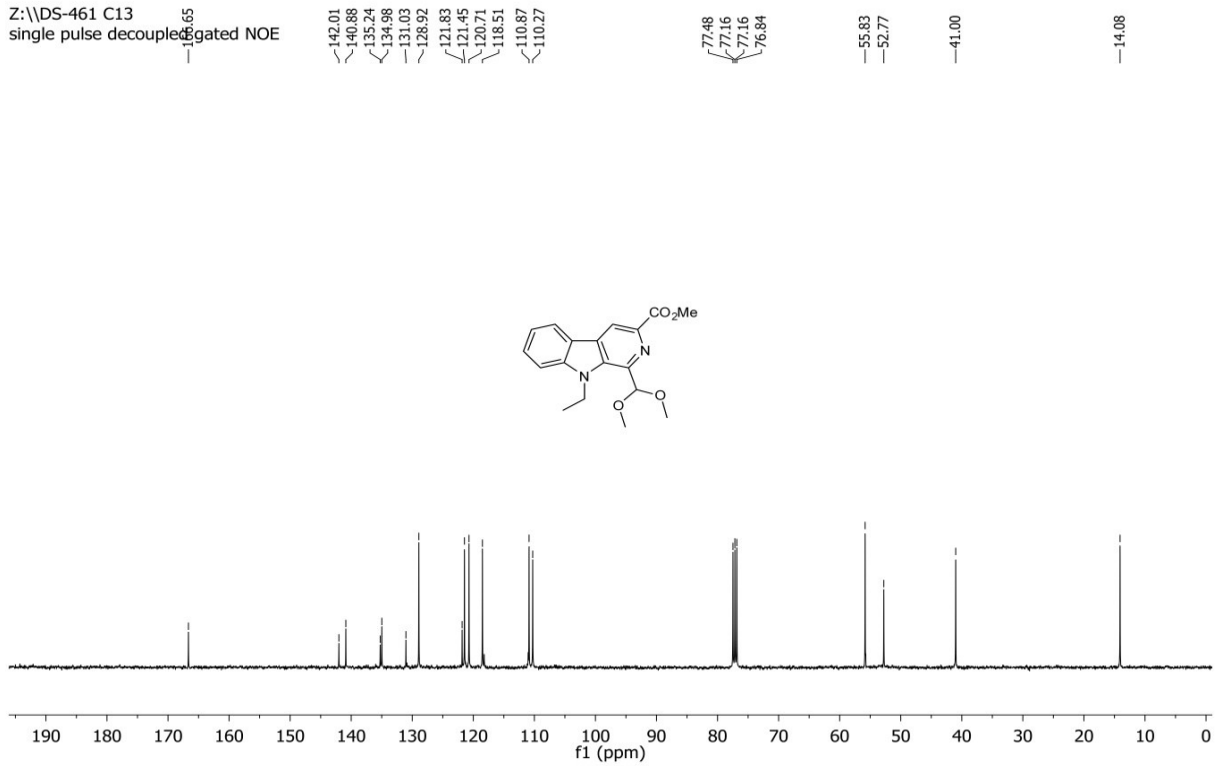


Figure S-2:- ^{13}C-NMR spectrum of methyl 1-(dimethoxymethyl)-9-ethyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(9b).**

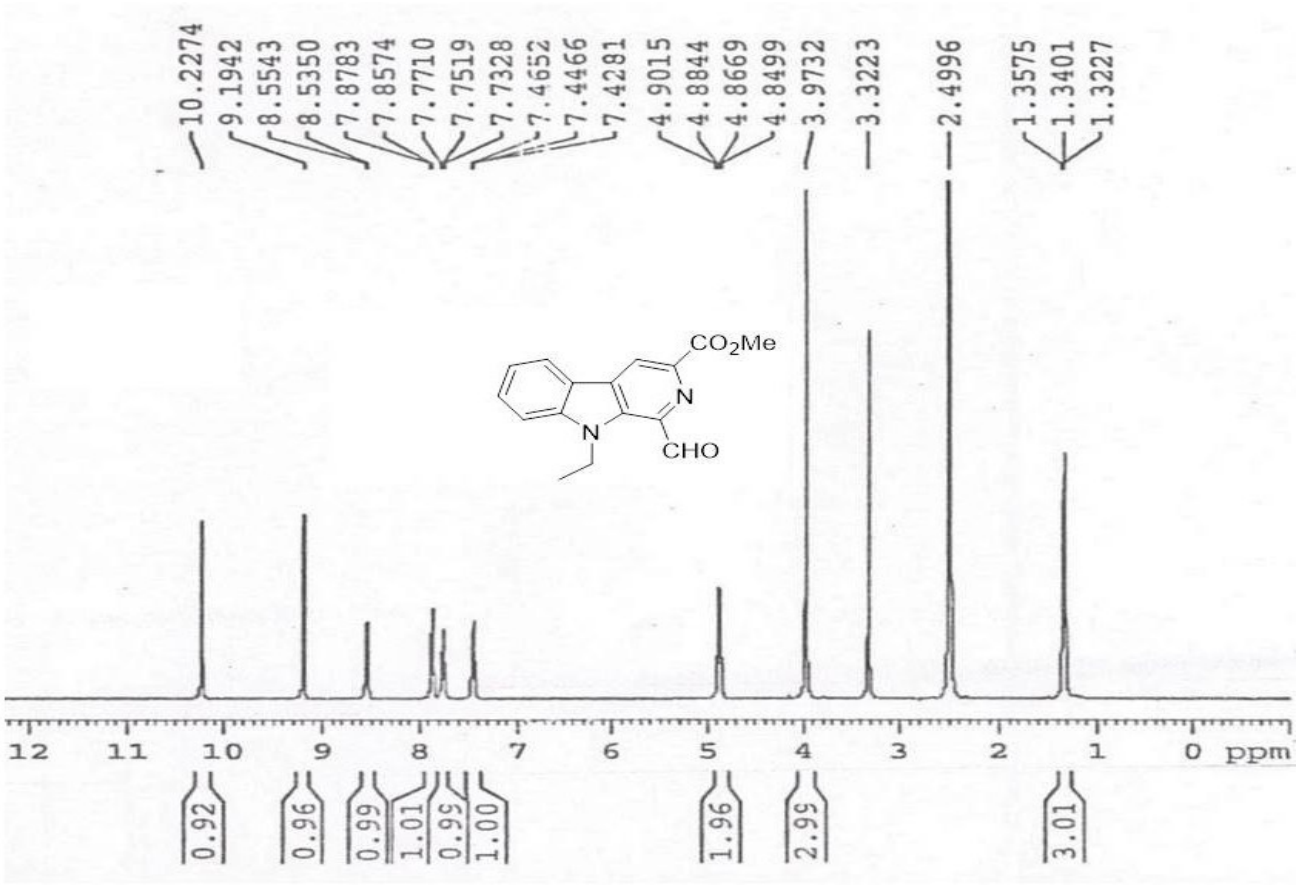


Figure S-3:- ^{1}H-NMR spectrum of methyl 9-ethyl-1-formyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(10b).**

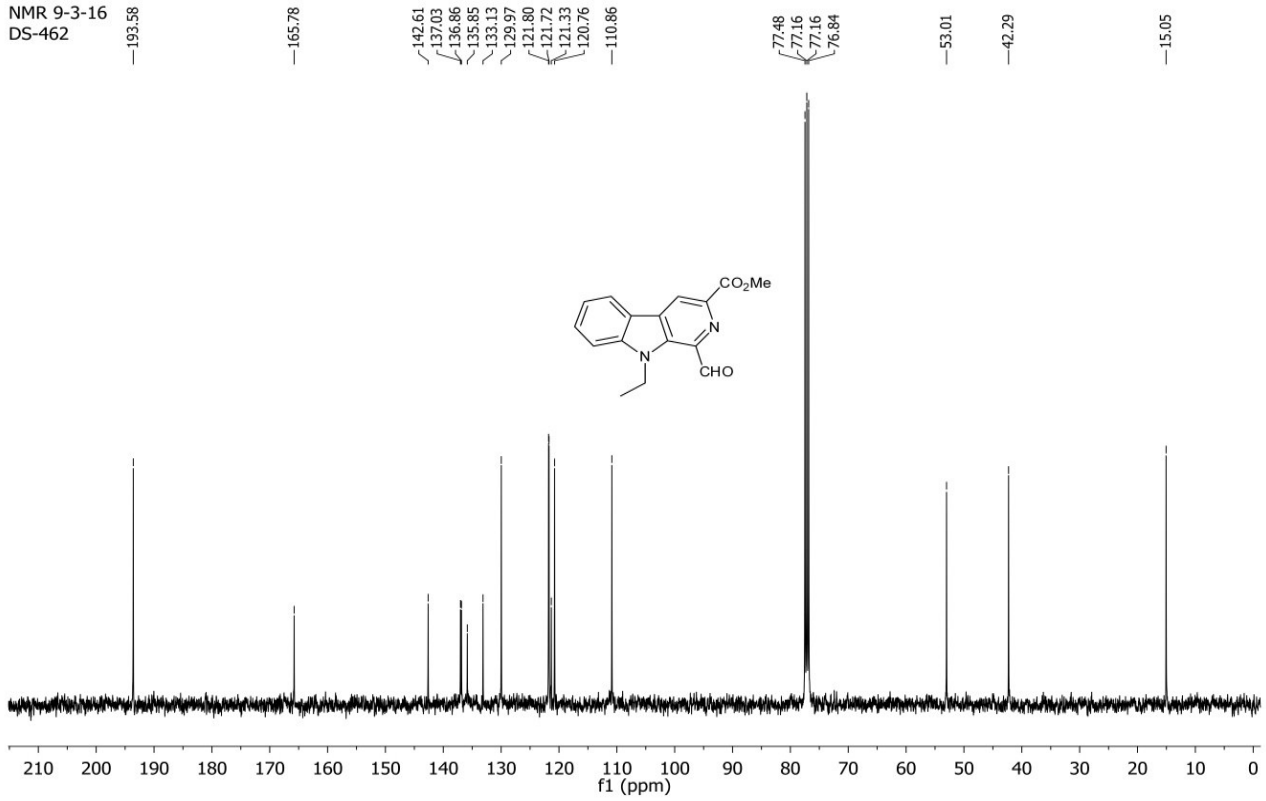


Figure S-4:- ^{13}C-NMR spectrum of methyl 9-ethyl-1-formyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(10b).**

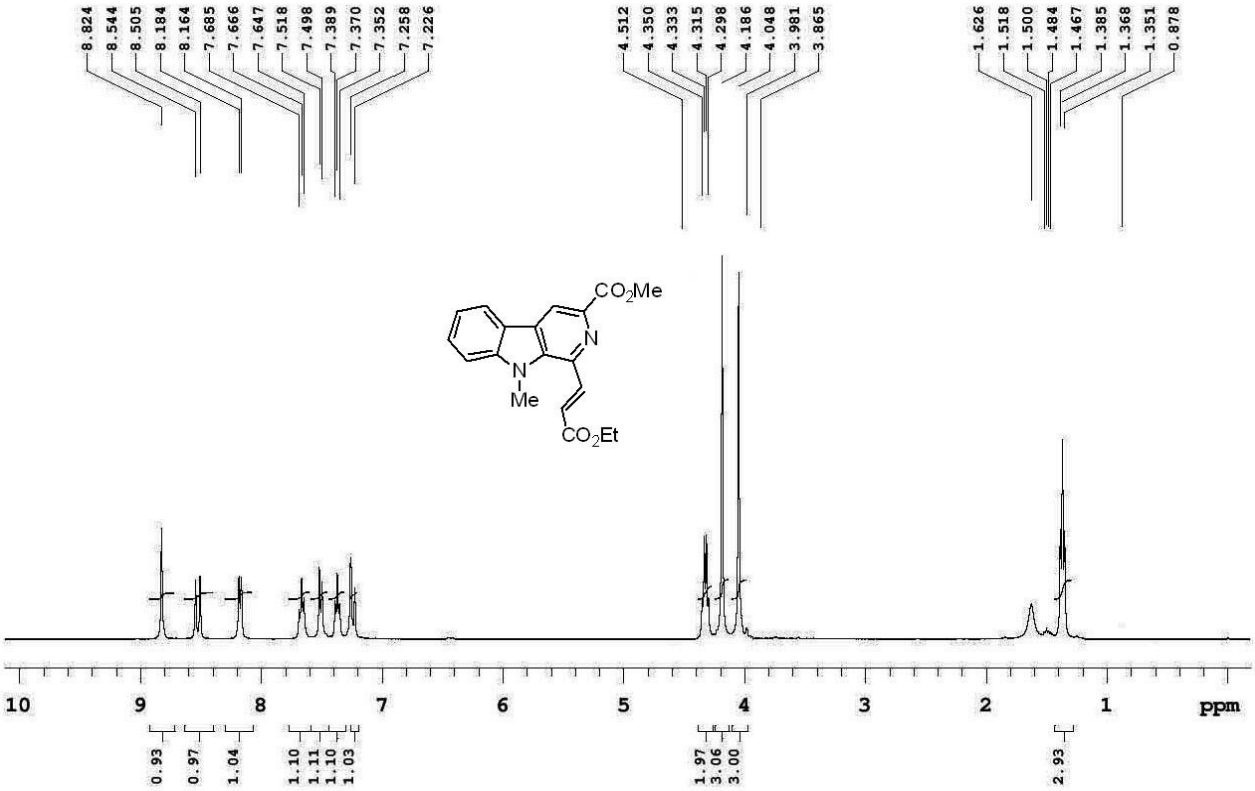


Figure S-5:- ^{1}H-NMR spectrum of (*E*)-methyl 1-(3-ethoxy-3-oxoprop-1-en-1-yl)-9-methyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(11a).**

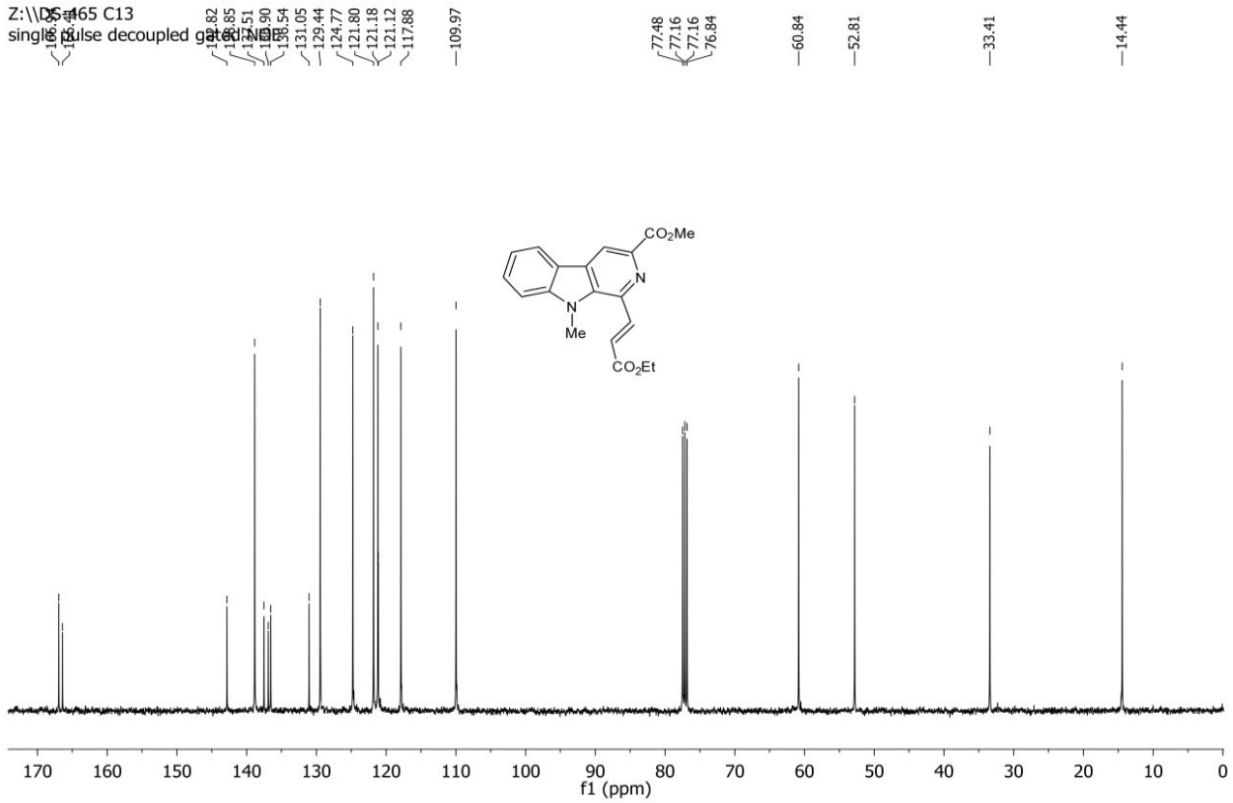


Figure S-6:- ^{13}C-NMR spectrum of (*E*)-methyl 1-(3-ethoxy-3-oxoprop-1-en-1-yl)-9-methyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(11a).**

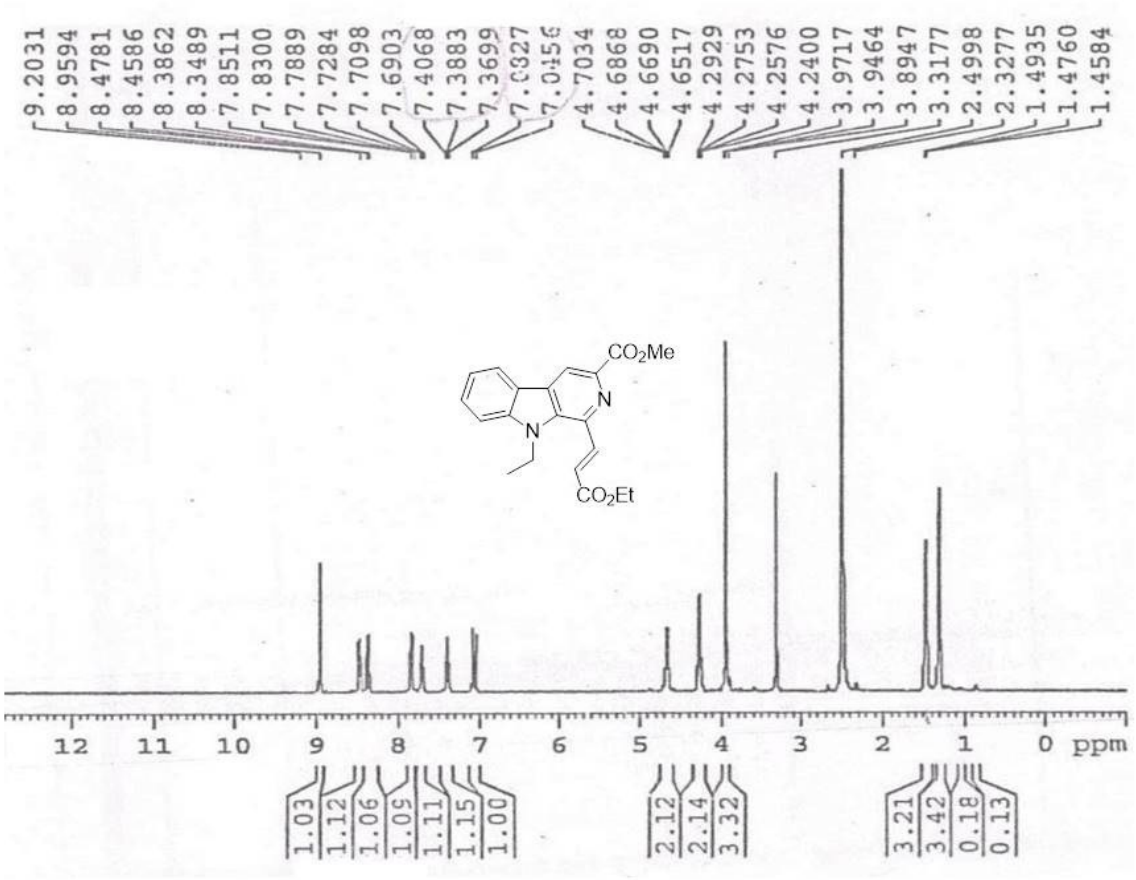


Figure S-7:- ^{1}H-NMR spectrum of (*E*)-methyl 1-(3-ethoxy-3-oxoprop-1-en-1-yl)-9-ethyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(11b).**

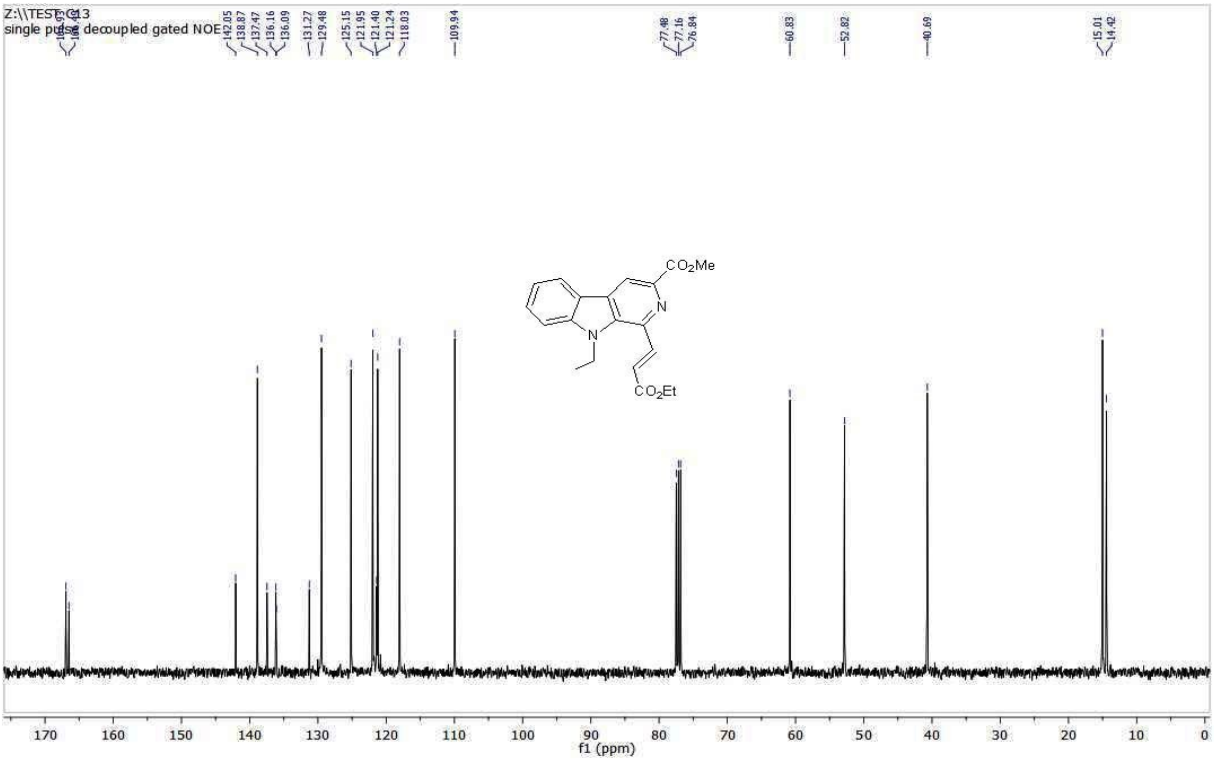


Figure S-8:- ^{13}C-NMR spectrum of (*E*)-methyl 1-(3-ethoxy-3-oxoprop-1-en-1-yl)-9-ethyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(11b).**

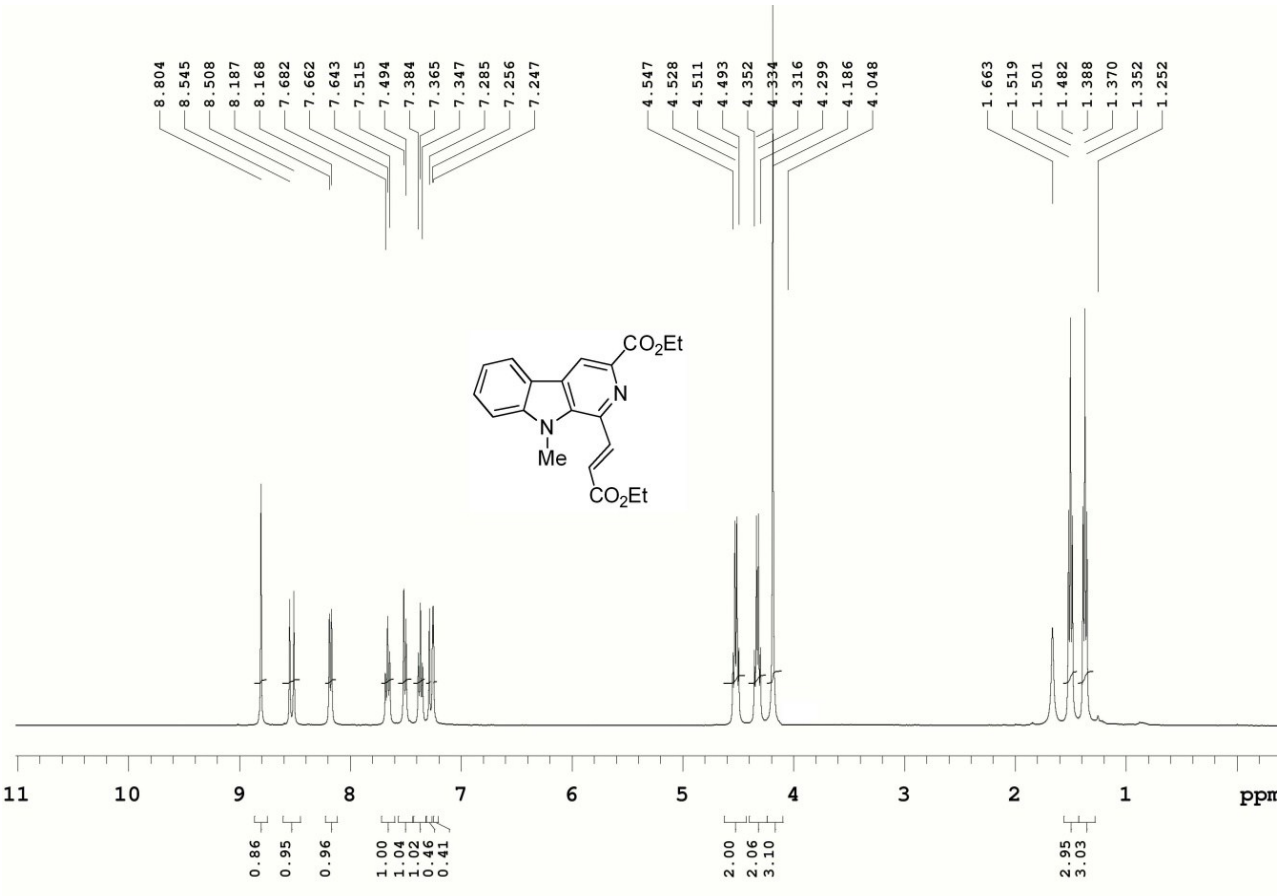


Figure S-9:- ^{1}H-NMR spectrum of (*E*)-ethyl 1-(3-ethoxy-3-oxoprop-1-en-1-yl)-9-methyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(11c).**

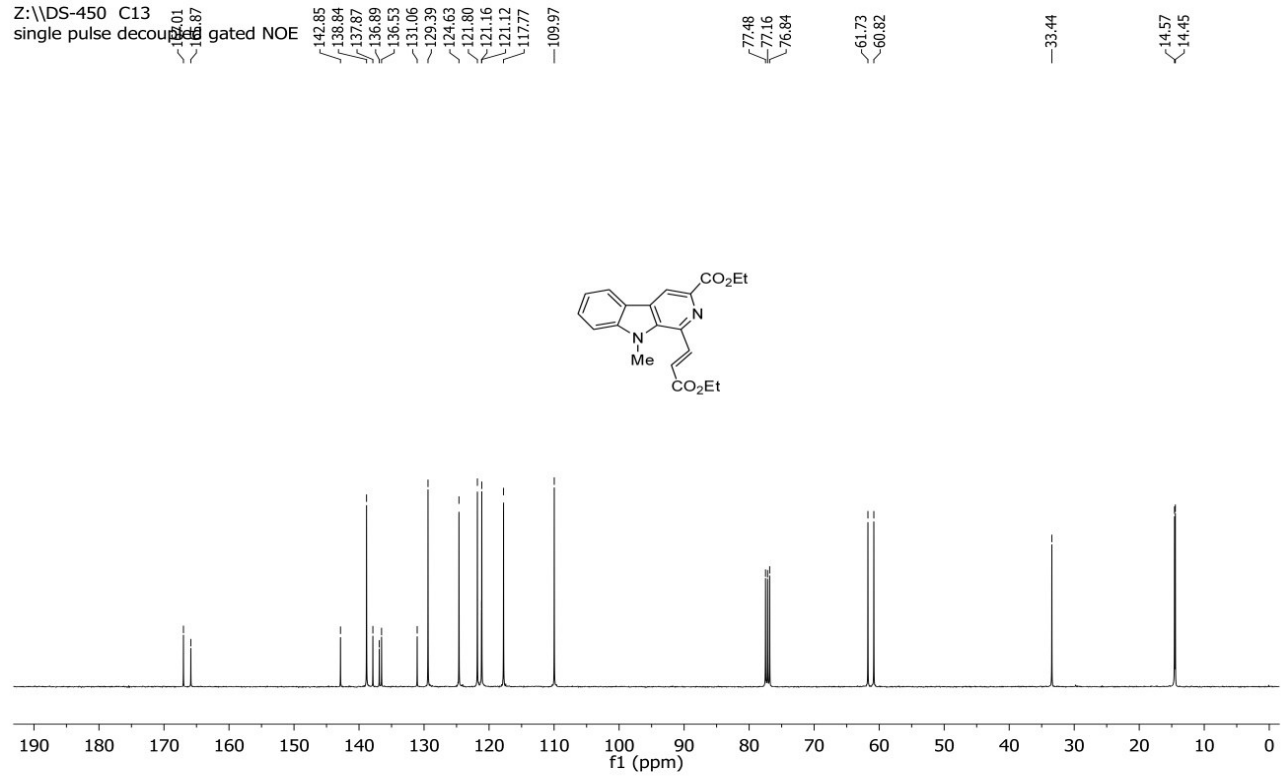


Figure S-10:- ^{13}C-NMR spectrum of (*E*)-ethyl 1-(3-ethoxy-3-oxoprop-1-en-1-yl)-9-methyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(11c).**

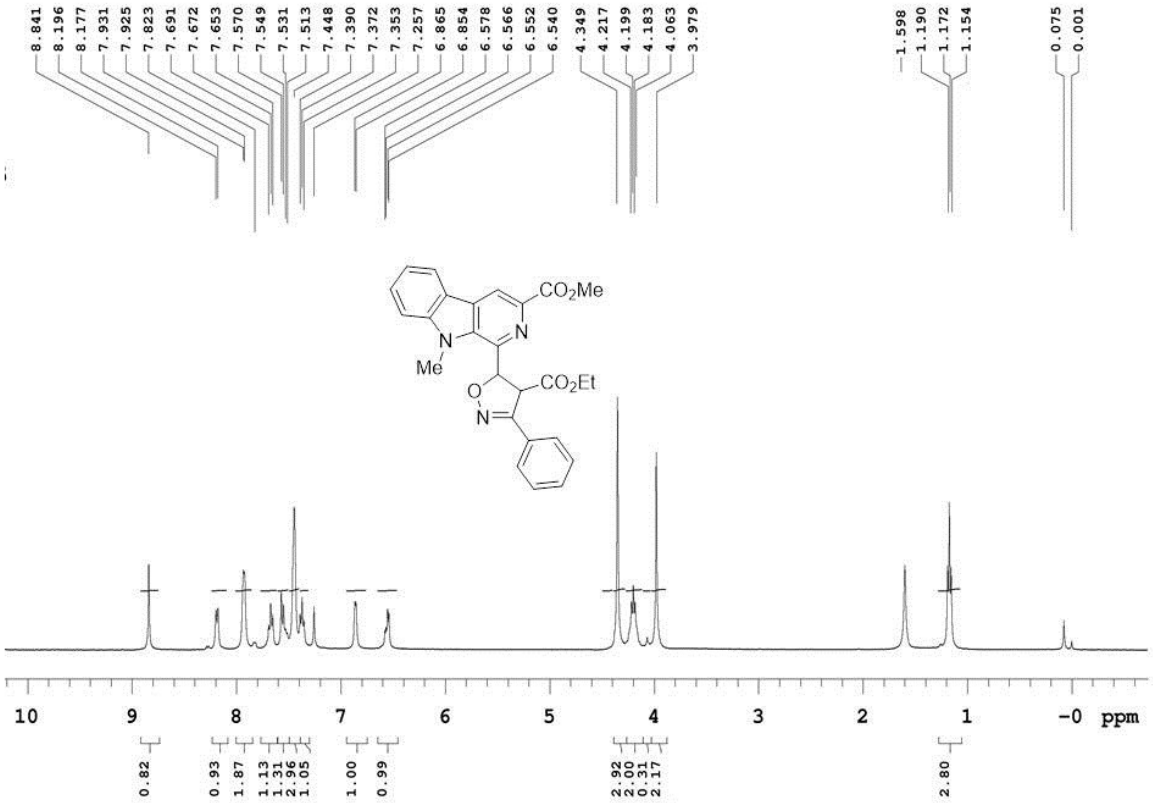


Figure S-11:- ^{1}H-NMR spectrum of ethyl 4-(3-(methoxycarbonyl)-9-methyl-9*H*-pyrido[3,4-*b*]indol-1-yl)-3-phenyl-4,5-dihydroisoxazole-5-carboxylate **(11aA)**.

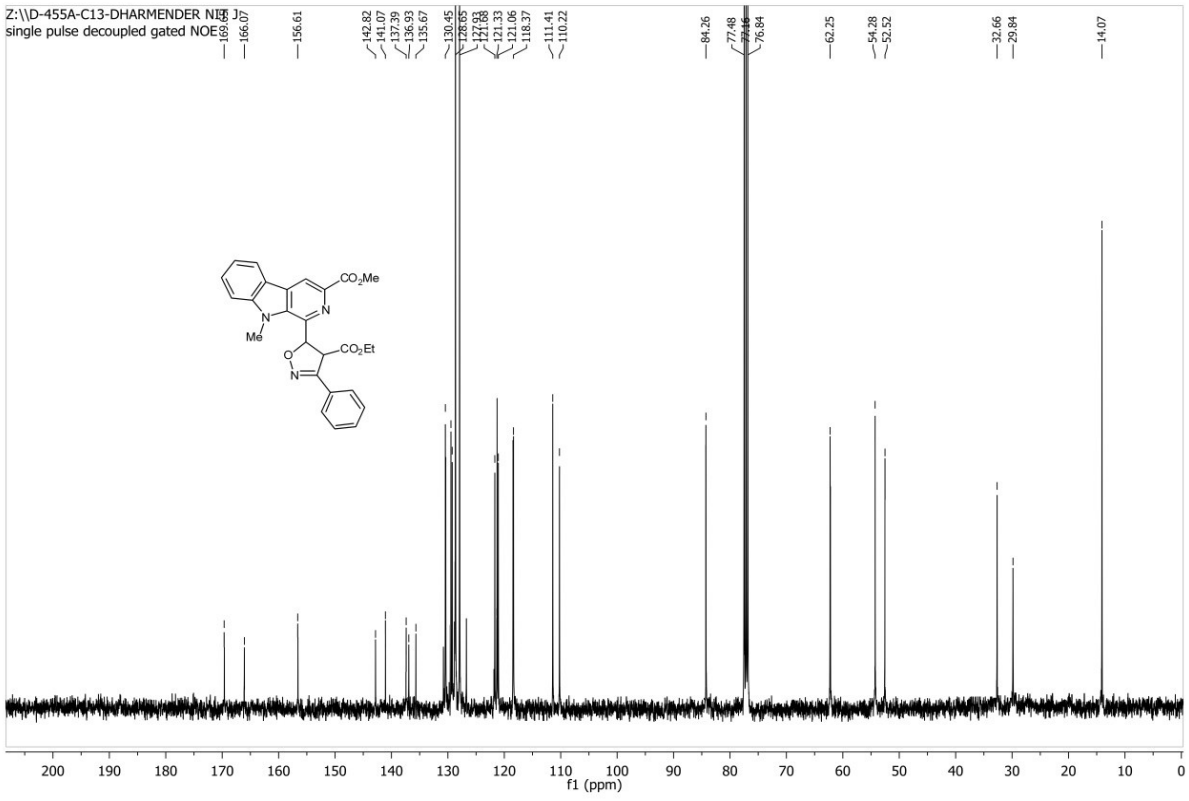


Figure S-12:- ^{13}C-NMR spectrum of ethyl 4-(3-(methoxycarbonyl)-9-methyl-9*H*-pyrido[3,4-*b*]indol-1-yl)-3-

phenyl-4,5-dihydroisoxazole-5-carboxylate **(11aA)**.

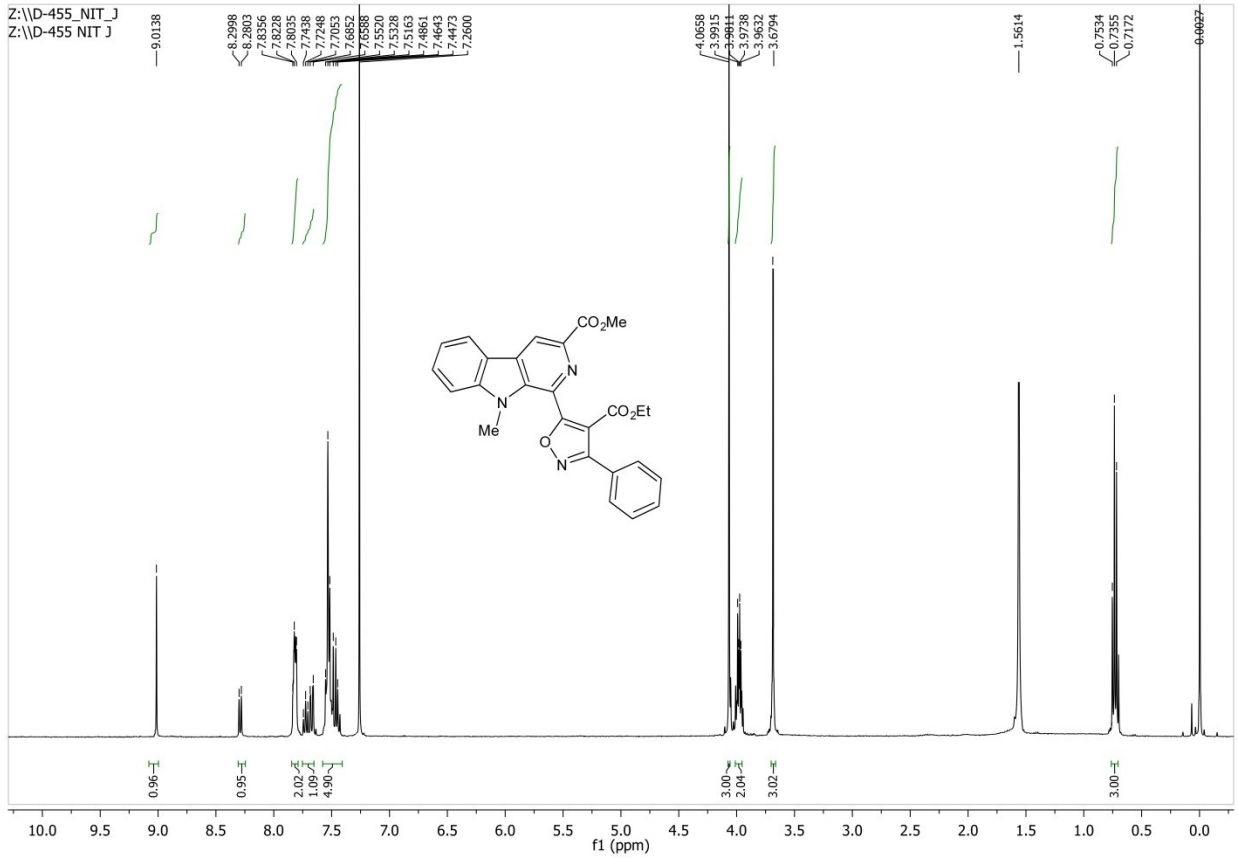


Figure S-13:- ^{1}H-NMR spectrum of ethyl 5-(3-(methoxycarbonyl)-9-methyl-9H-pyrido[3,4-b]indol-1-yl)-3-phenylisoxazole-4-carboxylate **(12aA).**

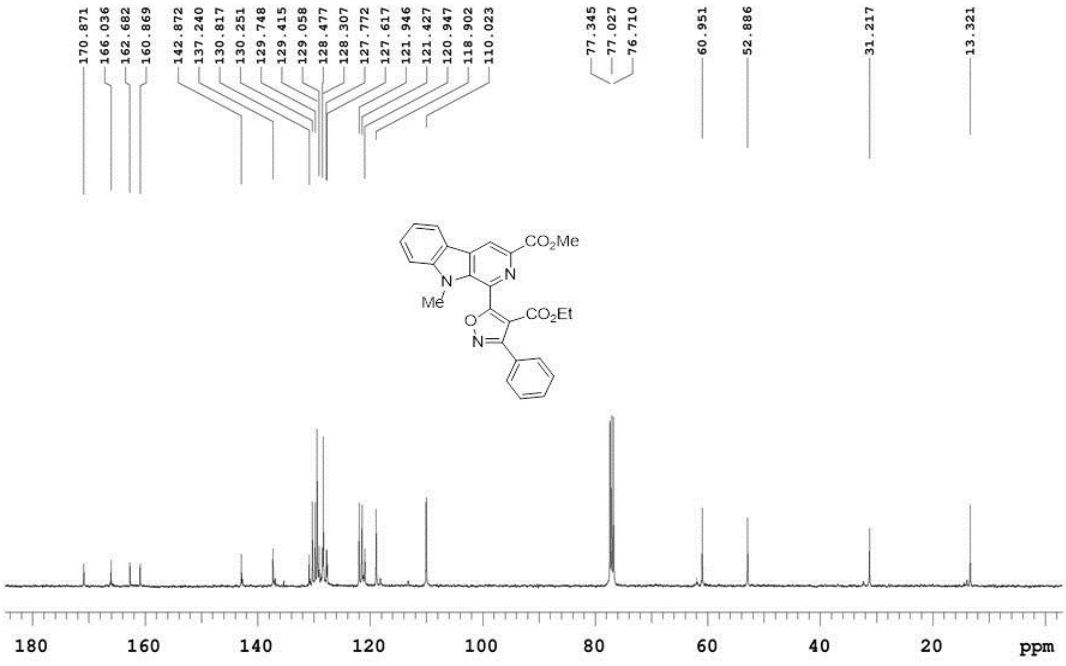


Figure S-14:- ^{13}C-NMR spectrum of ethyl 5-(3-(methoxycarbonyl)-9-methyl-9*H*-pyrido[3,4-*b*]indol-1-yl)-3-phenylisoxazole-4-carboxylate **(12aA).**

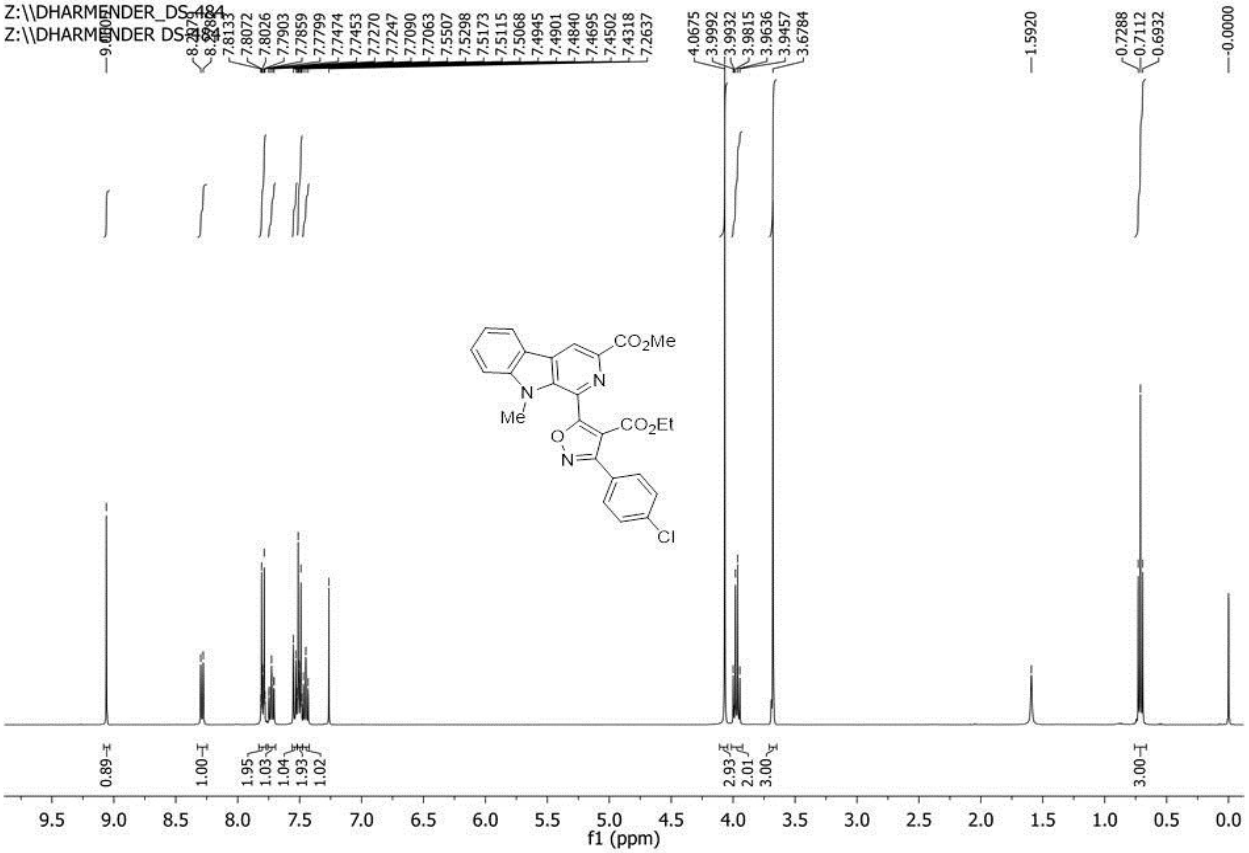


Figure S-15:- ^{1}H-NMR spectrum of ethyl 3-(4-chlorophenyl)-5-(3-(methoxycarbonyl)-9-methyl-9*H*-pyrido [3,4-*b*]indol-1-yl)isoxazole-4-carboxylate **(12aB).**

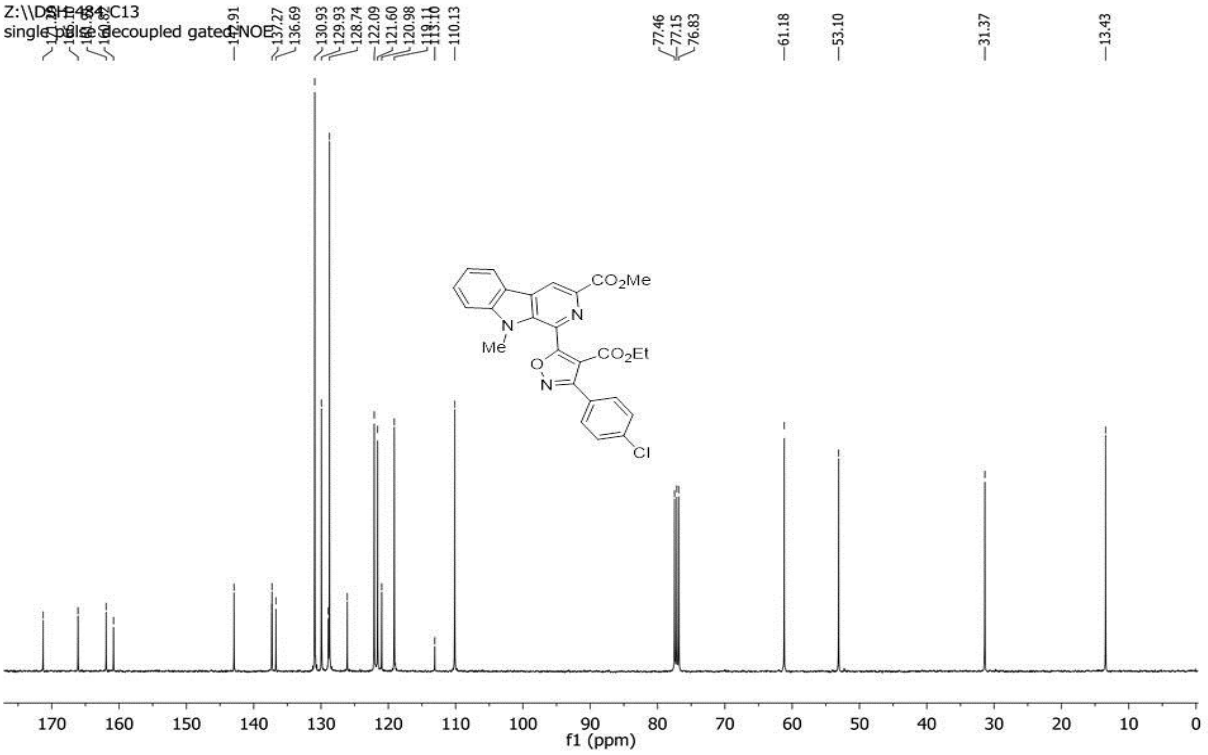


Figure S-16:- ^{13}C-NMR spectrum of ethyl 3-(4-chlorophenyl)-5-(3-(methoxycarbonyl)-9-methyl-9*H*-pyrido[3,4-*b*]indol-1-yl)isoxazole-4-carboxylate **(12aB).**

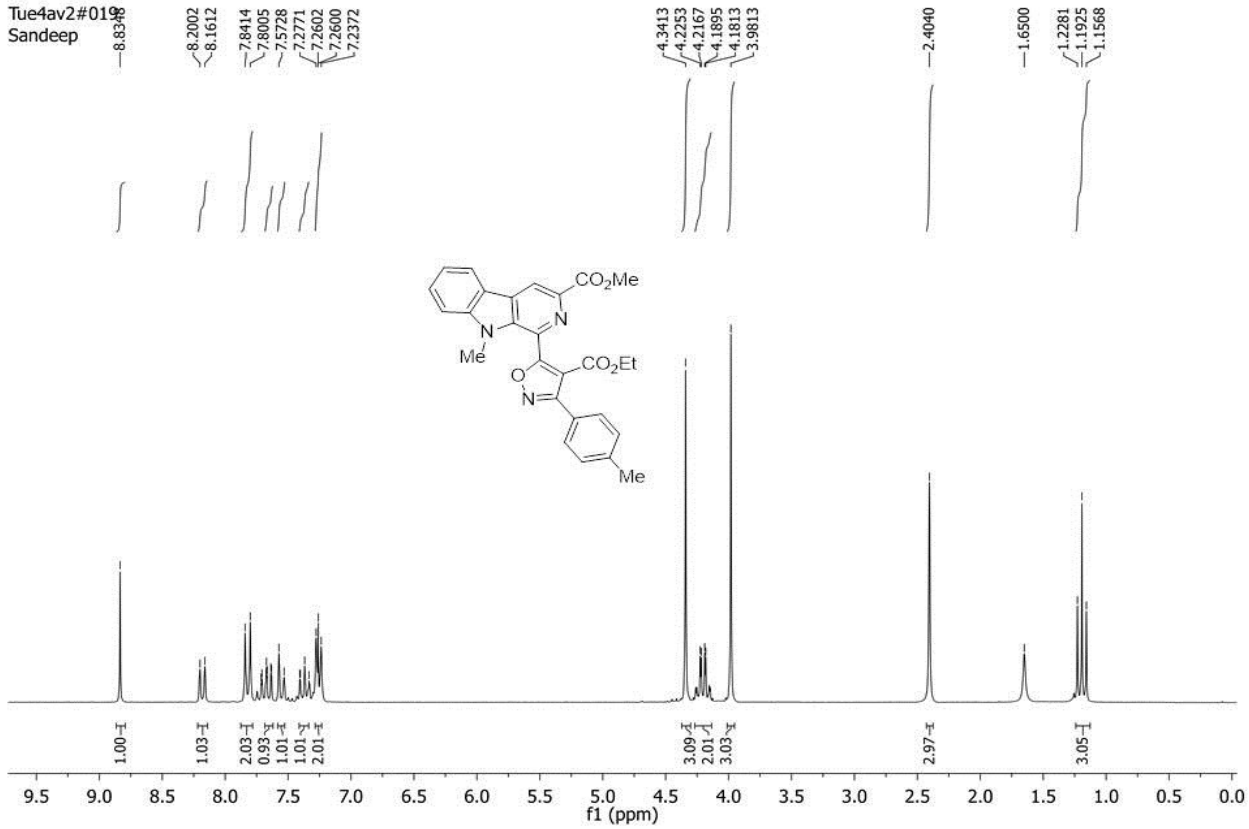


Figure S-17:- ^{1}H-NMR spectrum of ethyl 5-(3-(methoxycarbonyl)-9-methyl-9*H*-pyrido[3,4-*b*]indol-1-yl)-3-(*p*-tolyl)isoxazole-4-carboxylate **(12aC).**

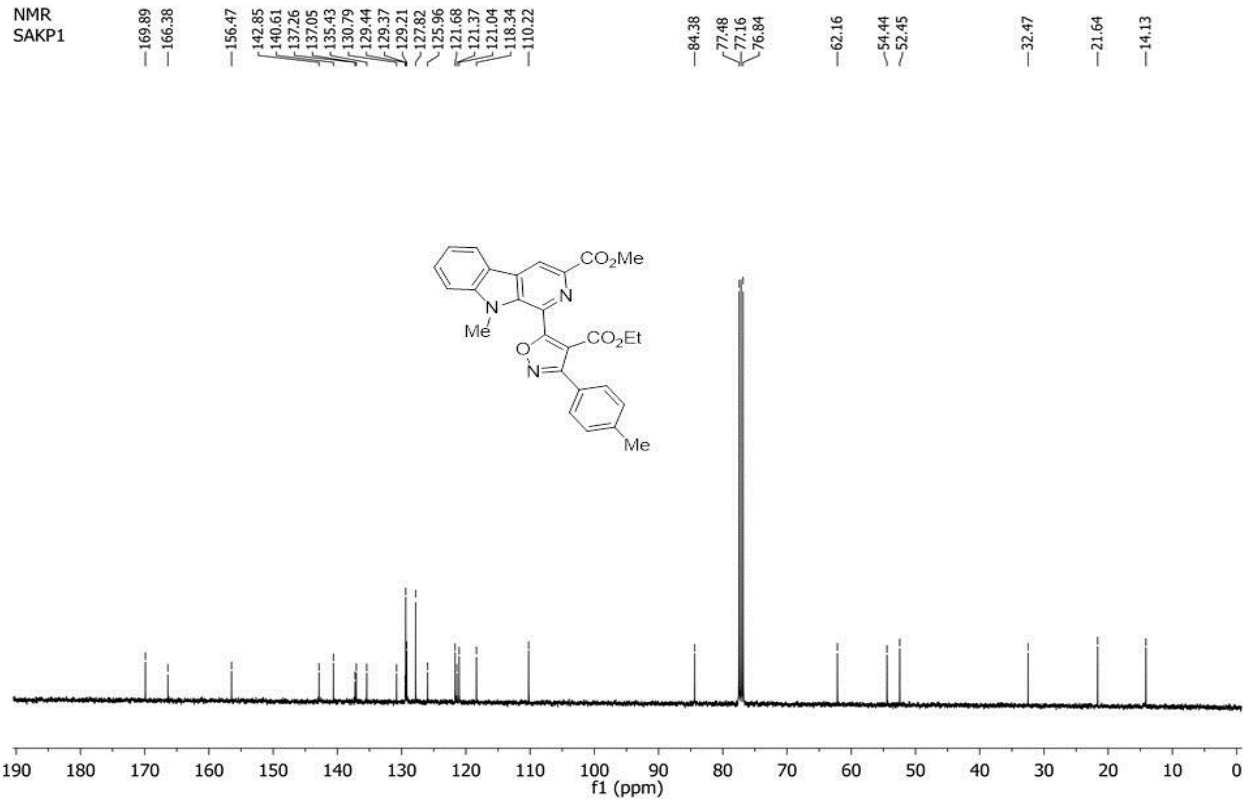


Figure S-18:- ^{13}C-NMR spectrum of ethyl 5-(3-(methoxycarbonyl)-9-methyl-9*H*-pyrido[3,4-*b*]indol-1-yl)-3-(*p*-tolyl)isoxazole-4-carboxylate **(12aC).**

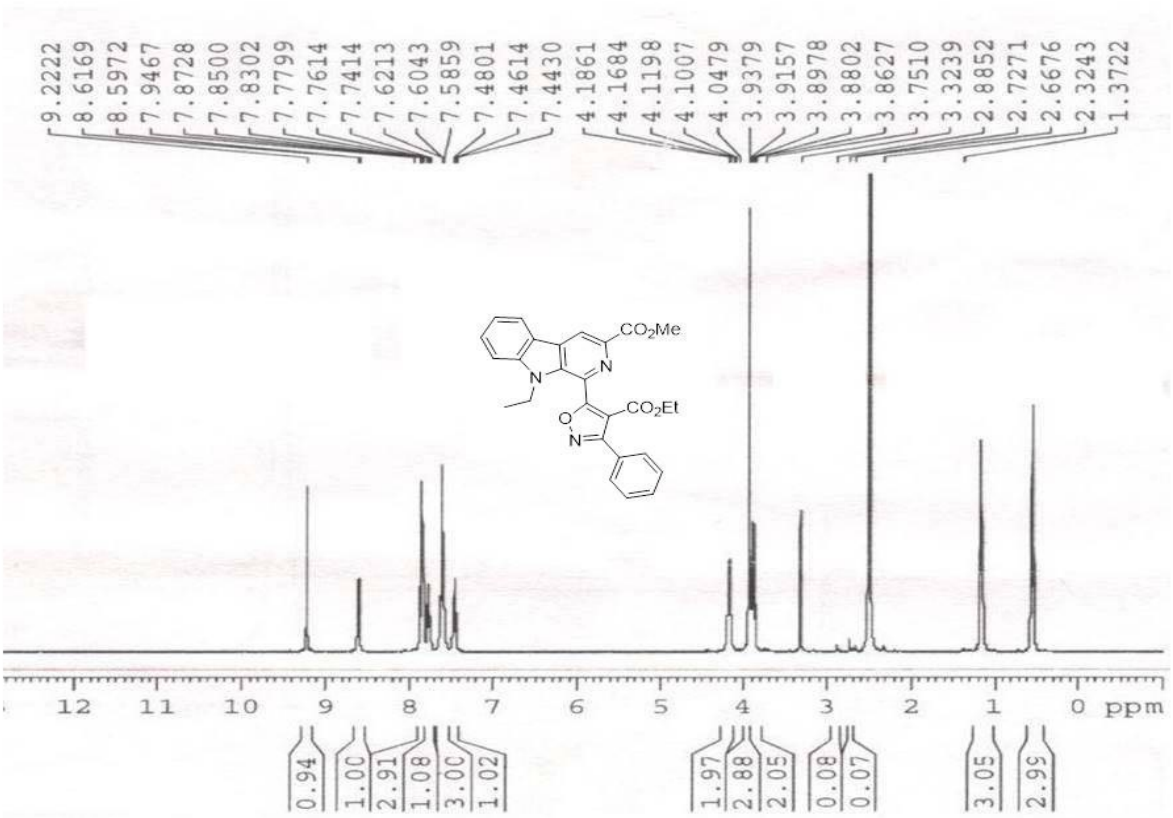


Figure S-19:- ^{1}H-NMR spectrum of ethyl 5-(9-ethyl-3-(methoxycarbonyl)-9*H*-pyrido[3,4-*b*]indol-1-yl)-3-phenylisoxazole-4-carboxylate **(12bA).**

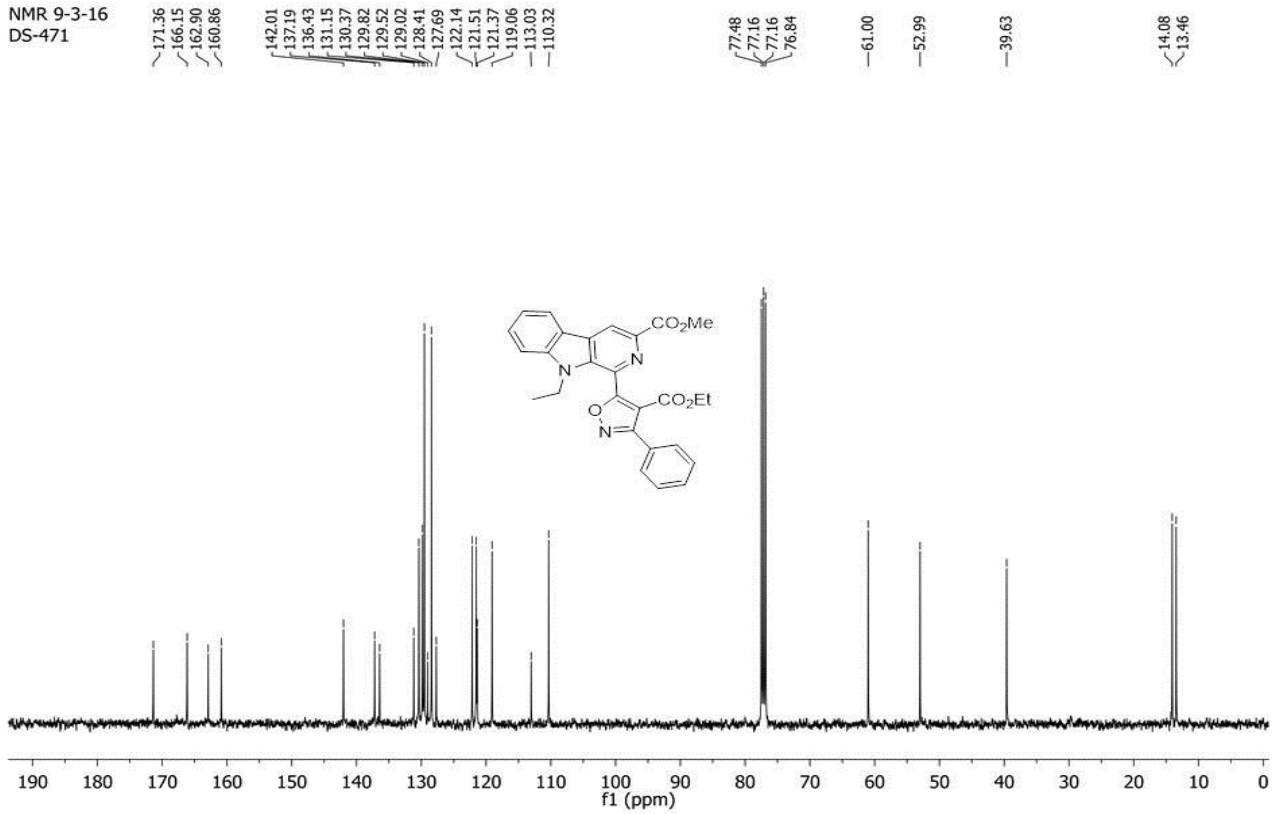


Figure S-20:- ^{13}C-NMR spectrum of ethyl 5-(9-ethyl-3-(methoxycarbonyl)-9*H*-pyrido[3,4-*b*]indol-1-yl)-3-phenylisoxazole-4-carboxylate **(12bA).**

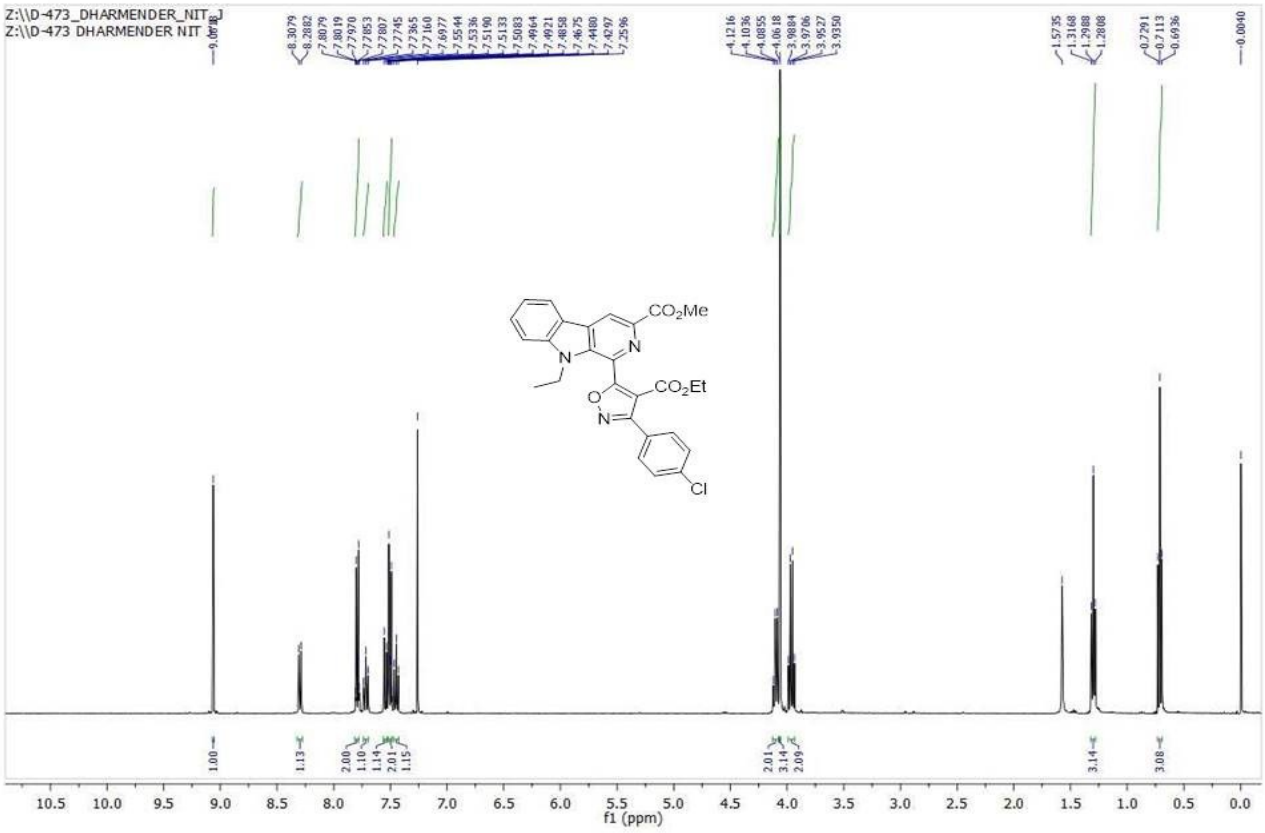


Figure S-21:- ^{1}H-NMR spectrum of ethyl 3-(4-chlorophenyl)-5-(9-ethyl-3-(methoxycarbonyl)-9*H*-pyrido[3,4-*b*]indol-1-yl)isoxazole-4-carboxylate **(12bB).**

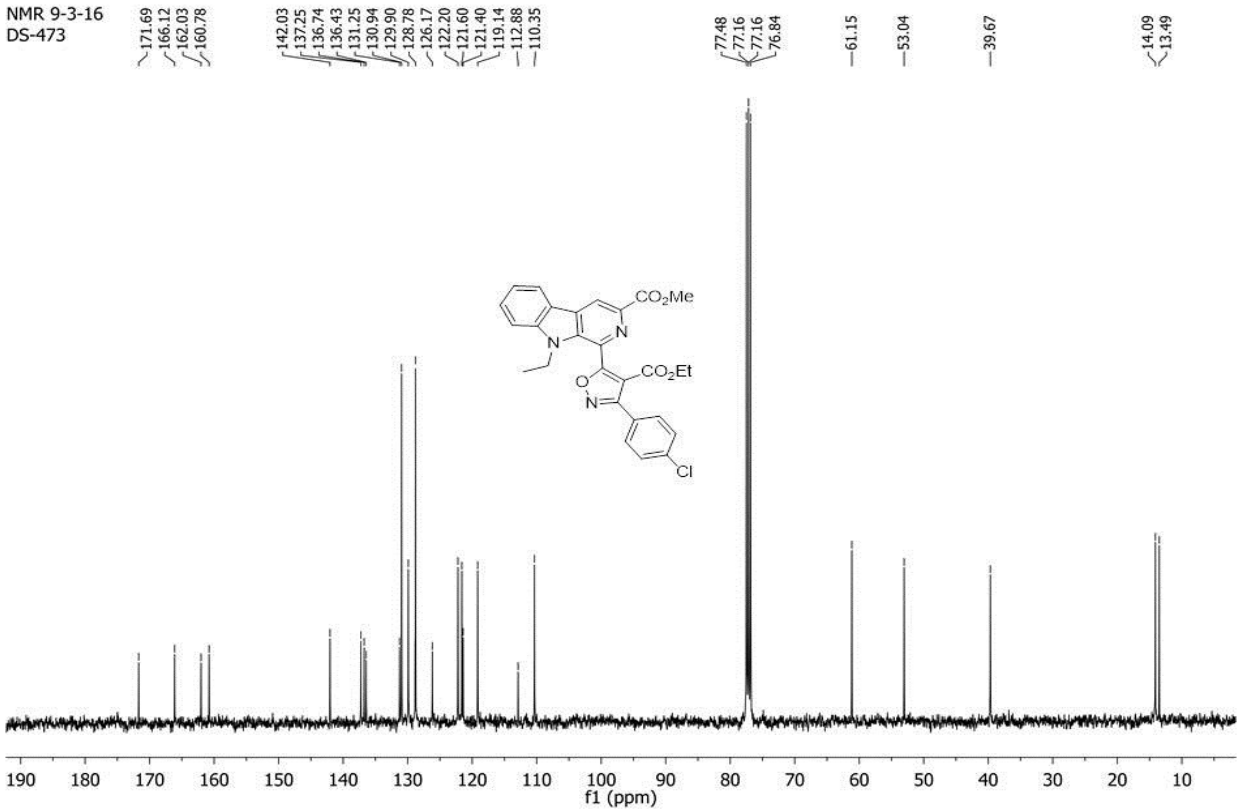


Figure S-22:- ^{13}C-NMR spectrum of ethyl 3-(4-chlorophenyl)-5-(9-ethyl-3-(methoxycarbonyl)-9*H*-pyrido[3,4-*b*]indol-1-yl)isoxazole-4-carboxylate **(12bB).**

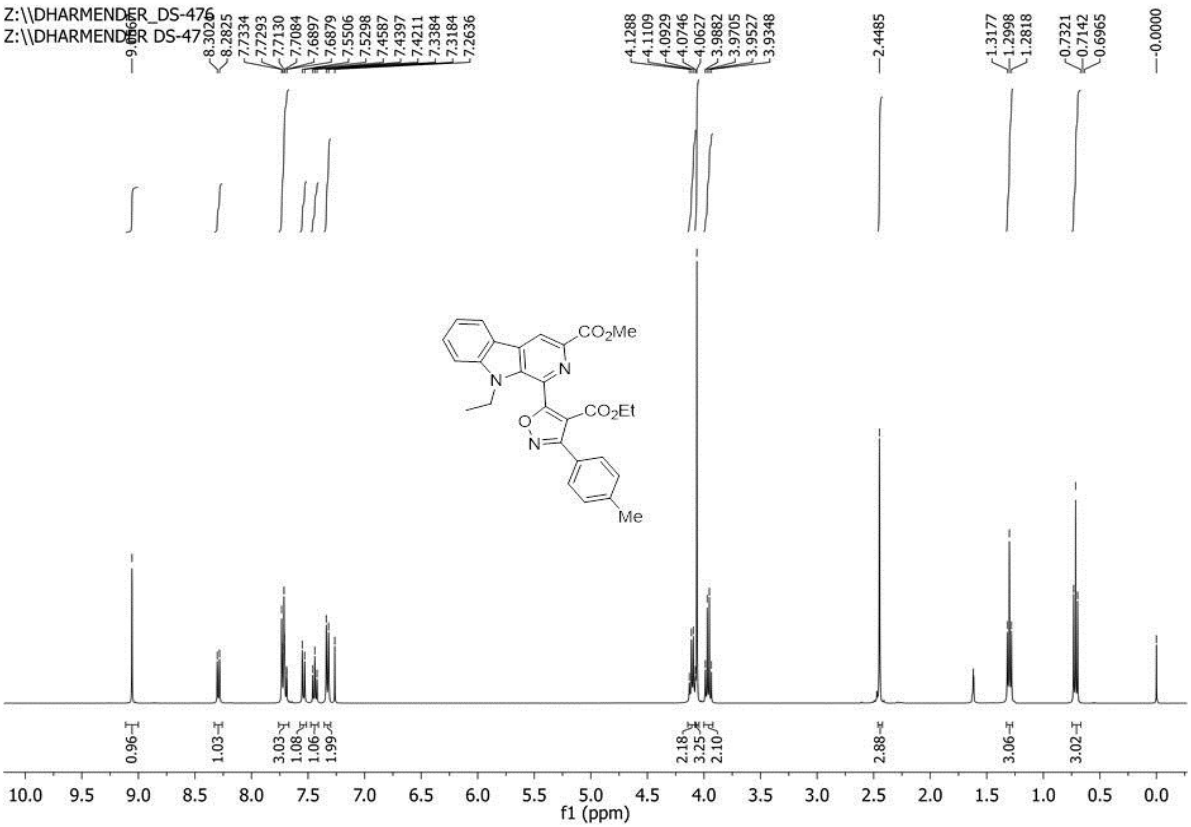


Figure S-23:- ^{1}H-NMR spectrum of ethyl 5-(9-ethyl-3-(methoxycarbonyl)-9*H*-pyrido[3,4-*b*]indol-1-yl)-3-(*p*-tolyl)isoxazole-4-carboxylate **(12bC).**

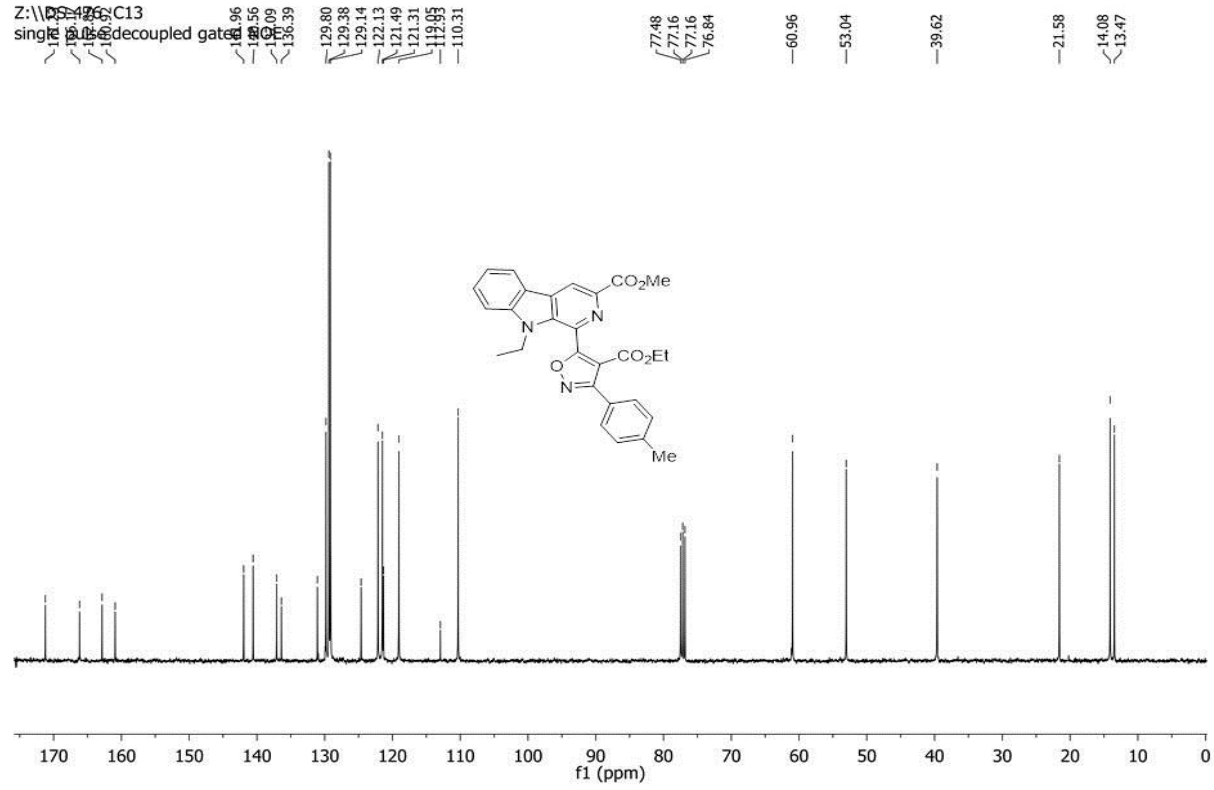


Figure S-24:- ^{13}C-NMR spectrum of ethyl 5-(9-ethyl-3-(methoxycarbonyl)-9*H*-pyrido[3,4-*b*]indol-1-yl)-3-(*p*-tolyl)isoxazole-4-carboxylate **(12bC).**

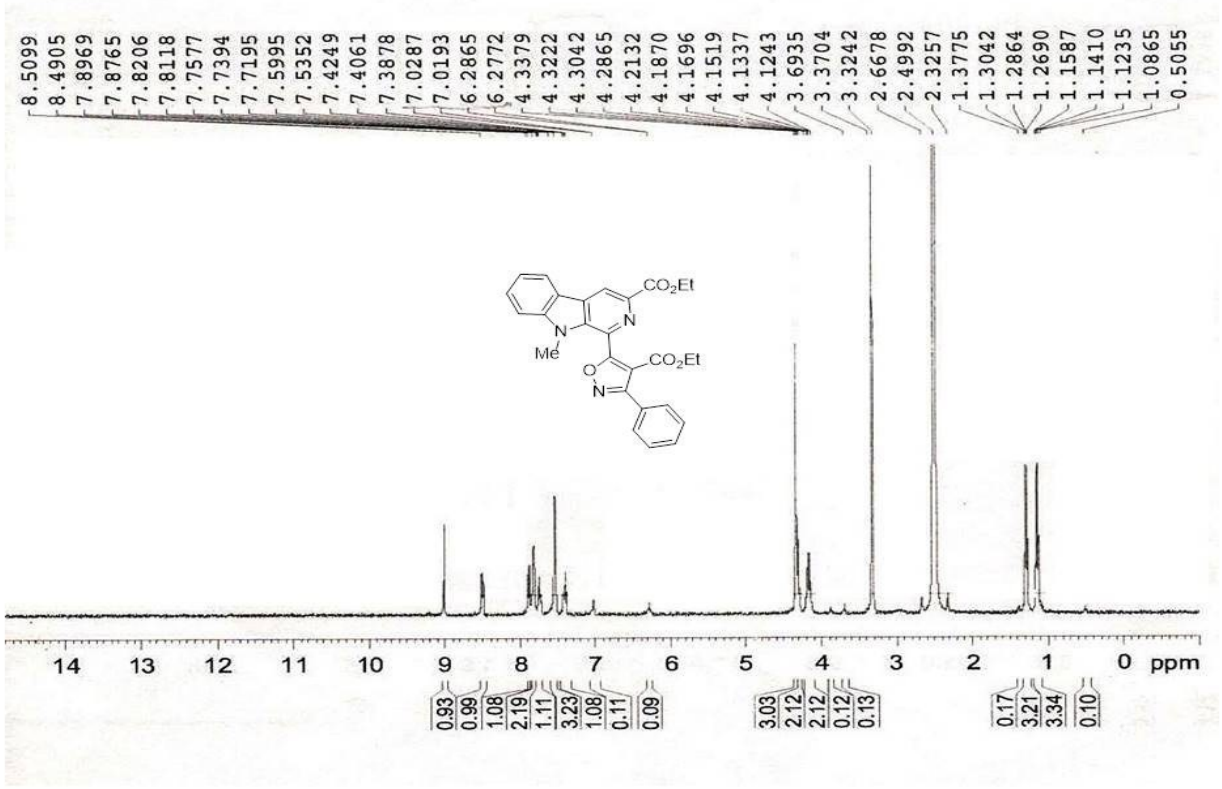


Figure S-25:- ^{1}H-NMR spectrum of ethyl 5-(3-(ethoxycarbonyl)-9-methyl-9*H*-pyrido[3,4-*b*]indol-1-yl)-3-phenylisoxazole-4-carboxylate **(12cA).**

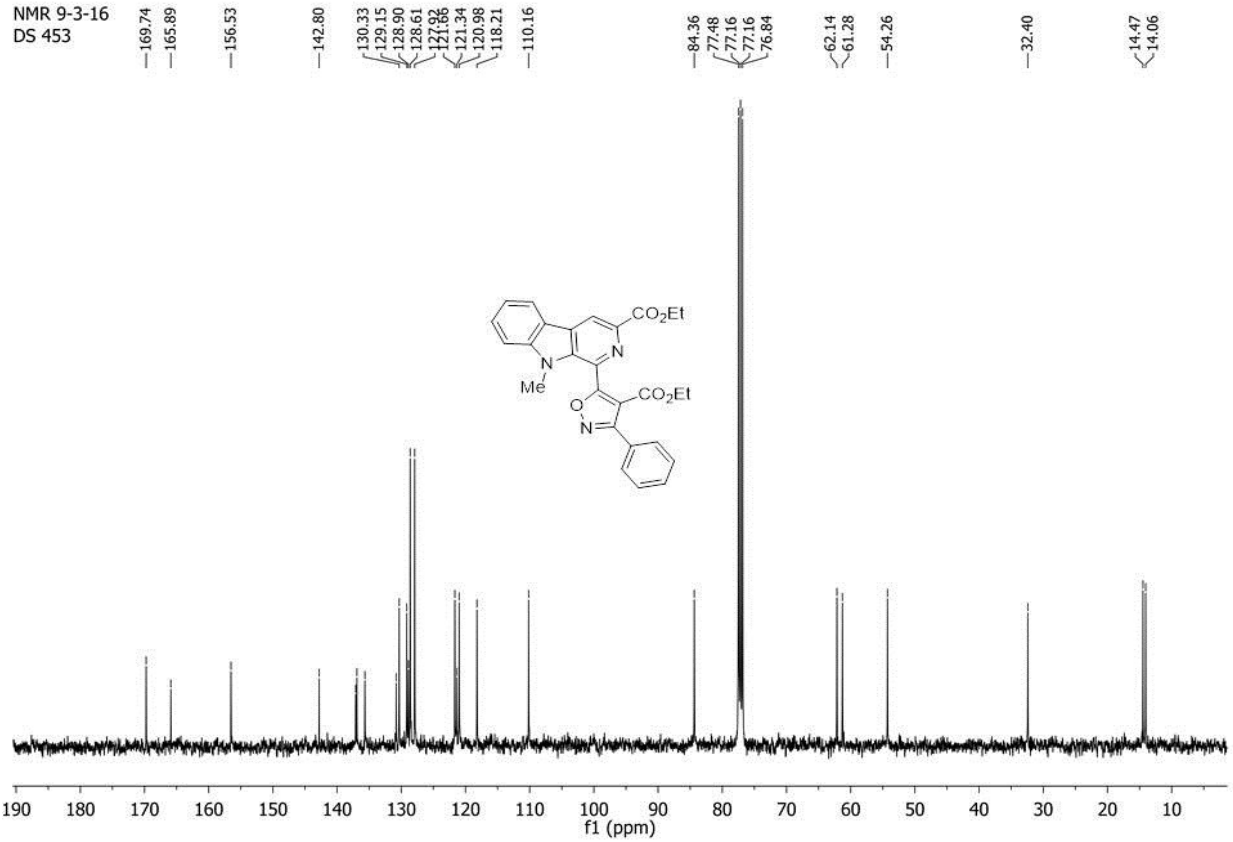


Figure S-26:- ^{13}C-NMR spectrum of ethyl 5-(3-(ethoxycarbonyl)-9-methyl-9*H*-pyrido[3,4-*b*]indol-1-yl)-3-phenylisoxazole-4-carboxylate **(12cA).**

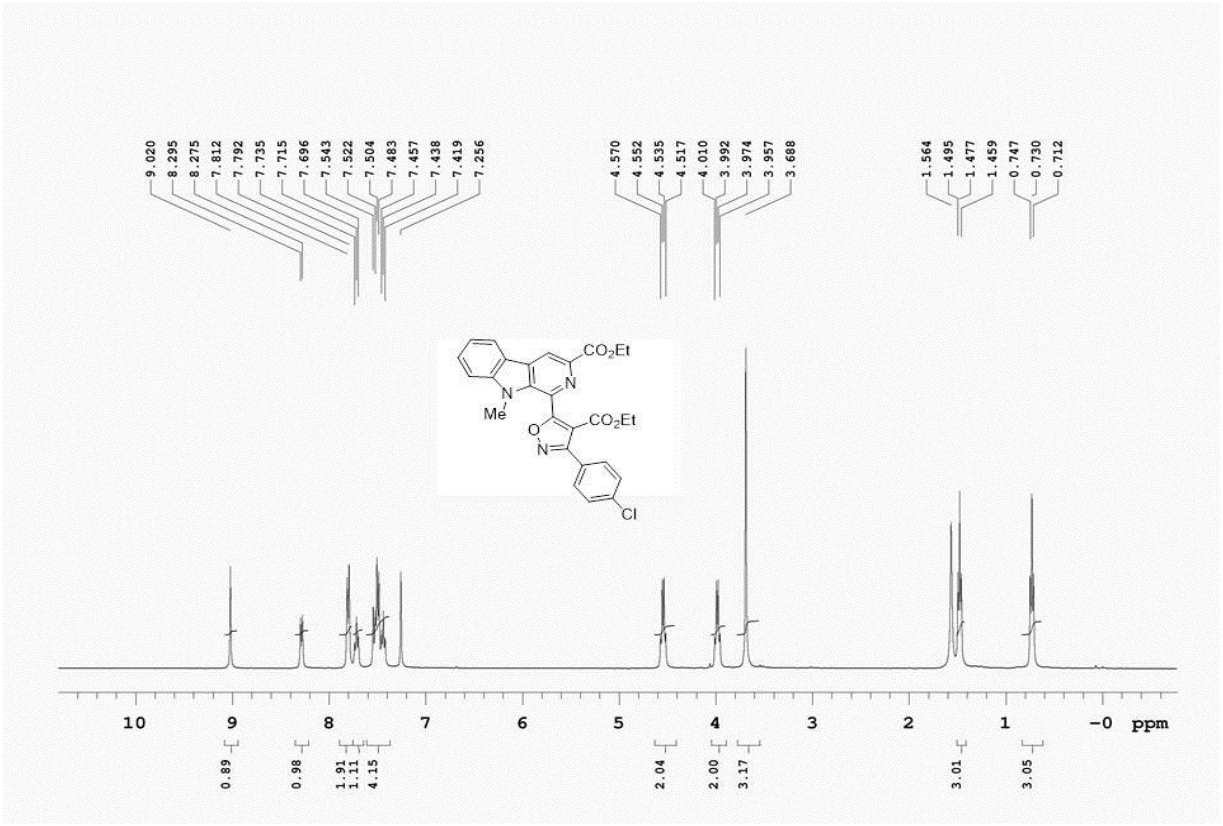


Figure S-27:- ^{1}H-NMR spectrum of ethyl 3-(4-chlorophenyl)-5-(3-(ethoxycarbonyl)-9-methyl-9*H*-pyrido[3,4-*b*]indol-1-yl)isoxazole-4-carboxylate **(12cB).**

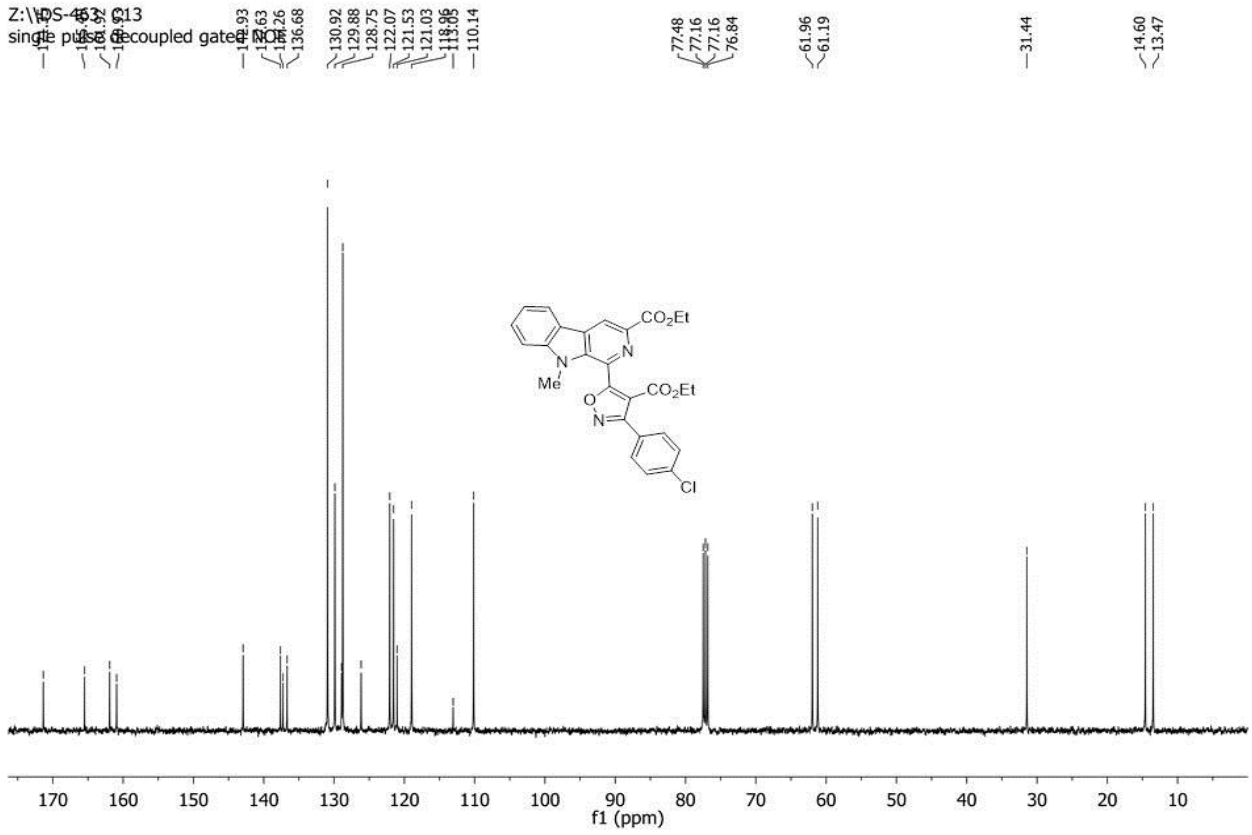


Figure S-28:- ^{13}C-NMR spectrum of ethyl 3-(4-chlorophenyl)-5-(3-(ethoxycarbonyl)-9-methyl-9*H*-pyrido[3,4-*b*]indol-1-yl)isoxazole-4-carboxylate **(12cB).**

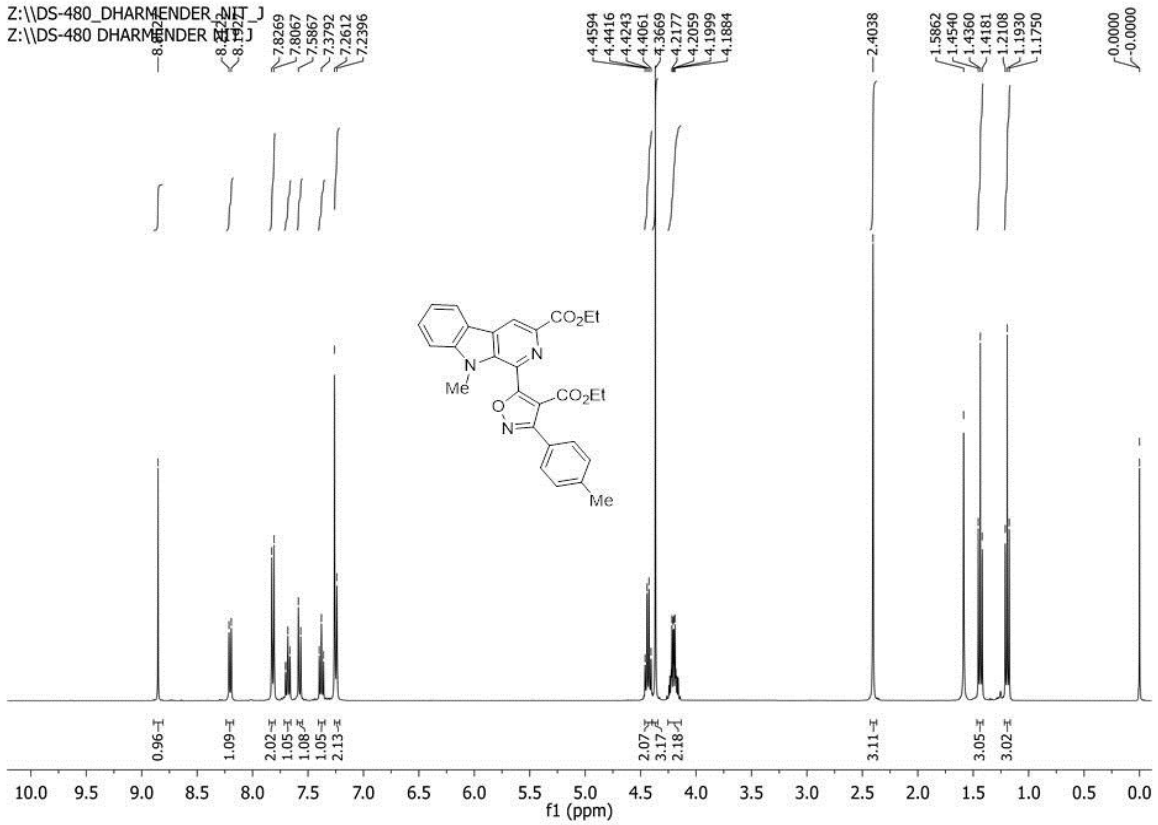


Figure S-29:- ^{1}H-NMR spectrum of ethyl 5-(3-(ethoxycarbonyl)-9-methyl-9*H*-pyrido[3,4-*b*]indol-1-yl)-3-(*p*-tolyl)isoxazole-4-carboxylate **(12cC).**

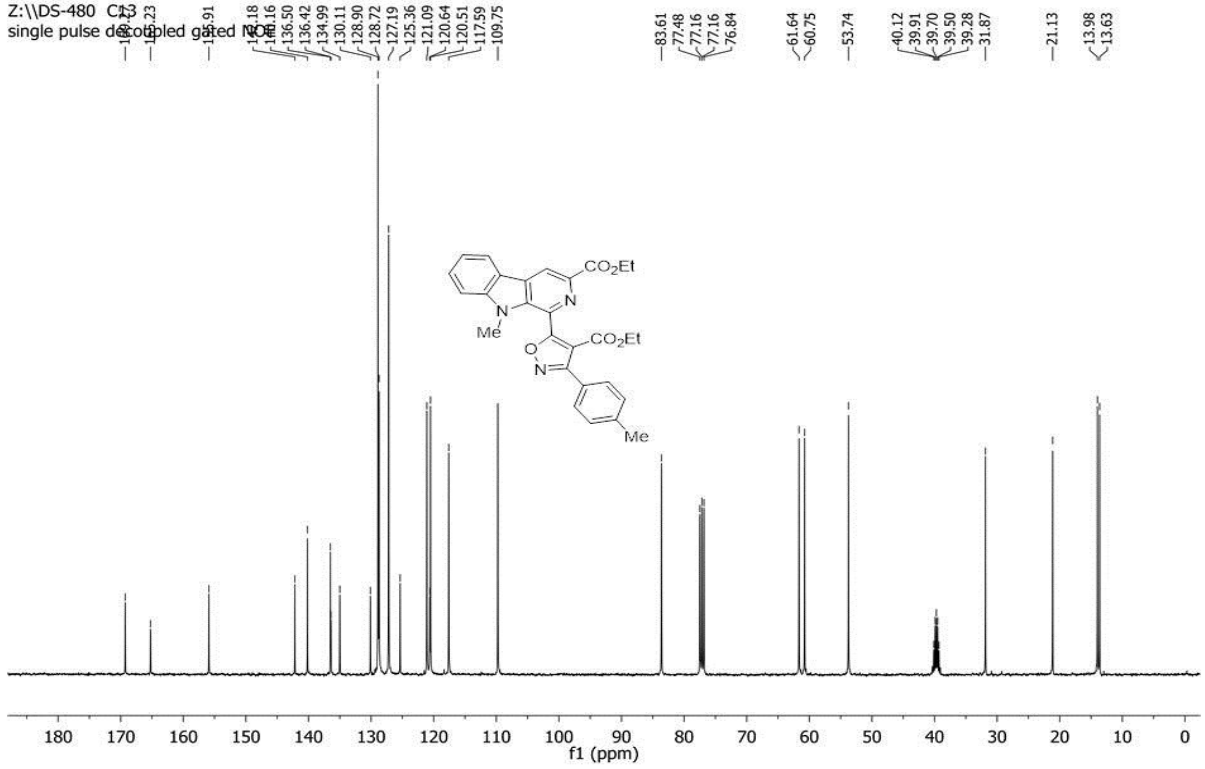


Figure S-30:- ^{13}C-NMR spectrum of ethyl 5-(3-(ethoxycarbonyl)-9-methyl-9*H*-pyrido[3,4-*b*]indol-1-yl)-3-(*p*-tolyl)isoxazole-4-carboxylate **(12cC).**

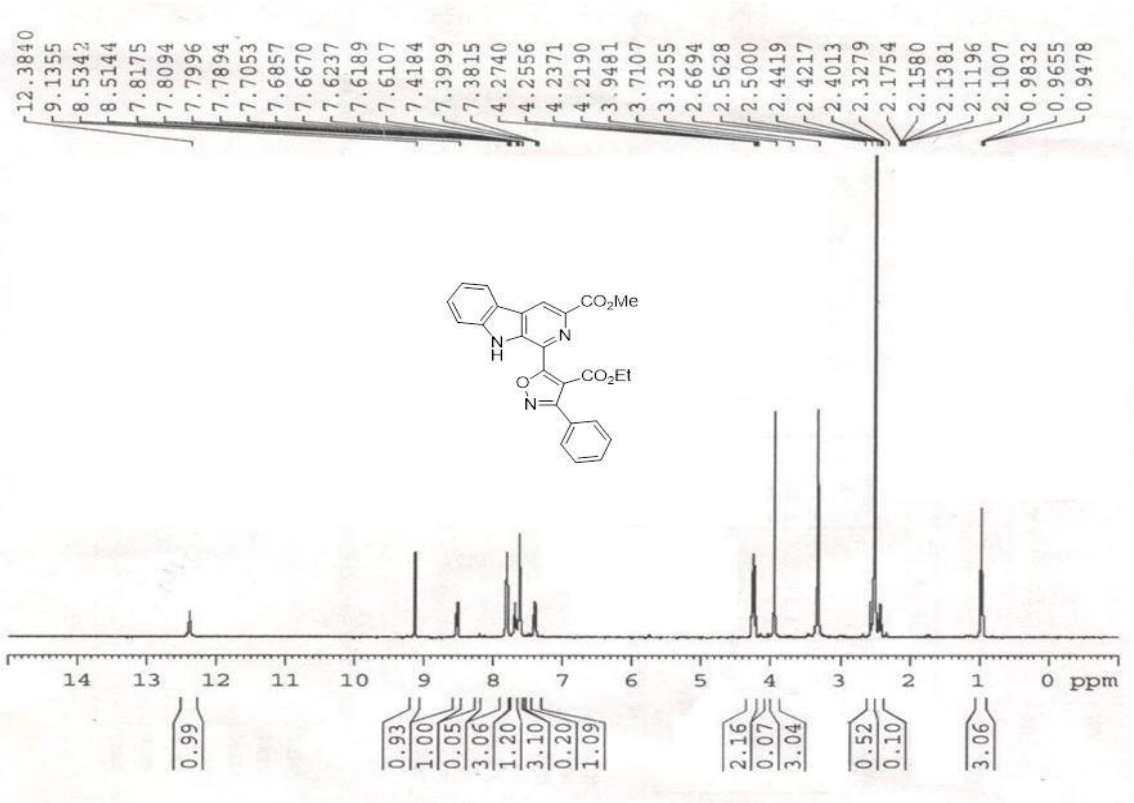


Figure S-31:- ^{1}H-NMR spectrum of ethyl 5-(3-(methoxycarbonyl)-9*H*-pyrido[3,4-*b*]indol-1-yl)-3-phenylisoxazole-4-carboxylate **(12dA).**

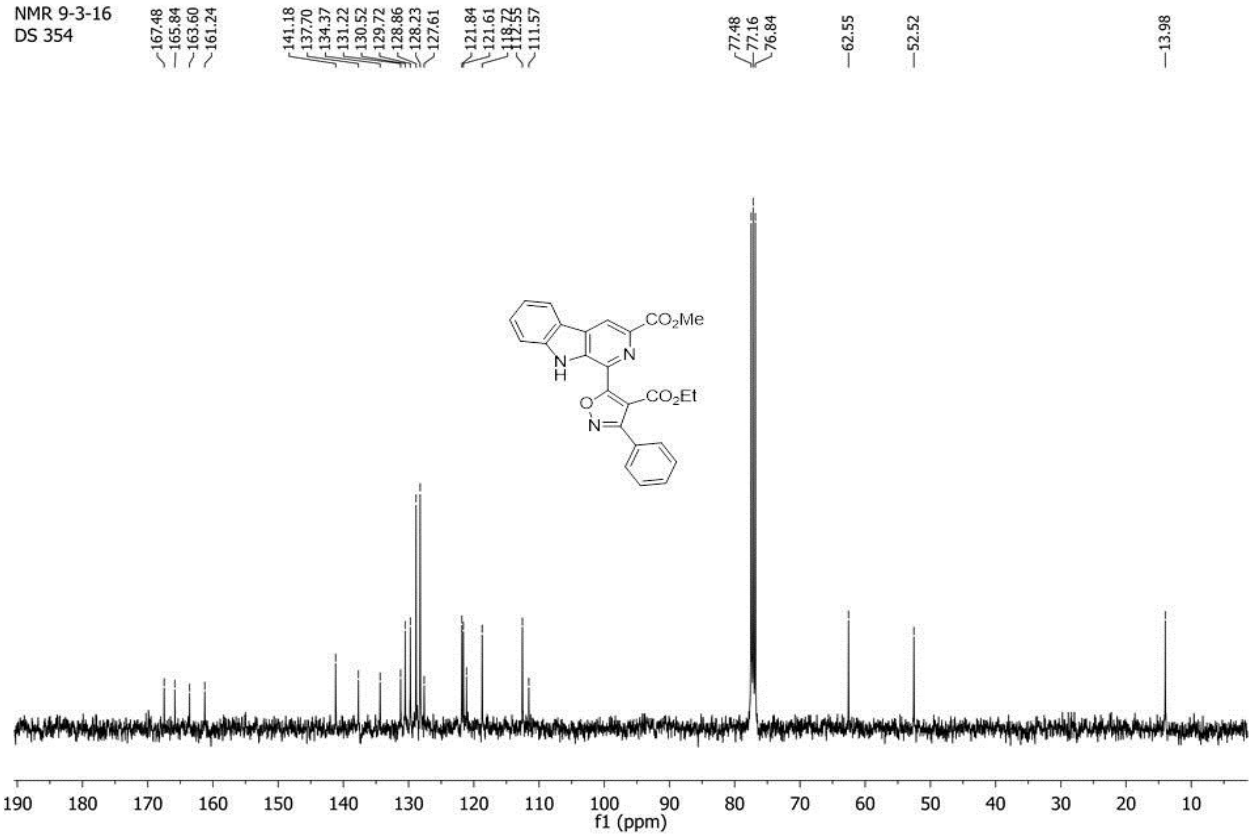


Figure S-32:- ^{13}C-NMR spectrum of ethyl 5-(3-(methoxycarbonyl)-9*H*-pyrido[3,4-*b*]indol-1-yl)-3-phenylisoxazole-4-carboxylate **(12dA).**

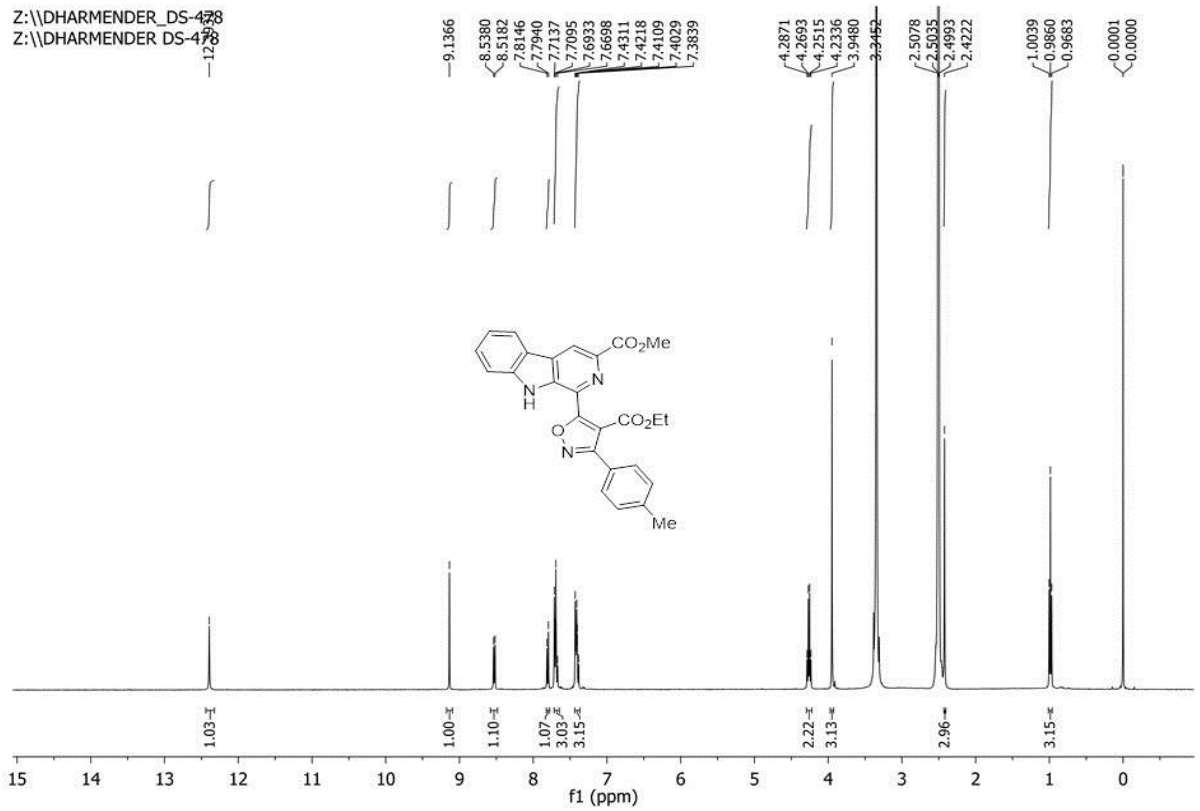


Figure S-33:- ^{1}H-NMR spectrum of ethyl 5-(3-(methoxycarbonyl)-9*H*-pyrido[3,4-*b*]indol-1-yl)-3-(*p*-tolyl)isoxazole-4-carboxylate (**12dC).**

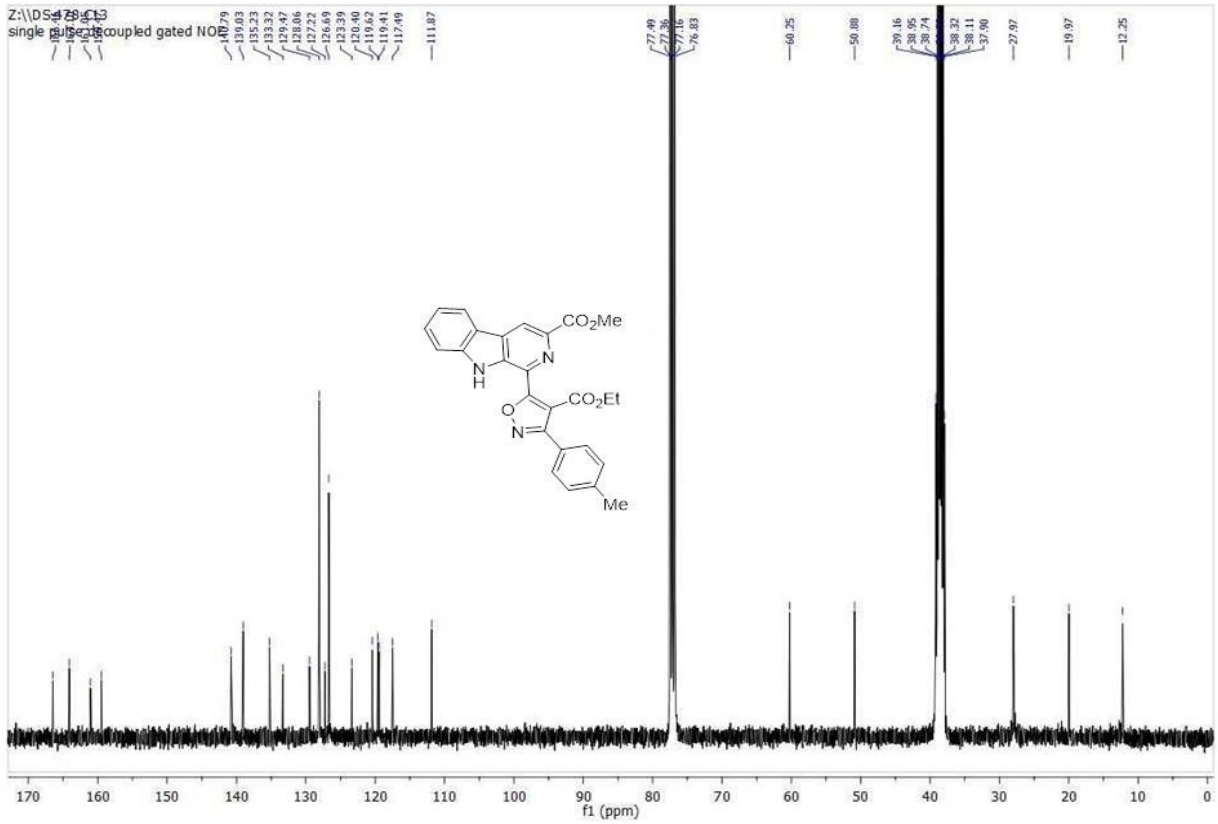


Figure S-34- ^{13}C-NMR spectrum of ethyl 5-(3-(methoxycarbonyl)-9*H*-pyrido[3,4-*b*]indol-1-yl)-3-(*p*-tolyl)isoxazole-4-carboxylate (**12dC).**

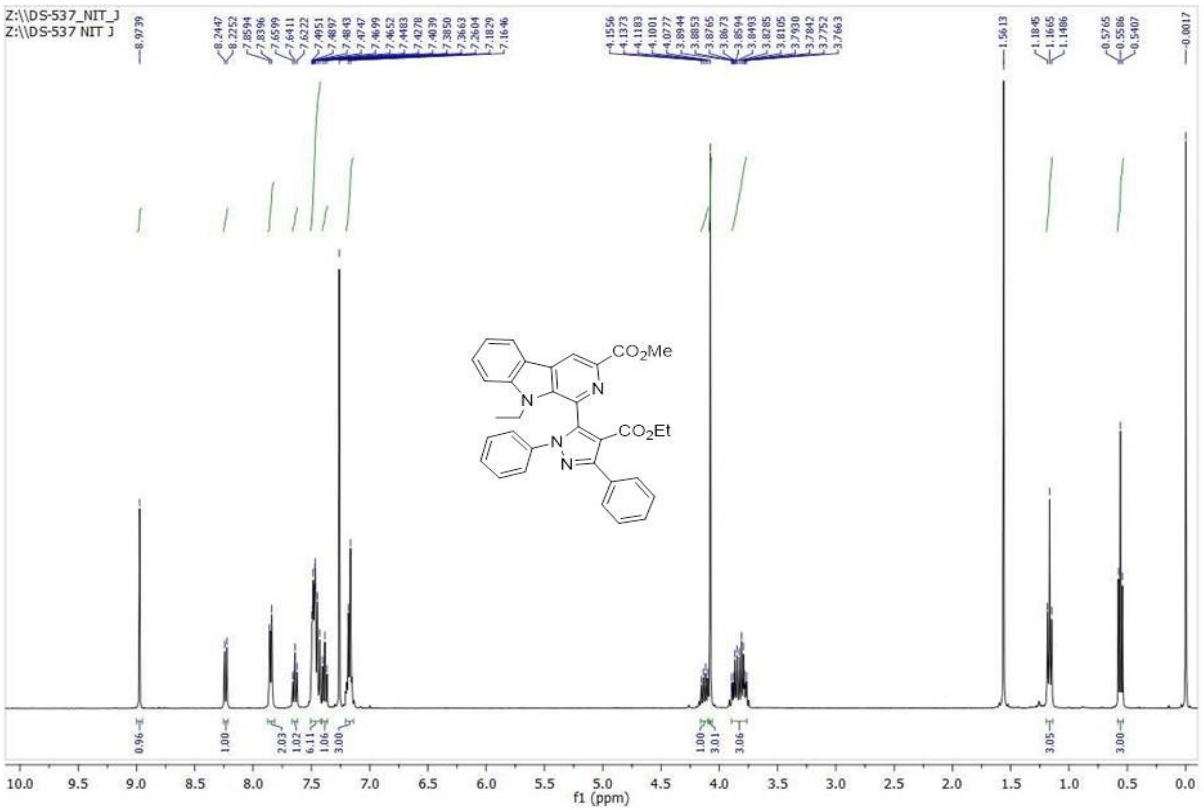


Figure S-35:- ^{1}H-NMR spectrum of methyl 1-(4-(ethoxycarbonyl)-1,3-diphenyl-1*H*-pyrazol-5-yl)-9-ethyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(14).**

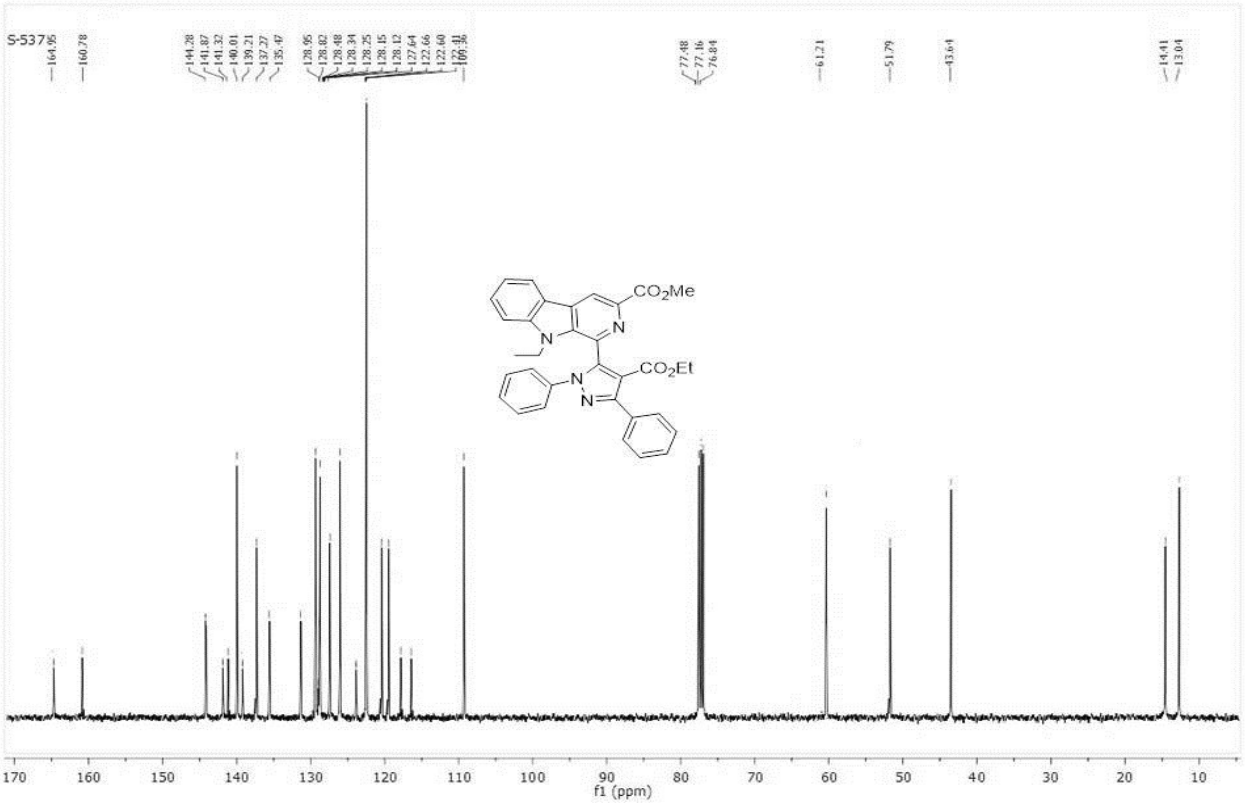


Figure S-36:- ^{13}C-NMR spectrum of methyl 1-(4-(ethoxycarbonyl)-1,3-diphenyl-1*H*-pyrazol-5-yl)-9-ethyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(14).**

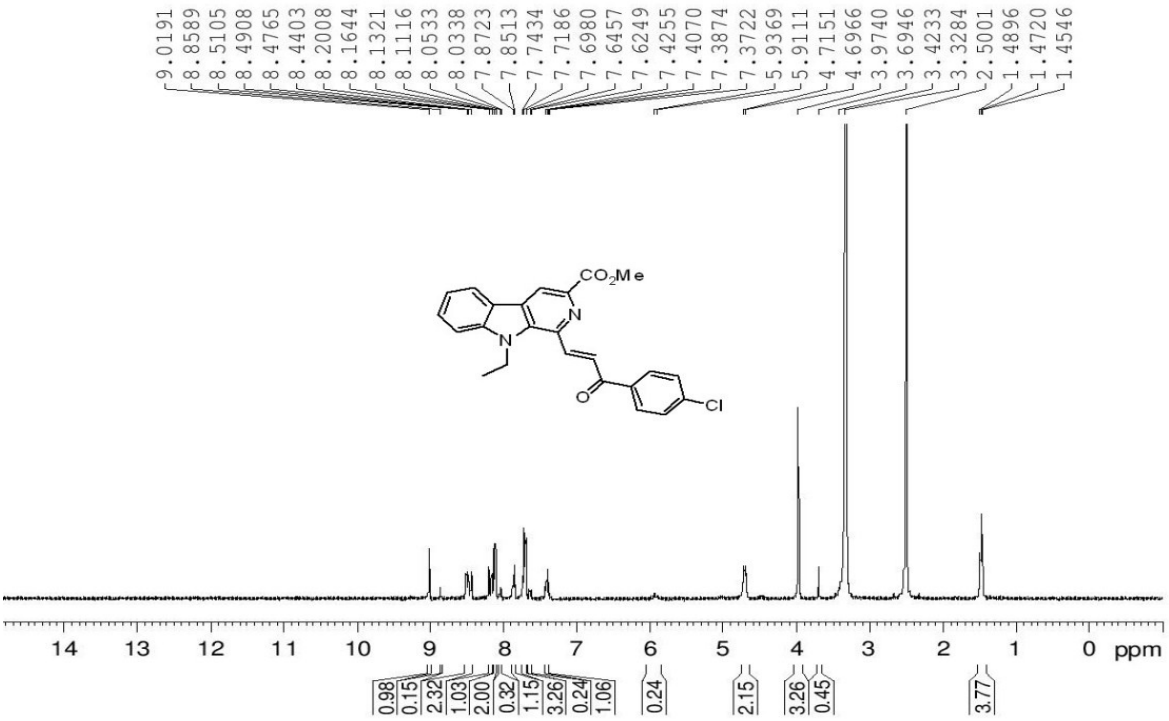


Figure S-37:- ^{1}H-NMR spectrum of (*E*)-methyl 1-(3-(4-chlorophenyl)-3-oxoprop-1-en-1-yl)-9-ethyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(16b).**

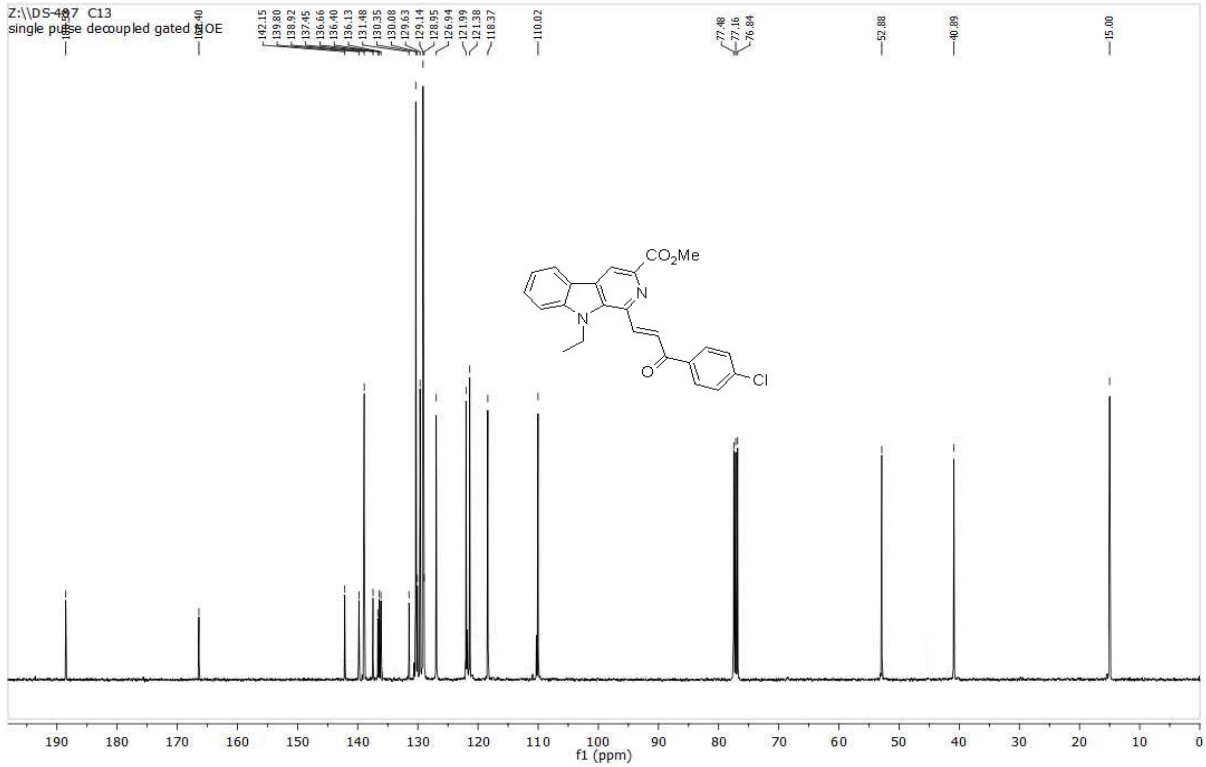


Figure S-38:- ^{13}C-NMR spectrum of (*E*)-methyl 1-(3-(4-chlorophenyl)-3-oxoprop-1-en-1-yl)-9-ethyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(16b).**

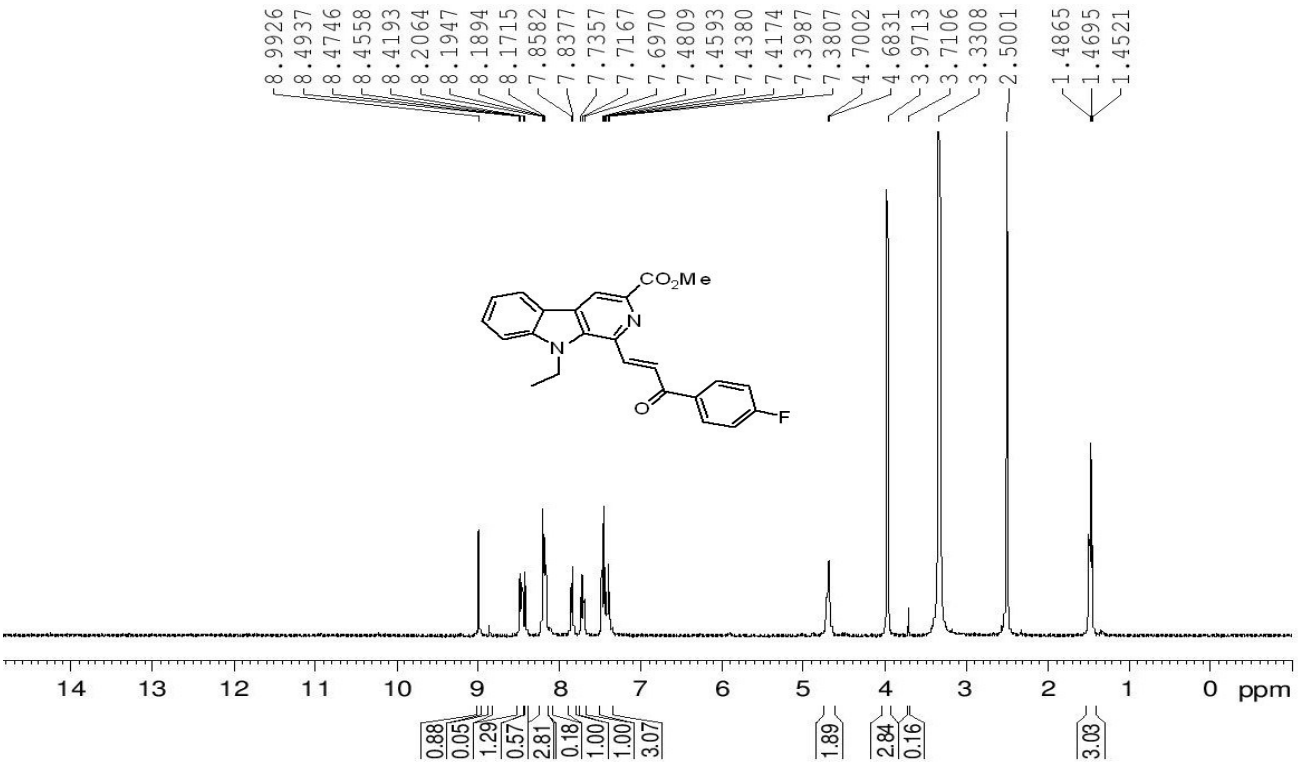


Figure S-39:- ^{1}H-NMR spectrum of (*E*)-methyl 9-ethyl-1-(3-(4-fluorophenyl)-3-oxoprop-1-en-1-yl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(16c).**

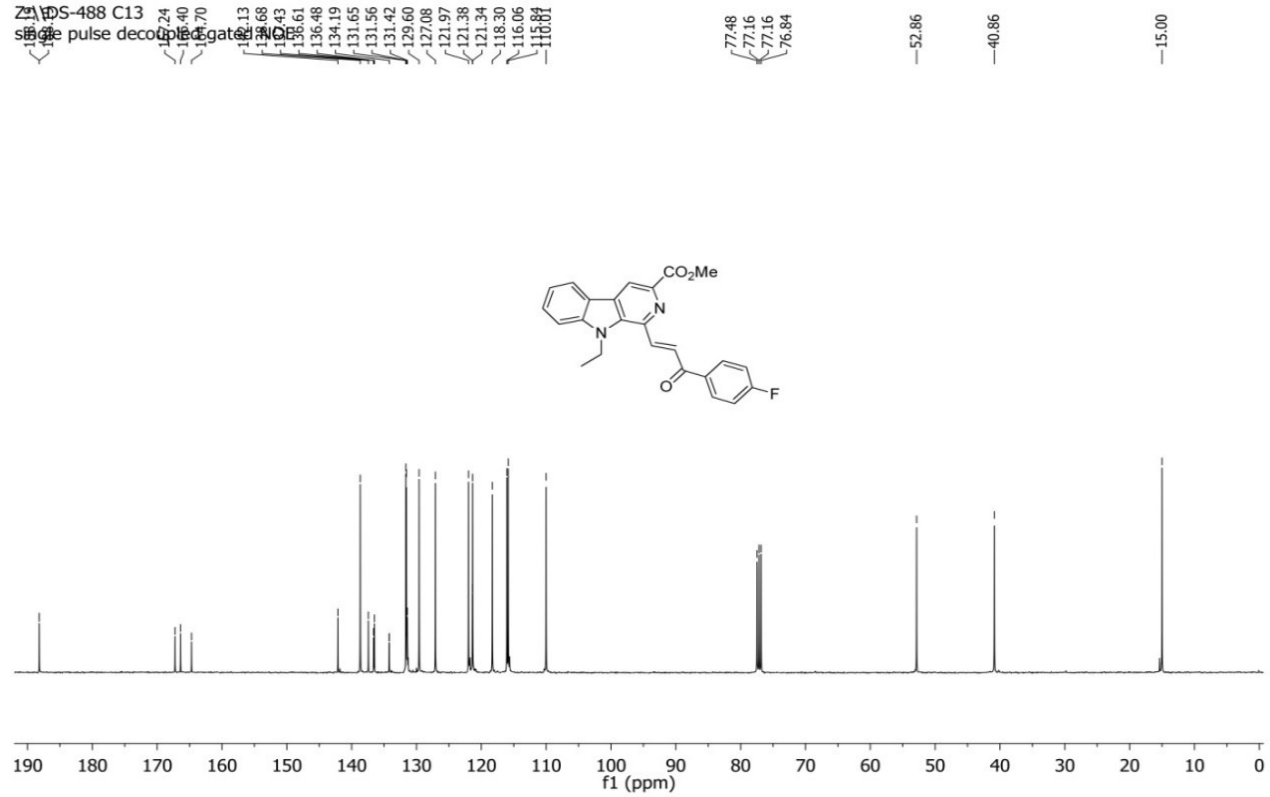


Figure S-40:- ^{13}C-NMR spectrum of (*E*)-methyl 9-ethyl-1-(3-(4-fluorophenyl)-3-oxoprop-1-en-1-yl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(16c).**

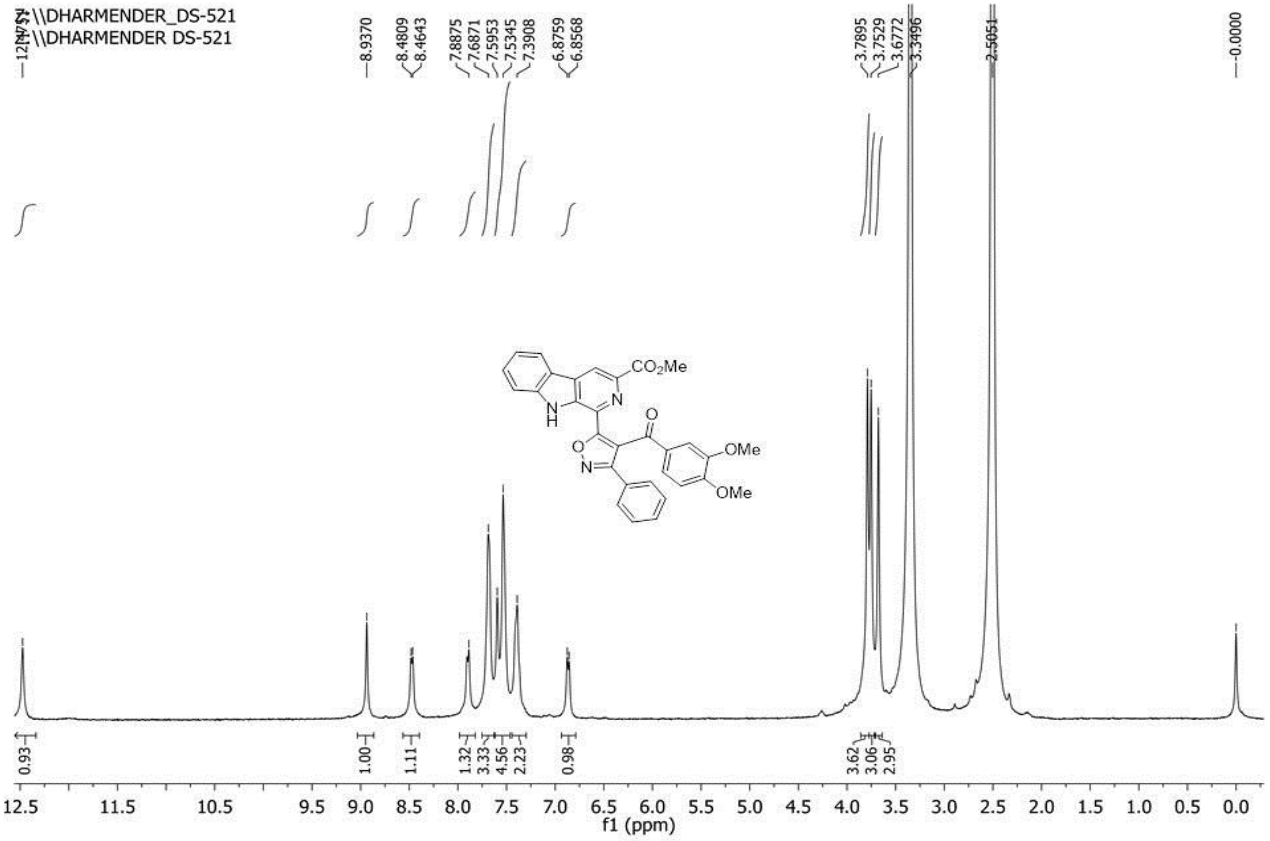


Figure S-41:- ^{1}H-NMR spectrum of methyl 1-(4-(3,4-dimethoxybenzoyl)-3-phenylisoxazol-5-yl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(18aA).**

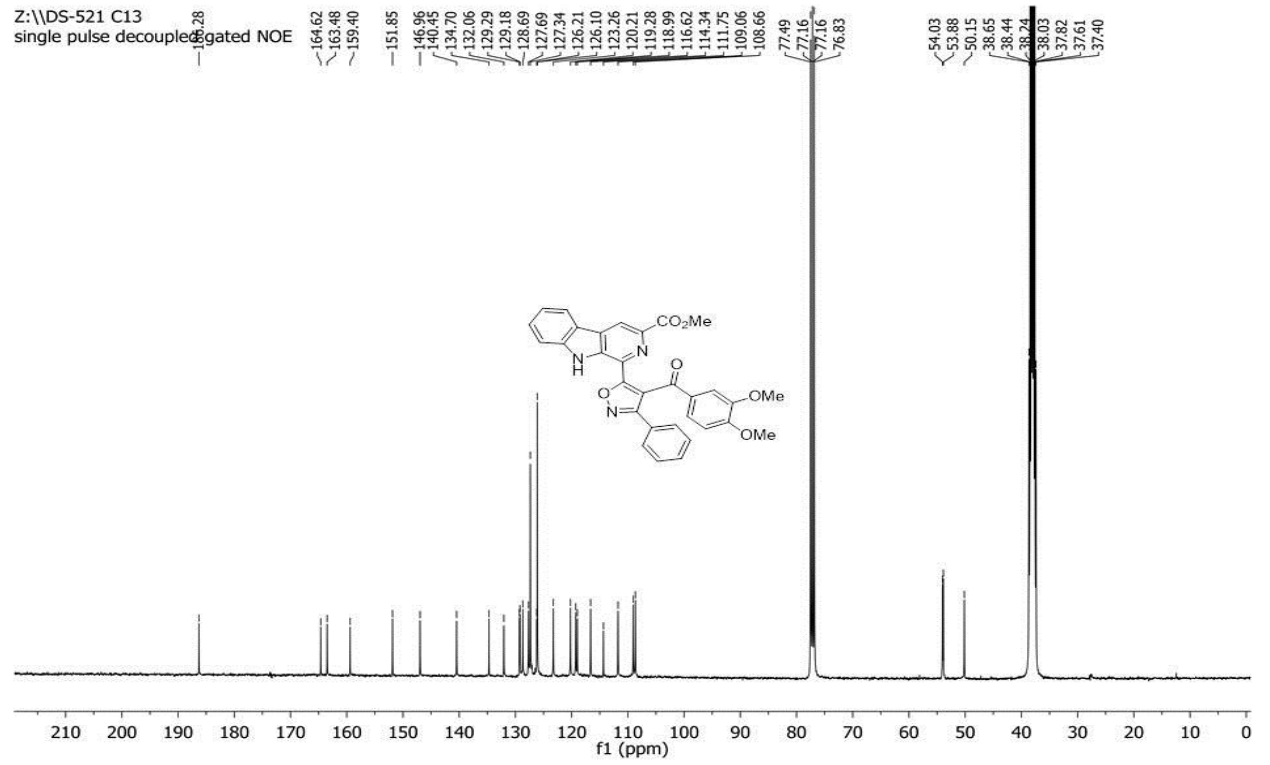


Figure S-42:- ^{13}C-NMR spectrum of methyl 1-(4-(3,4-dimethoxybenzoyl)-3-phenylisoxazol-5-yl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(18aA).**

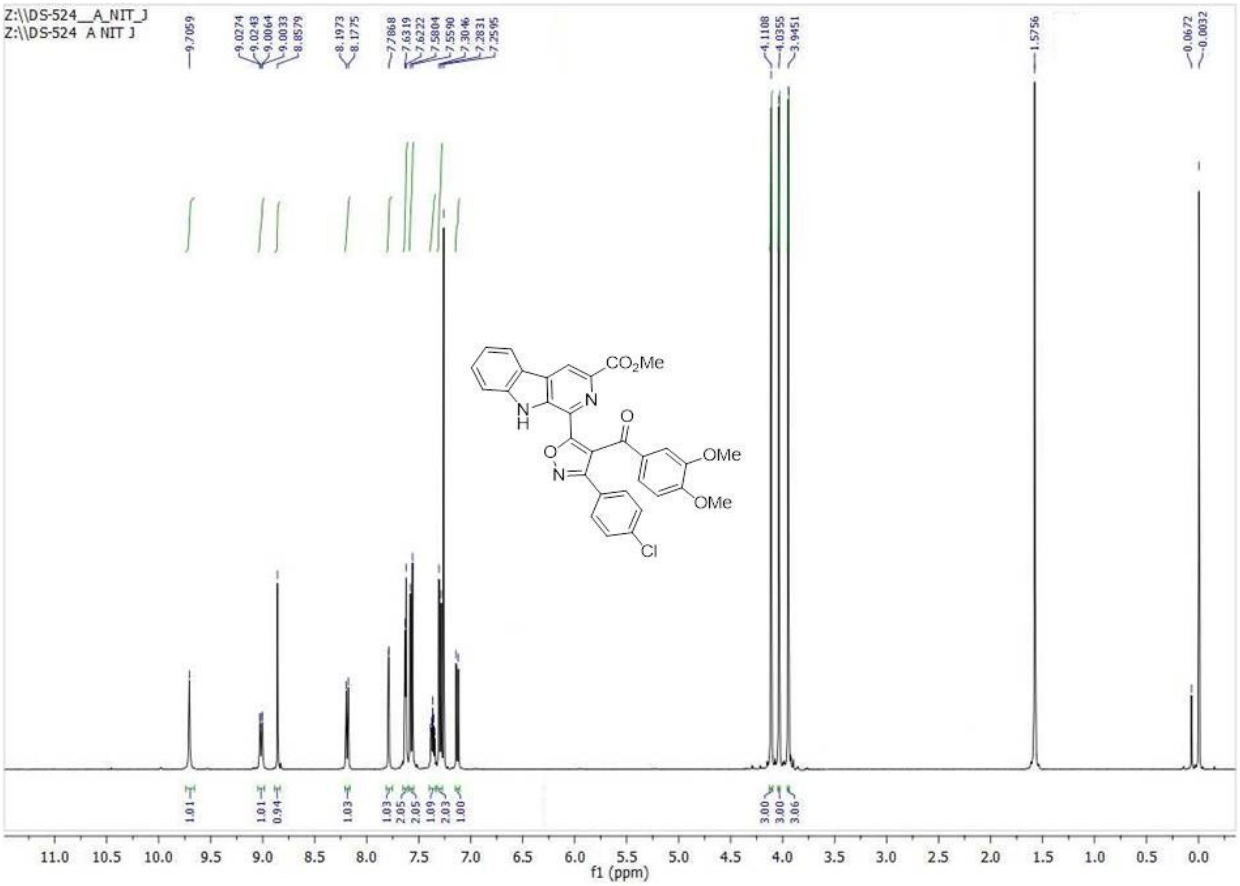


Figure S-43:- ^{1}H-NMR spectrum of methyl 1-(3-(4-chlorophenyl)-4-(3,4-dimethoxybenzoyl)isoxazol-5-yl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(18aB).**

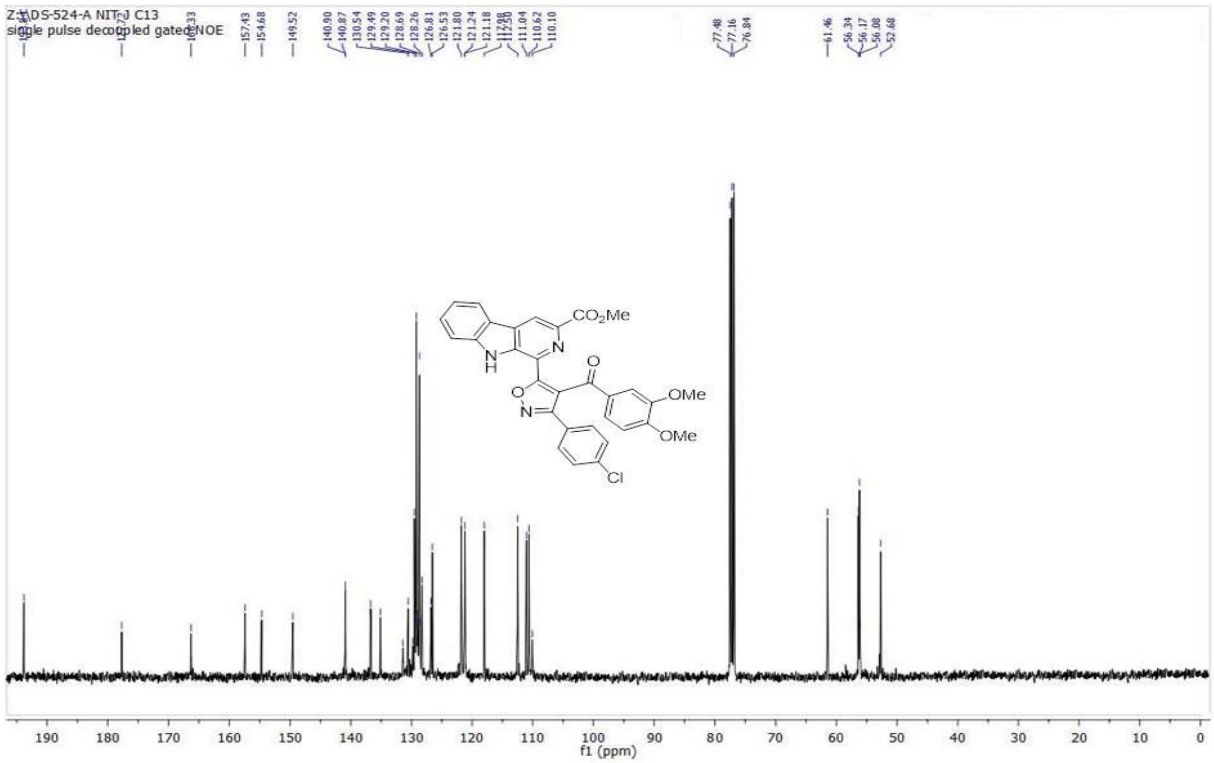


Figure S-44:- ^{13}C-NMR spectrum of methyl 1-(3-(4-chlorophenyl)-4-(3,4-dimethoxybenzoyl)isoxazol-5-yl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(18aB).**

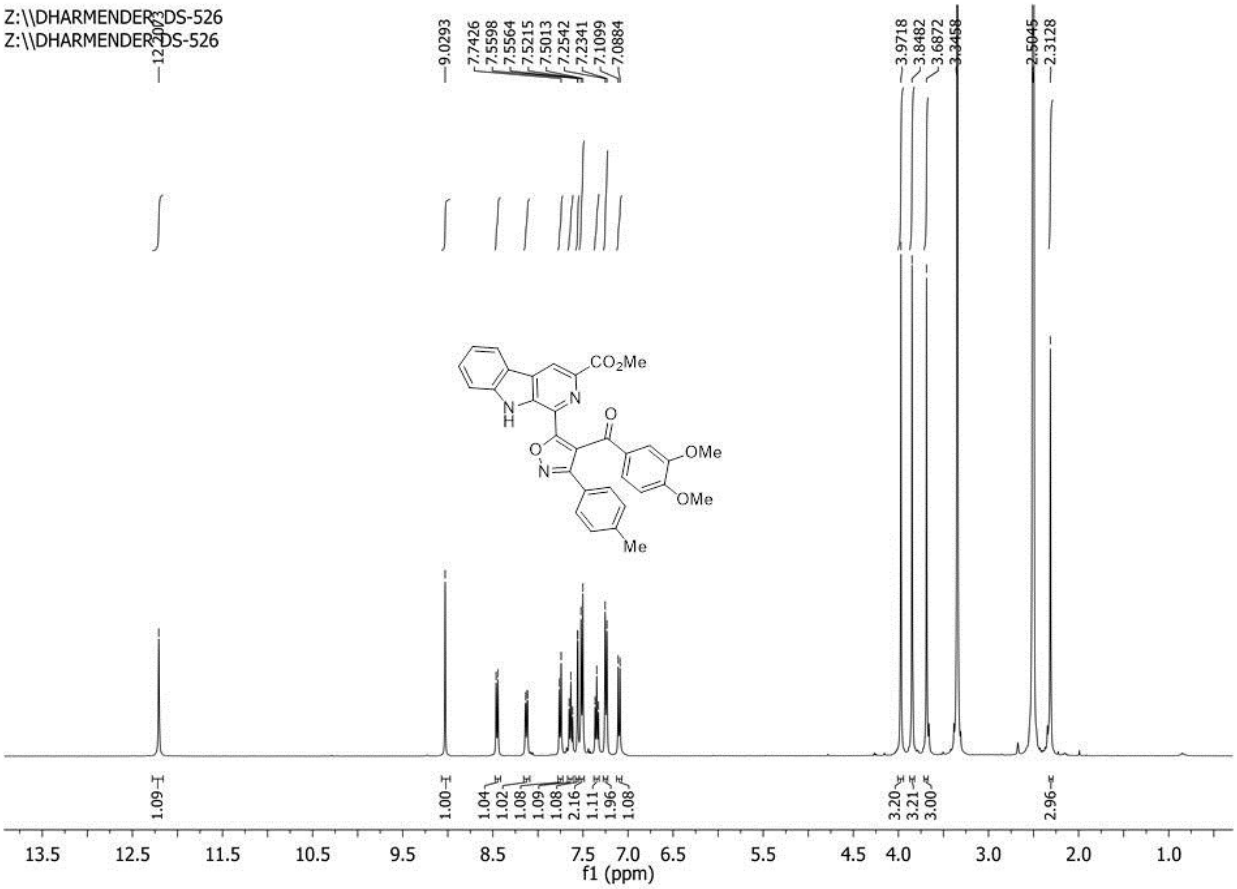


Figure S-45:- ^{1}H-NMR spectrum of methyl 1-(4-(3,4-dimethoxybenzoyl)-3-(*p*-tolyl)isoxazol-5-yl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(18aC).**

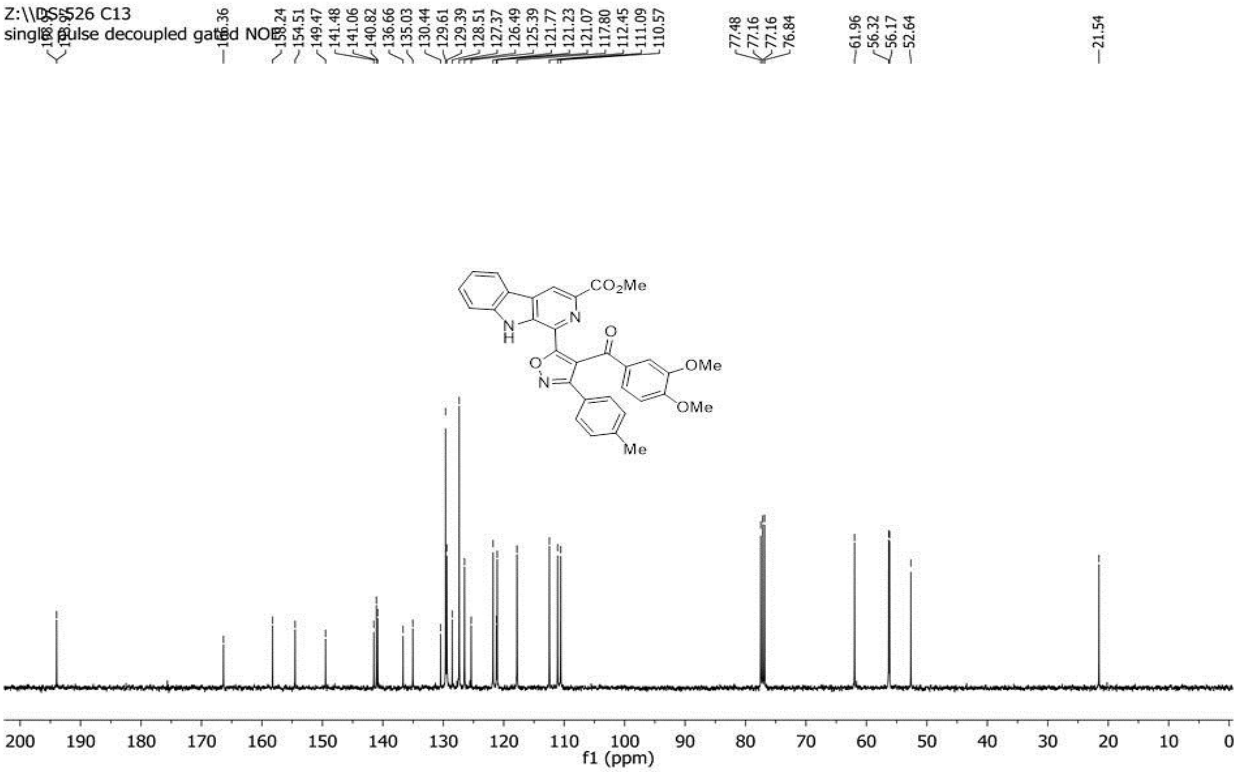


Figure S-46:- ^{13}C-NMR spectrum of methyl 1-(4-(3,4-dimethoxybenzoyl)-3-(*p*-tolyl)isoxazol-5-yl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(18aC).**

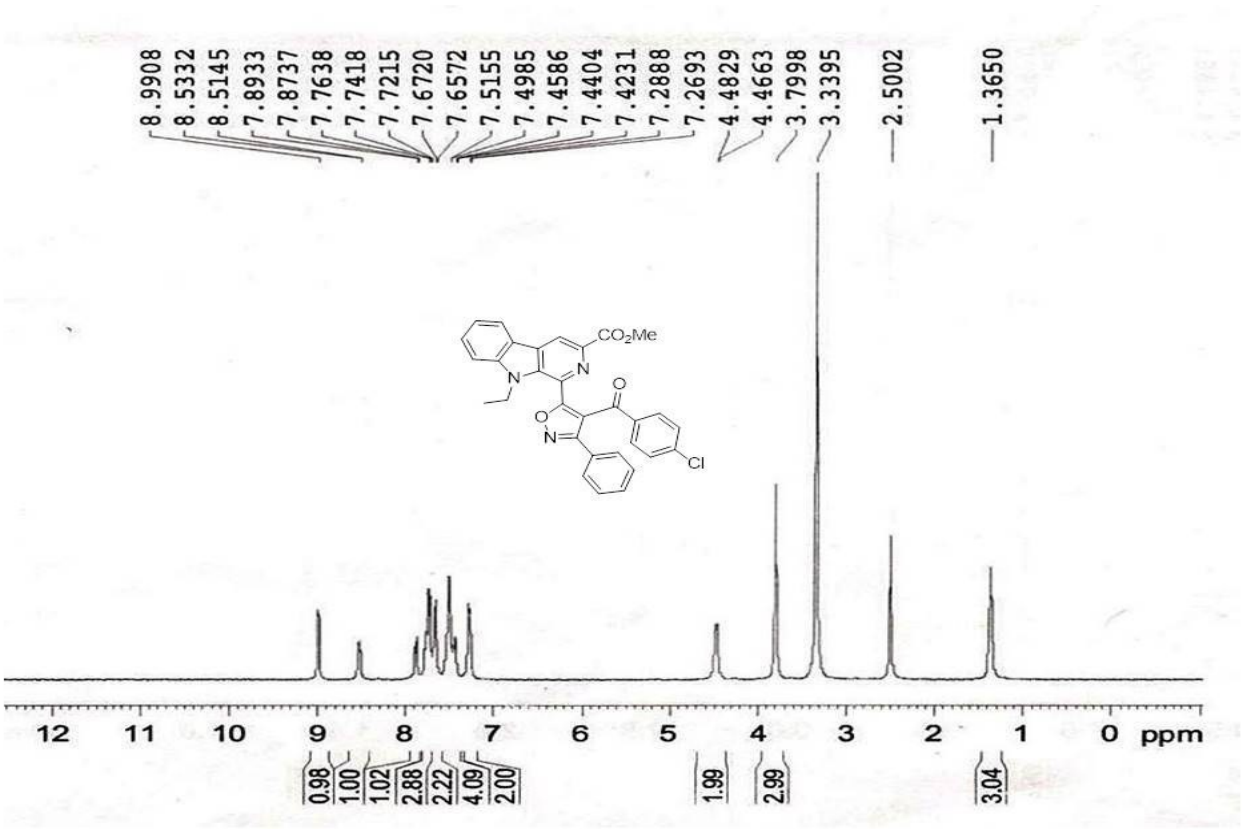


Figure S-47:- ^{1}H-NMR spectrum of methyl 1-(4-(4-chlorobenzoyl)-3-phenylisoxazol-5-yl)-9-ethyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(18bA).**

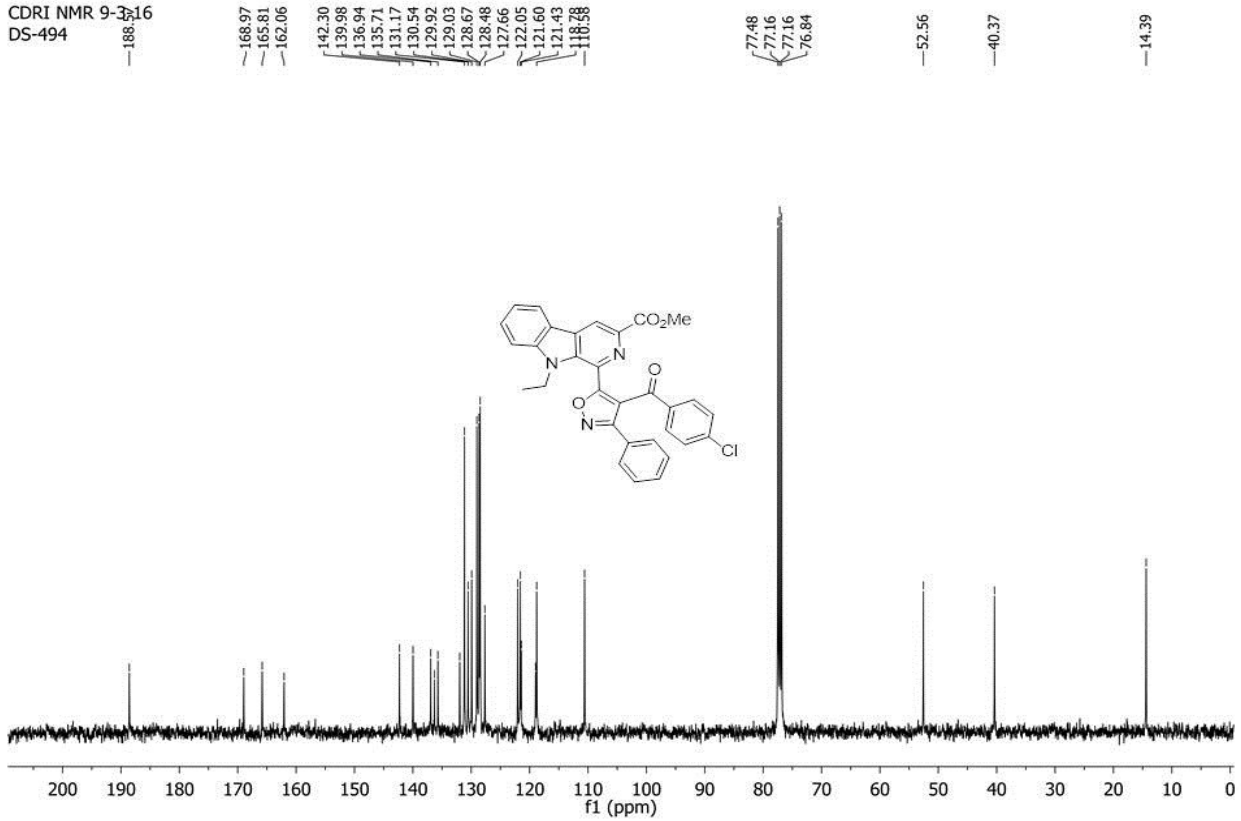


Figure S-48:- ^{13}C-NMR spectrum of methyl 1-(4-(4-chlorobenzoyl)-3-phenylisoxazol-5-yl)-9-ethyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(18bA).**

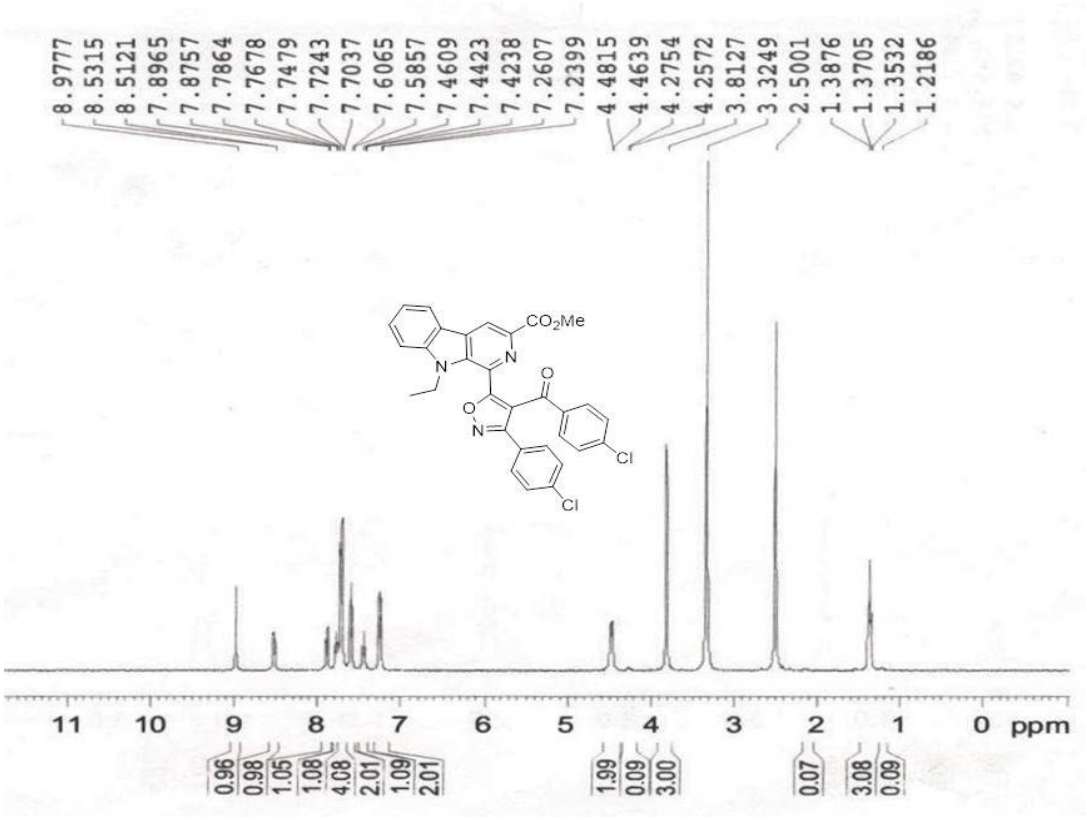


Figure S-49:- ^{1}H-NMR spectrum of methyl 1-(4-(4-chlorobenzoyl)-3-(4-chlorophenyl)isoxazol-5-yl)-9-ethyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(18bB).**

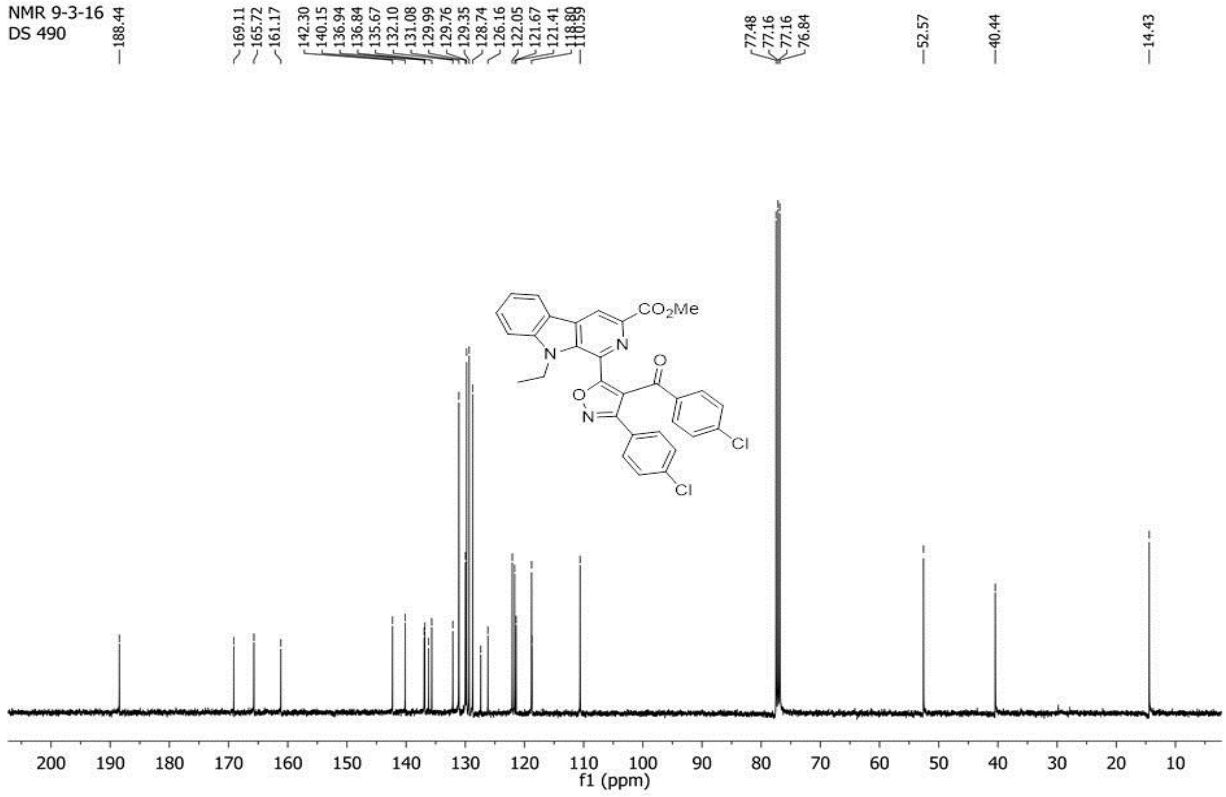


Figure S-50:- ^{13}C-NMR spectrum of methyl 1-(4-(4-chlorobenzoyl)-3-(4-chlorophenyl)isoxazol-5-yl)-9-ethyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(18bB).**

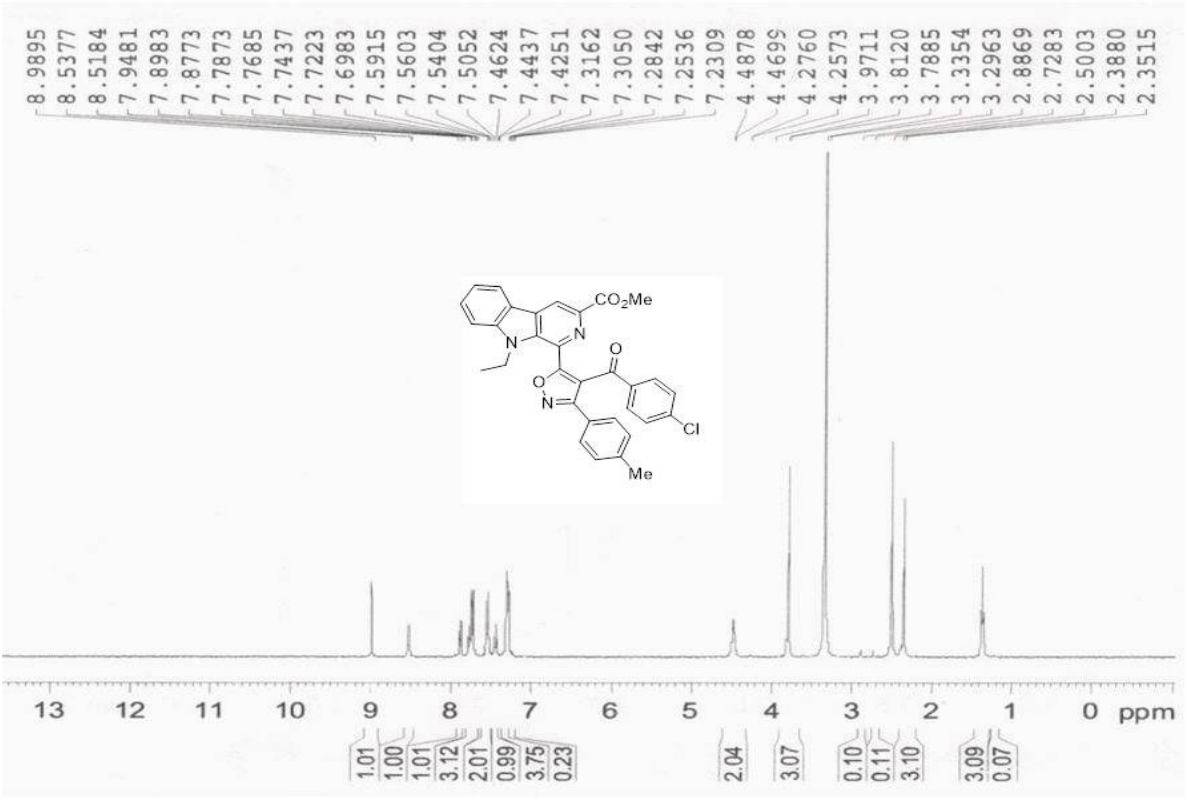


Figure S-51:- ^{1}H-NMR spectrum of methyl 1-(4-(4-chlorobenzoyl)-3-(*p*-tolyl)isoxazol-5-yl)-9-ethyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(18bC).**

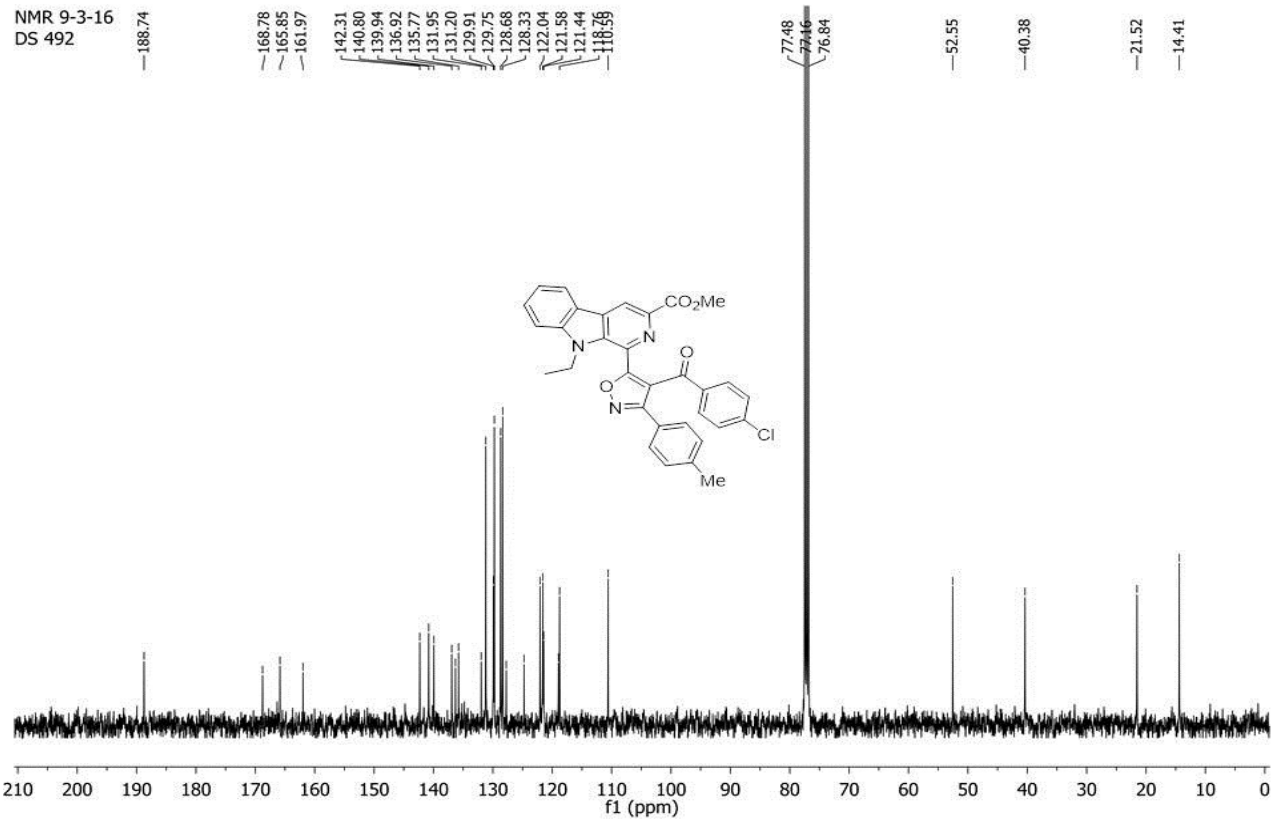


Figure S-52:- ^{13}C-NMR spectrum of methyl 1-(4-(4-chlorobenzoyl)-3-(*p*-tolyl)isoxazol-5-yl)-9-ethyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(18bC).**

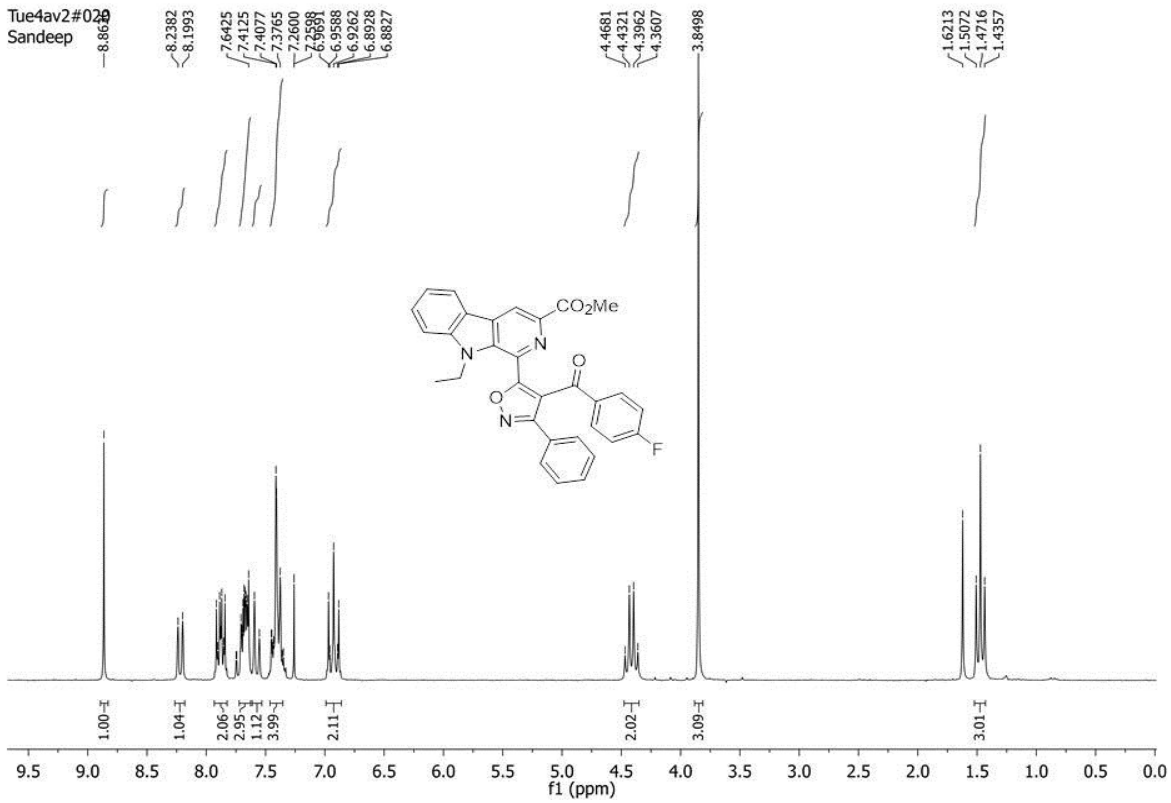


Figure S-53:- ^{1}H-NMR spectrum of methyl 9-ethyl-1-(4-(4-fluorobenzoyl)-3-phenylisoxazol-5-yl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(18cA).**

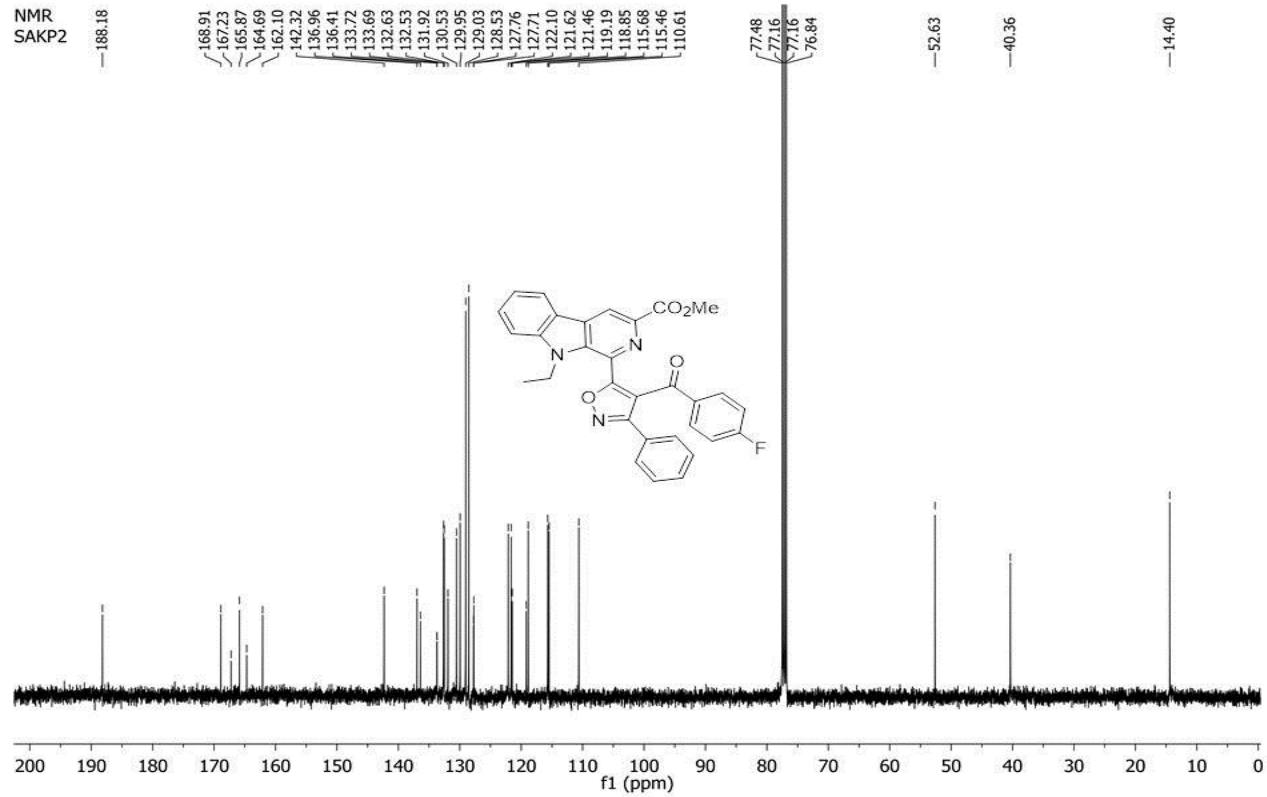


Figure S-54:- ^{13}C-NMR spectrum of methyl 9-ethyl-1-(4-(4-fluorobenzoyl)-3-phenylisoxazol-5-yl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(18cA).**

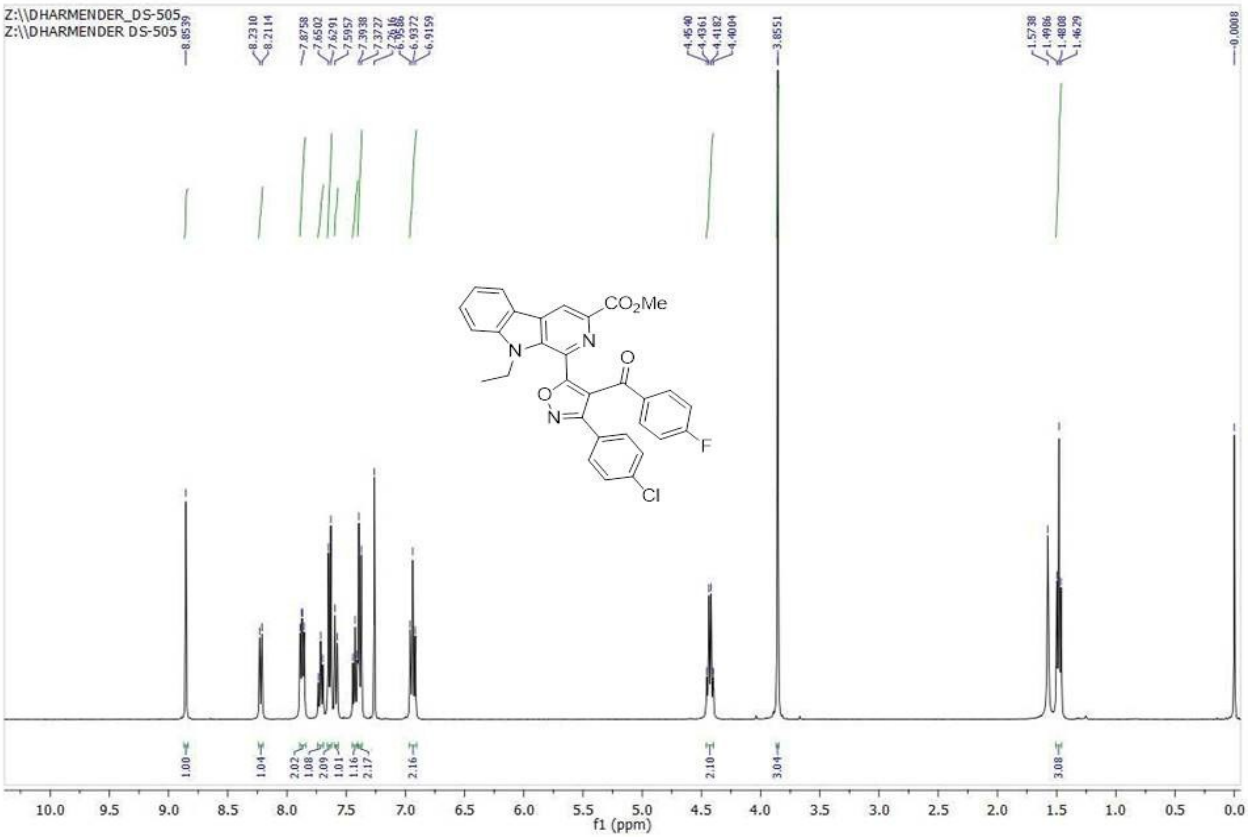


Figure S-55:- ^{1}H-NMR spectrum of methyl 1-(3-(4-chlorophenyl)-4-(4-fluorobenzoyl)isoxazol-5-yl)-9-ethyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(18cB).**

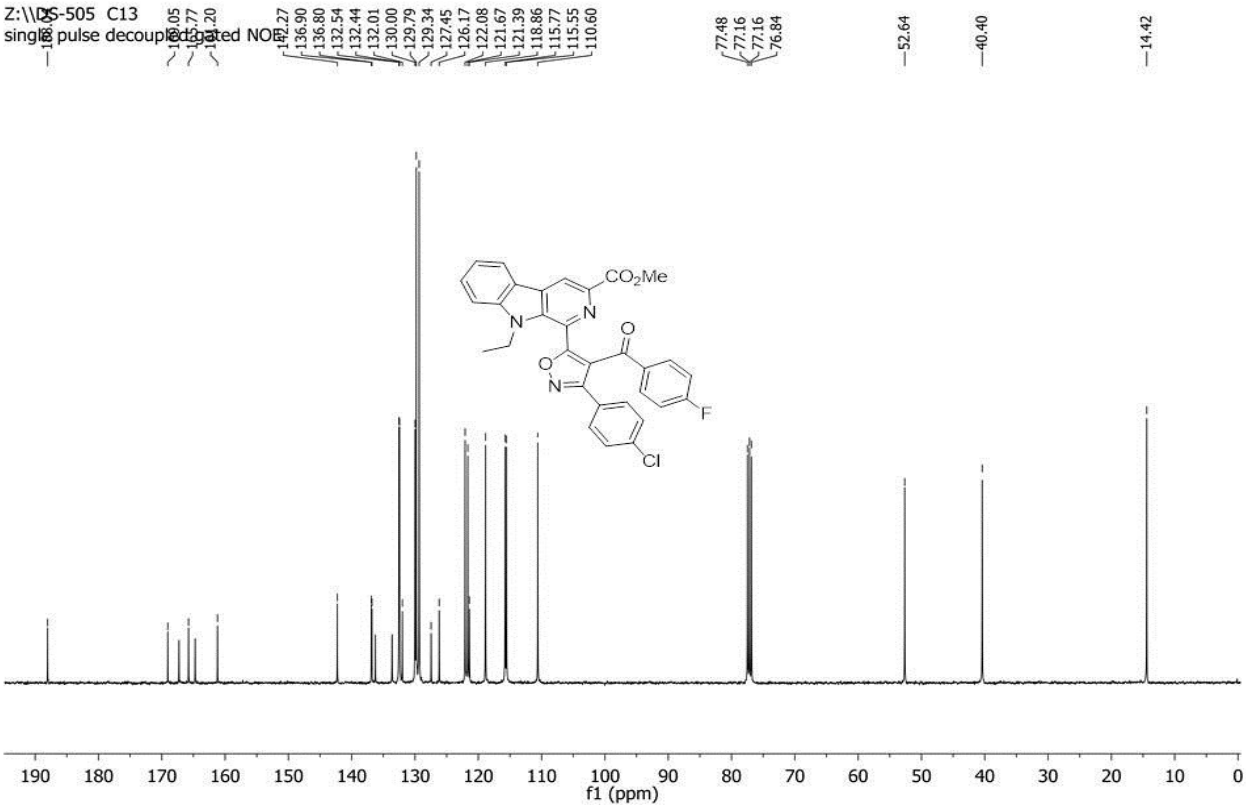


Figure S-56:- ^{13}C-NMR spectrum of methyl 1-(3-(4-chlorophenyl)-4-(4-fluorobenzoyl)isoxazol-5-yl)-9-ethyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(18cB).**

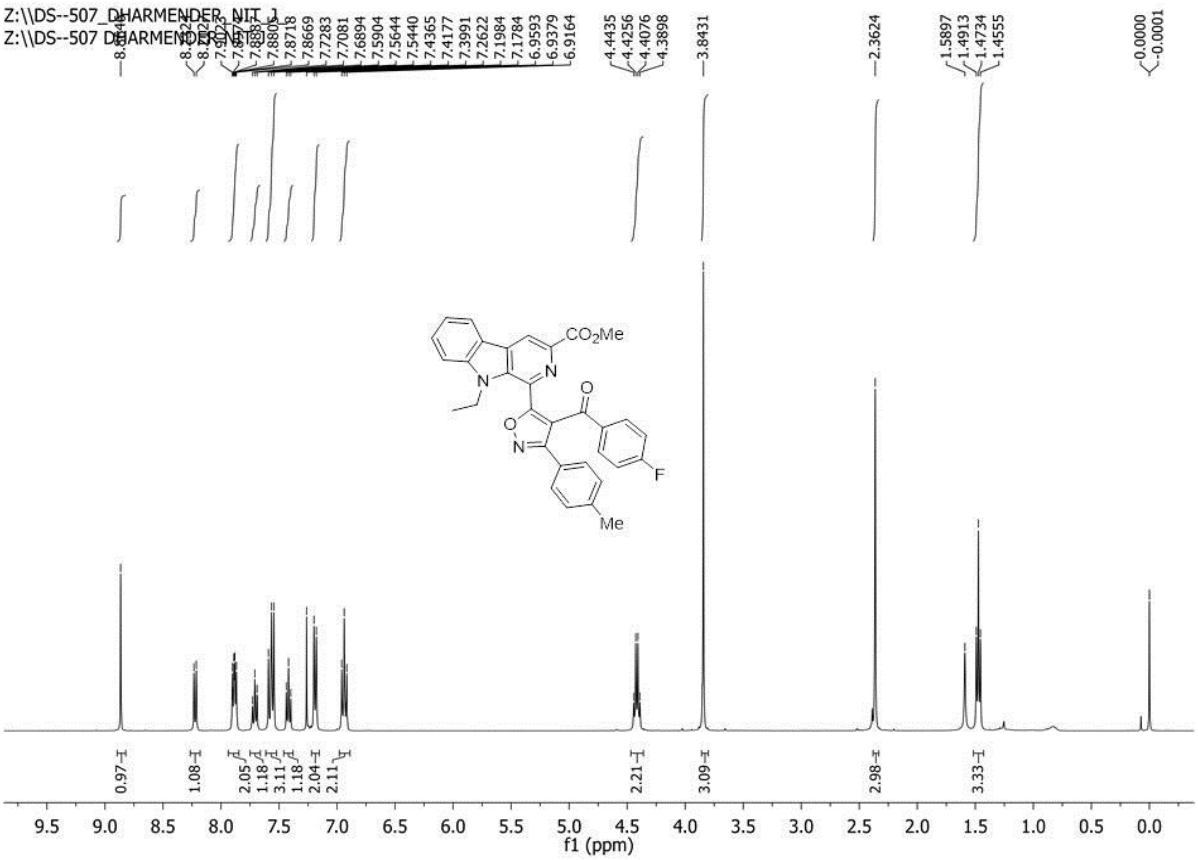


Figure S-57:- ^{1}H-NMR spectrum of methyl 9-ethyl-1-(4-(4-fluorobenzoyl)-3-(*p*-tolyl)isoxazol-5-yl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(18cC).**

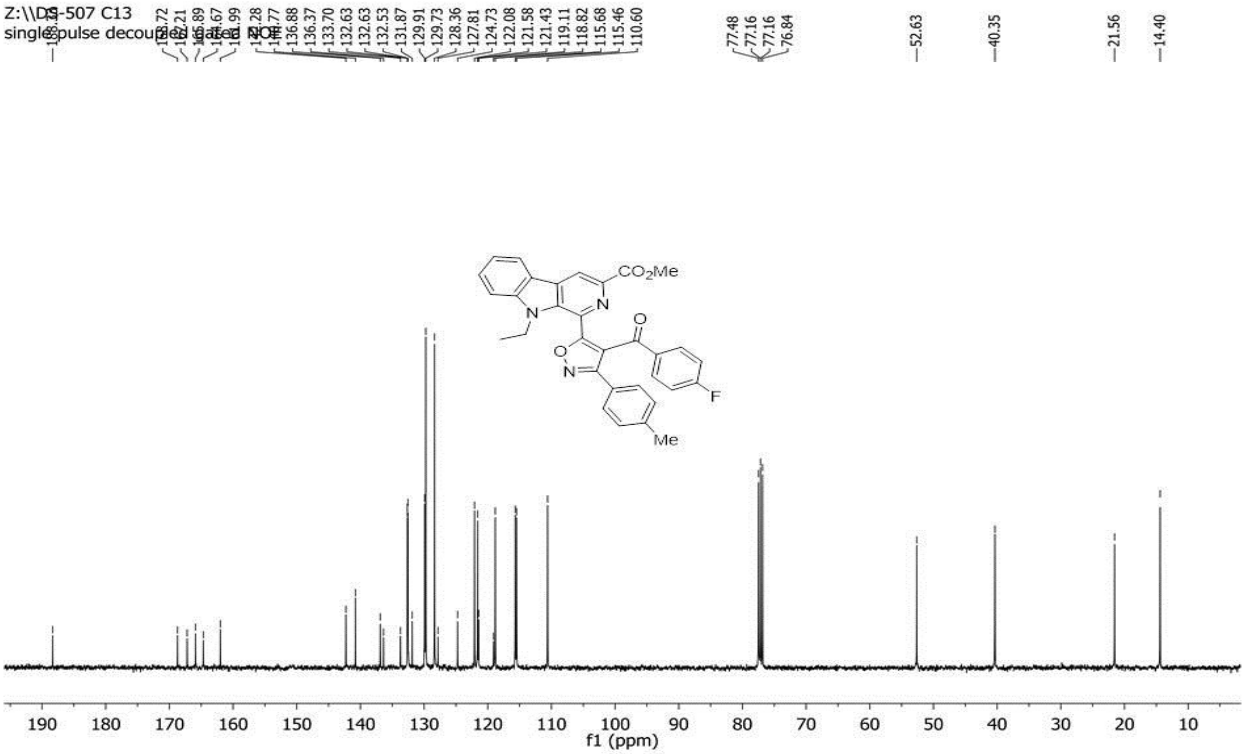


Figure S-58:- ^{13}C-NMR spectrum of methyl 9-ethyl-1-(4-(4-fluorobenzoyl)-3-(*p*-tolyl)isoxazol-5-yl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(18cC).**

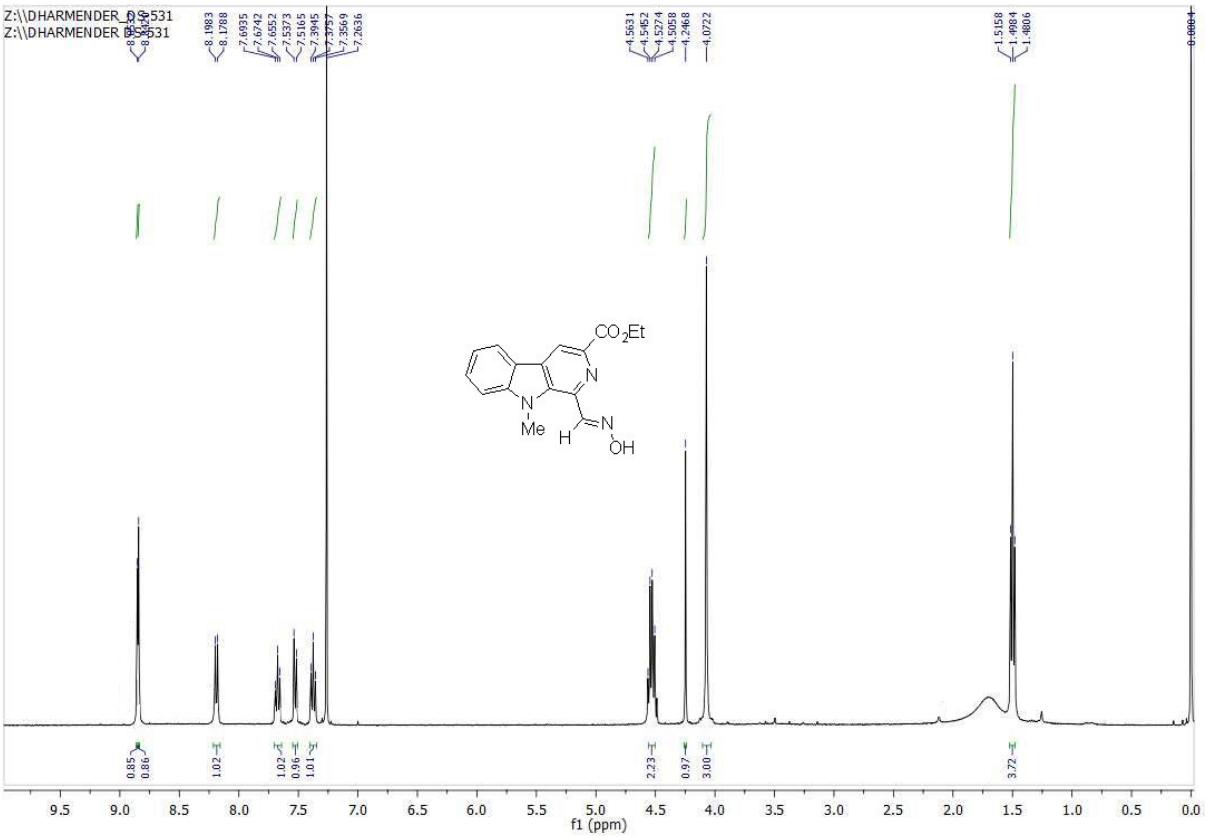


Figure S-59:- ^{1}H-NMR spectrum of (*E*)-ethyl 1-((hydroxyimino)methyl)-9-methyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(19).**

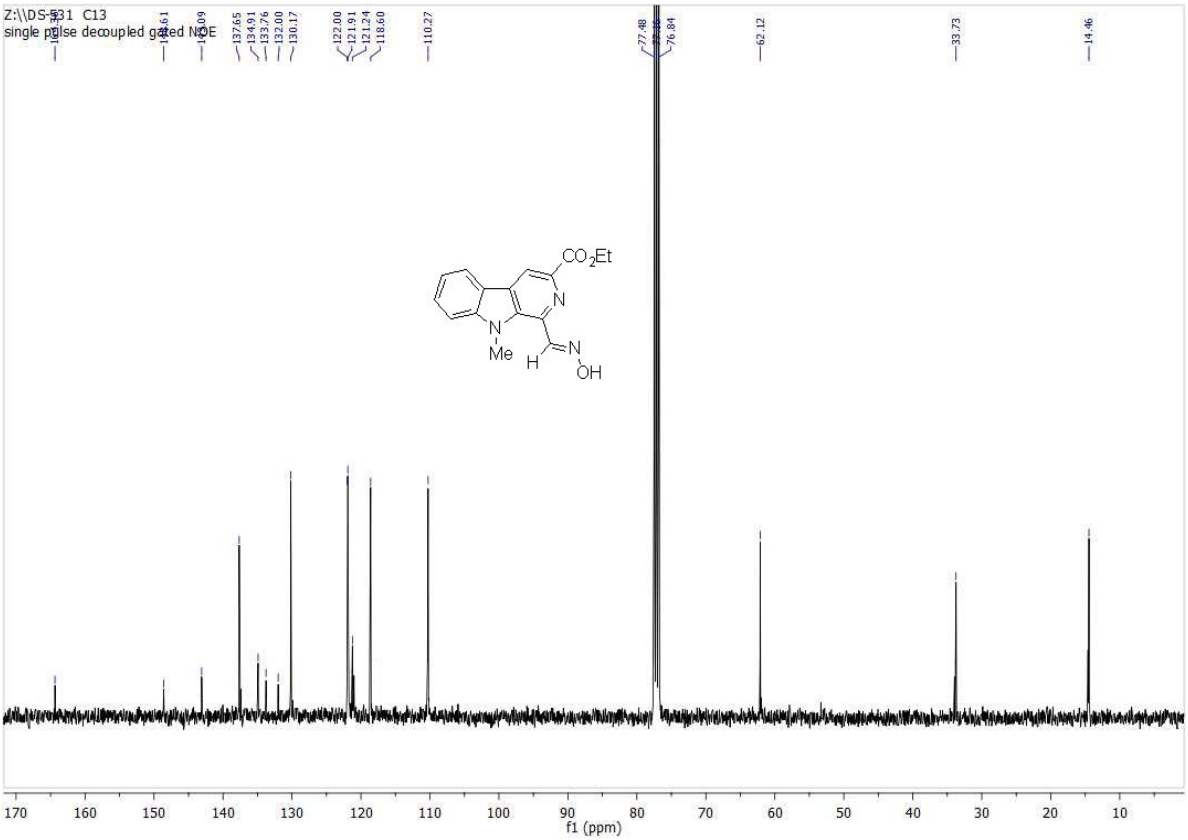


Figure S-60:- ^{13}C-NMR spectrum of (*E*)-ethyl 1-((hydroxyimino)methyl)-9-methyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(19).**

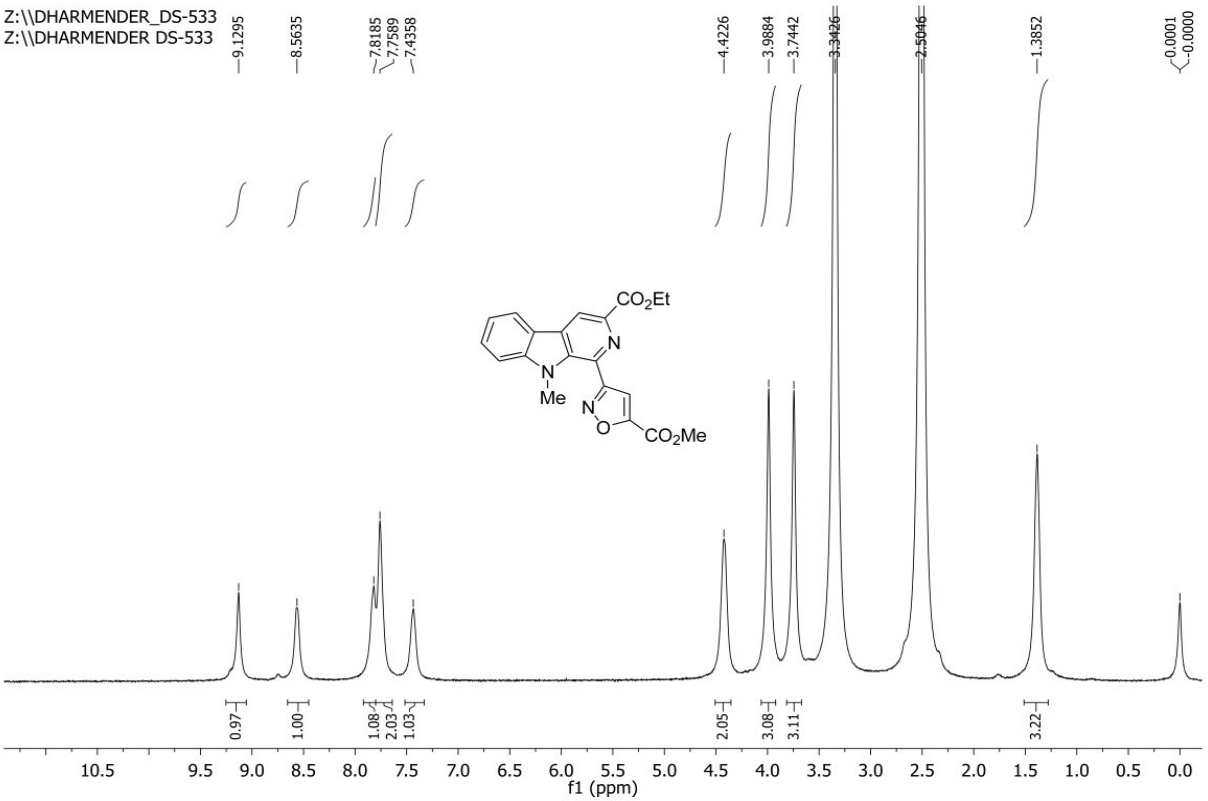


Figure S-61:- ^{1}H-NMR spectrum of methyl 3-(3-(ethoxycarbonyl)-9-methyl-9*H*-pyrido[3,4-*b*]indol-1-yl)isoxazole-5-carboxylate **(20X).**

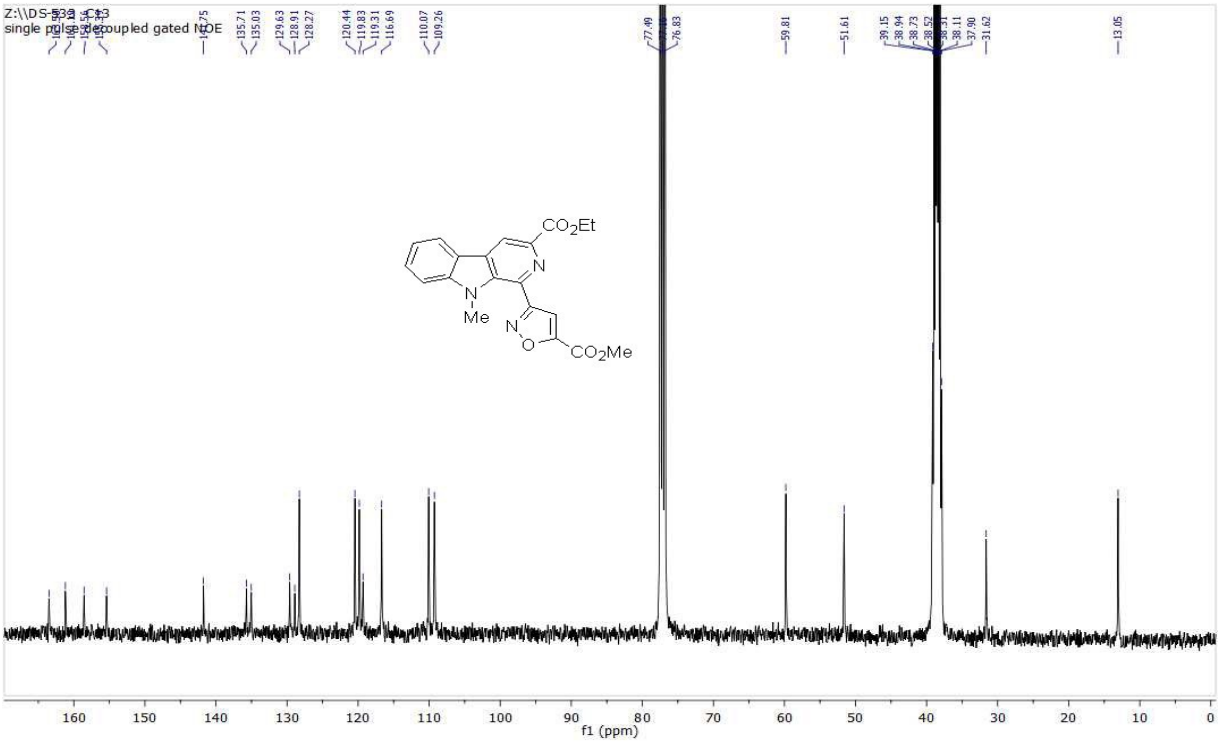


Figure S-62:- ^{13}C-NMR spectrum of methyl 3-(3-(ethoxycarbonyl)-9-methyl-9*H*-pyrido[3,4-*b*]indol-1-yl)isoxazole-5-carboxylate **(20X).**

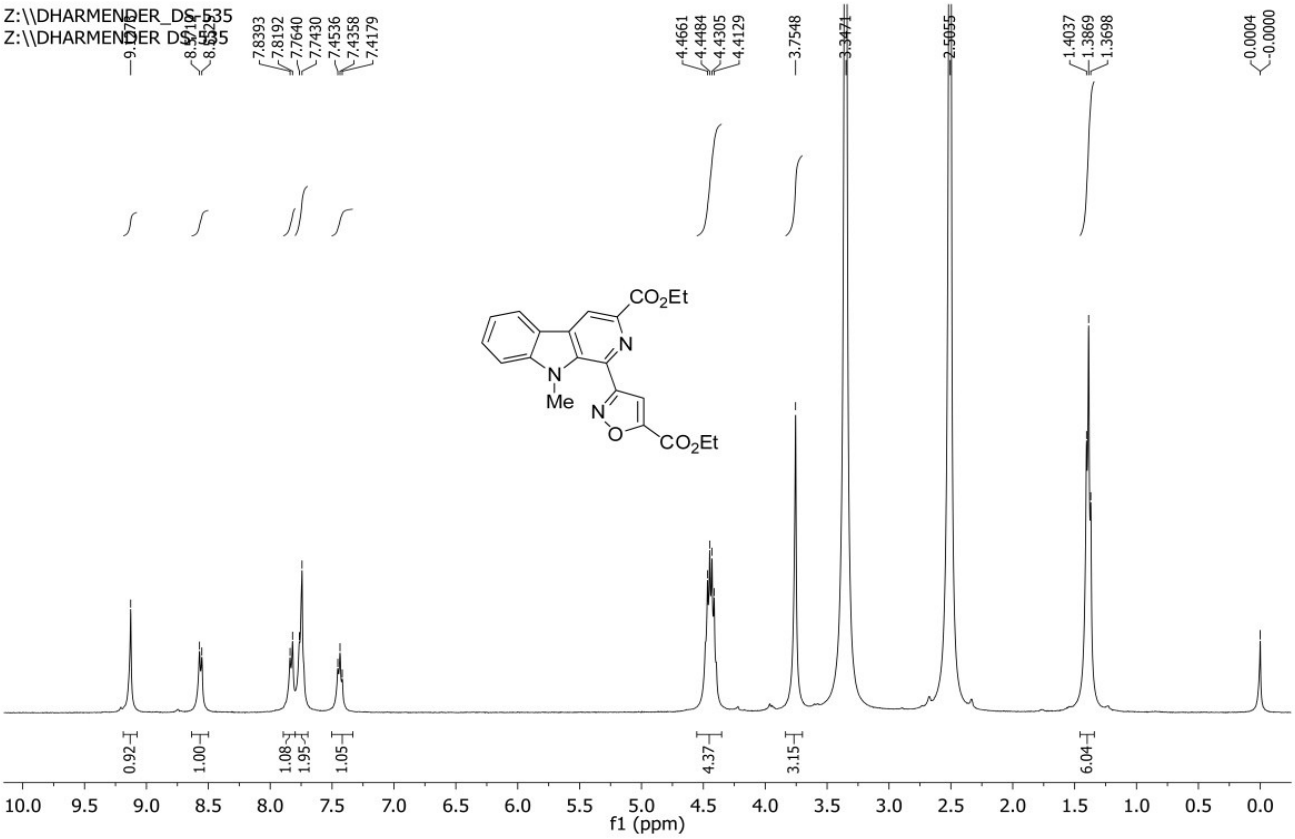


Figure S-63:- ^{1}H-NMR spectrum of ethyl 3-(3-(ethoxycarbonyl)-9-methyl-9*H*-pyrido[3,4-*b*]indol-1-yl)isoxazole-5-carboxylate **(20Y).**

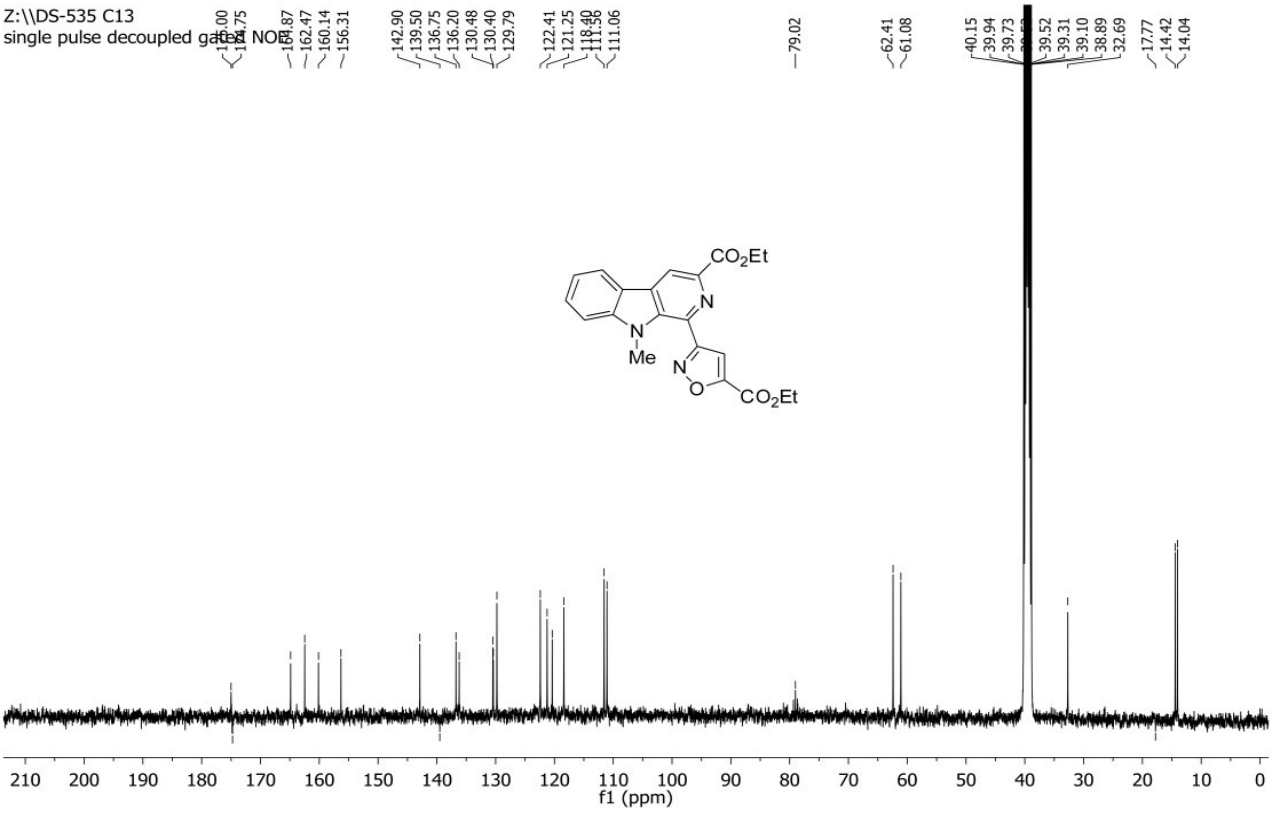


Figure S-64:- ^{13}C-NMR spectrum of ethyl 3-(3-(ethoxycarbonyl)-9-methyl-9*H*-pyrido[3,4-*b*]indol-1-yl)isoxazole-5-carboxylate **(20Y).**

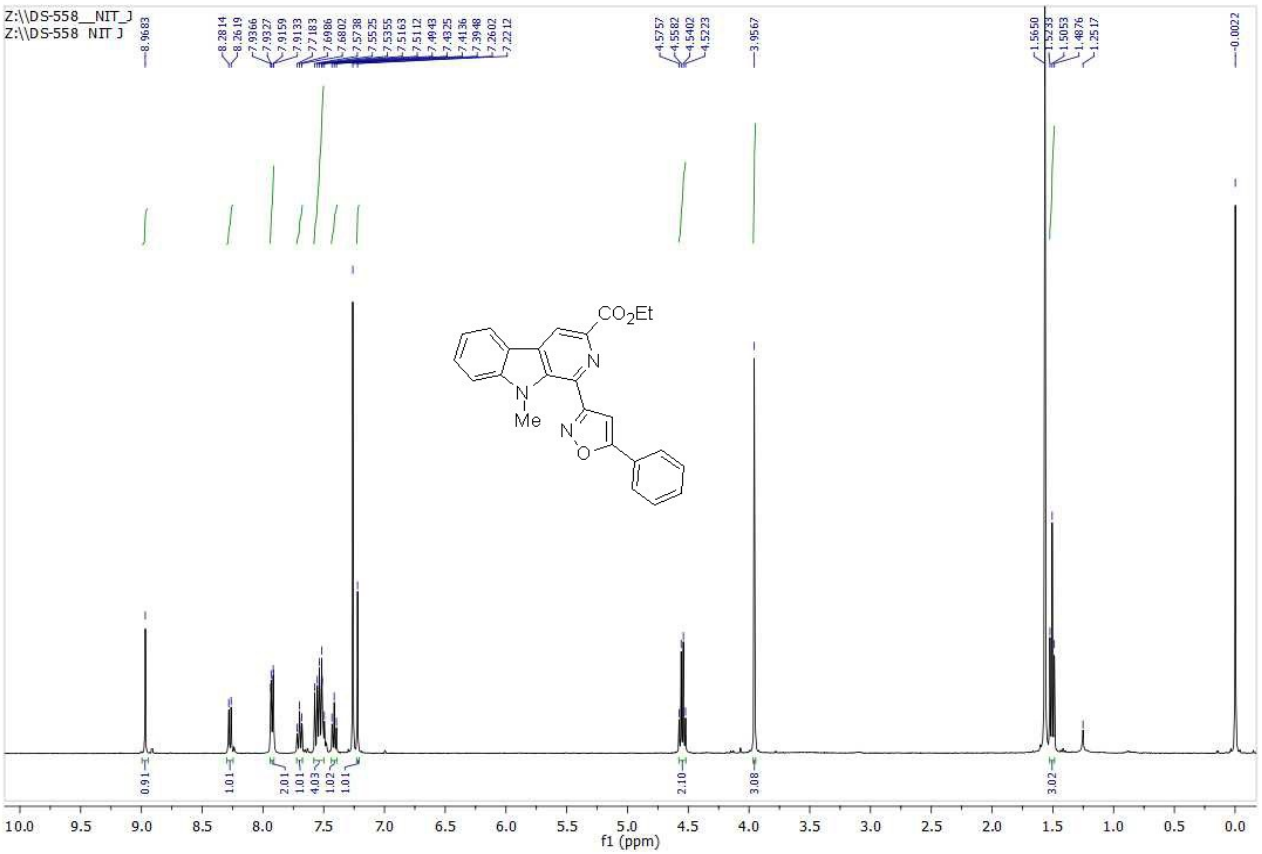


Figure S-65:- ^{1}H-NMR spectrum of ethyl 9-methyl-1-(5-phenylisoxazol-3-yl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(20Z).**

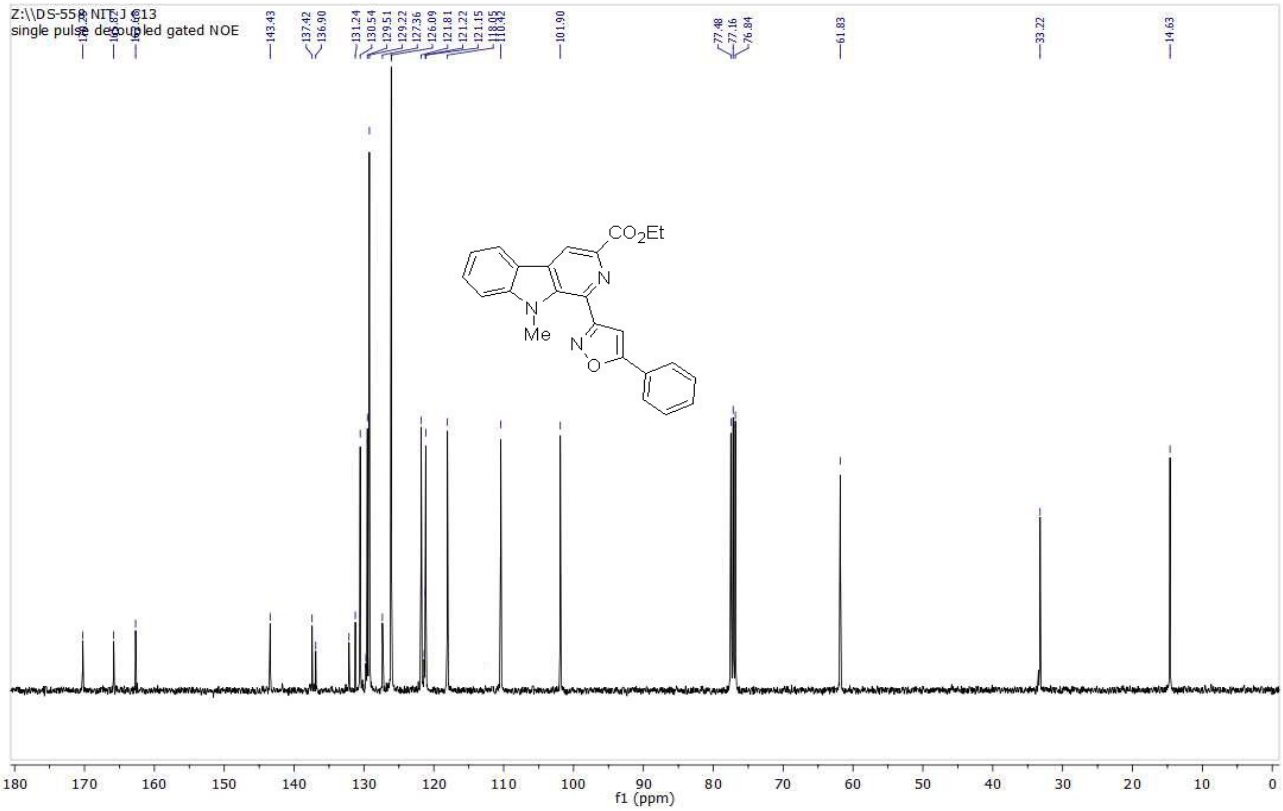


Figure S-66:- ^{13}C-NMR spectrum of ethyl 9-methyl-1-(5-phenylisoxazol-3-yl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(20Z).**

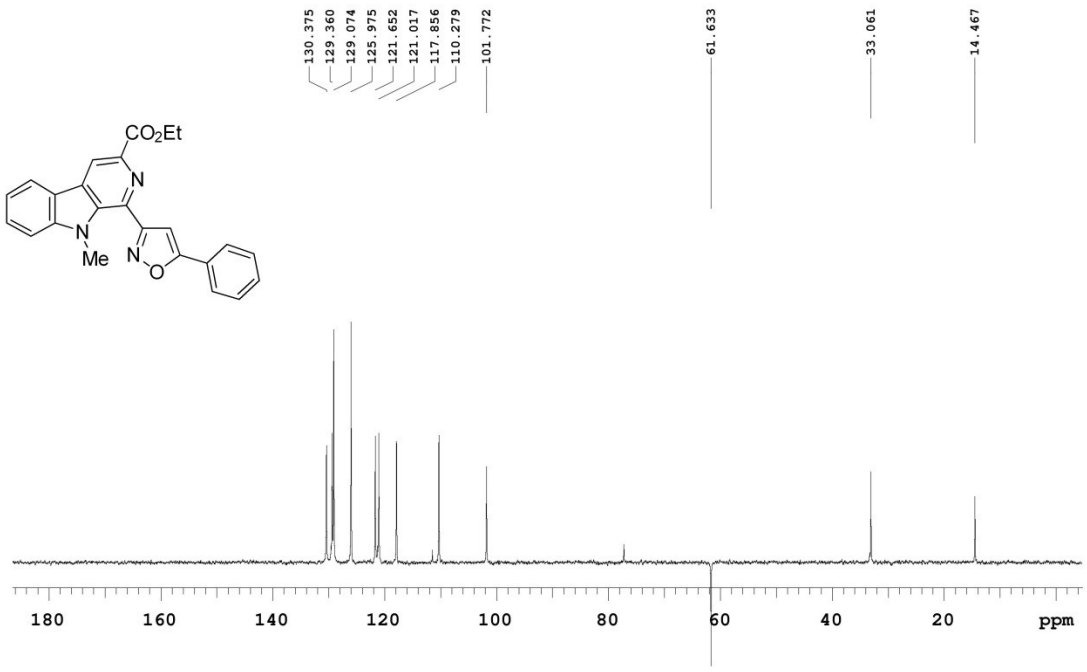


Figure S-67:- DEPT-135 NMR spectrum of ethyl 9-methyl-1-(5-phenylisoxazol-3-yl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(20Z).**

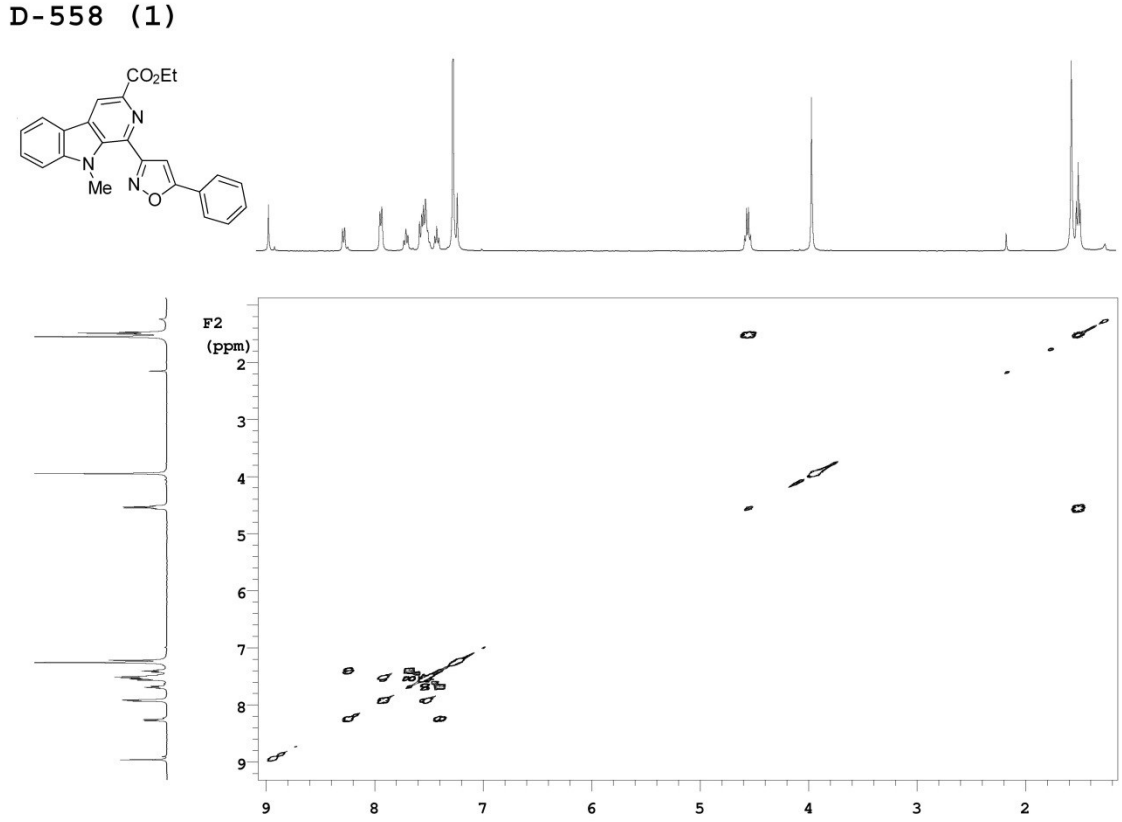


Figure S-68:- COSY-NMR spectrum of ethyl 9-methyl-1-(5-phenylisoxazol-3-yl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(20Z).**

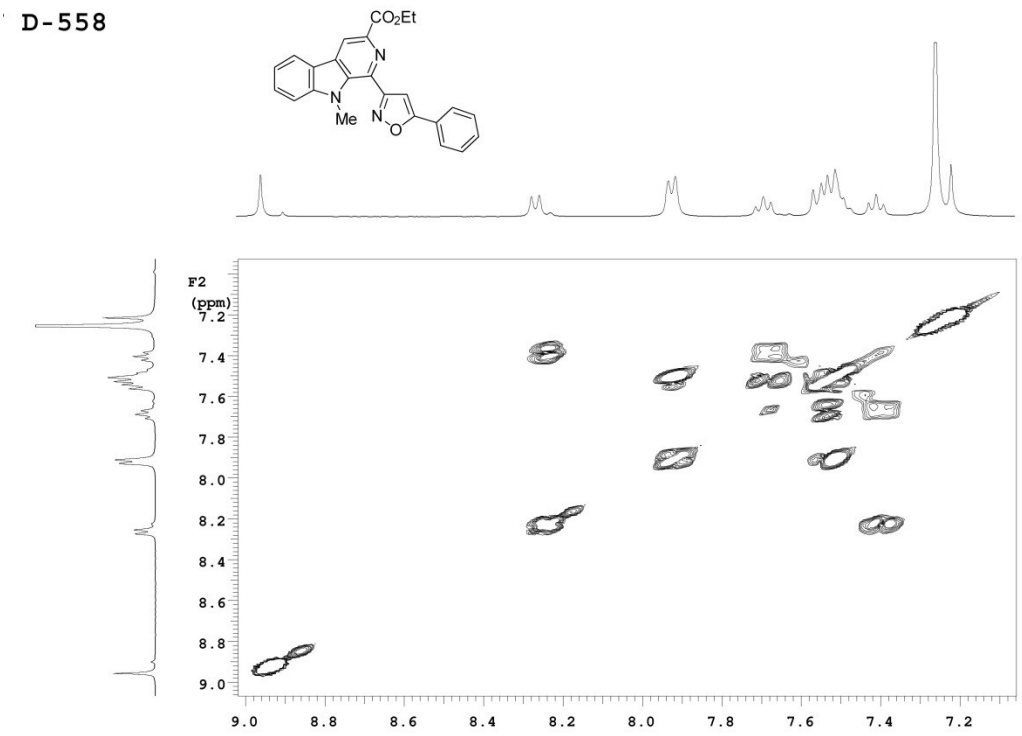


Figure S-69:- Expansion of COSY-NMR spectrum of ethyl 9-methyl-1-(5-phenylisoxazol-3-yl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(20Z)**

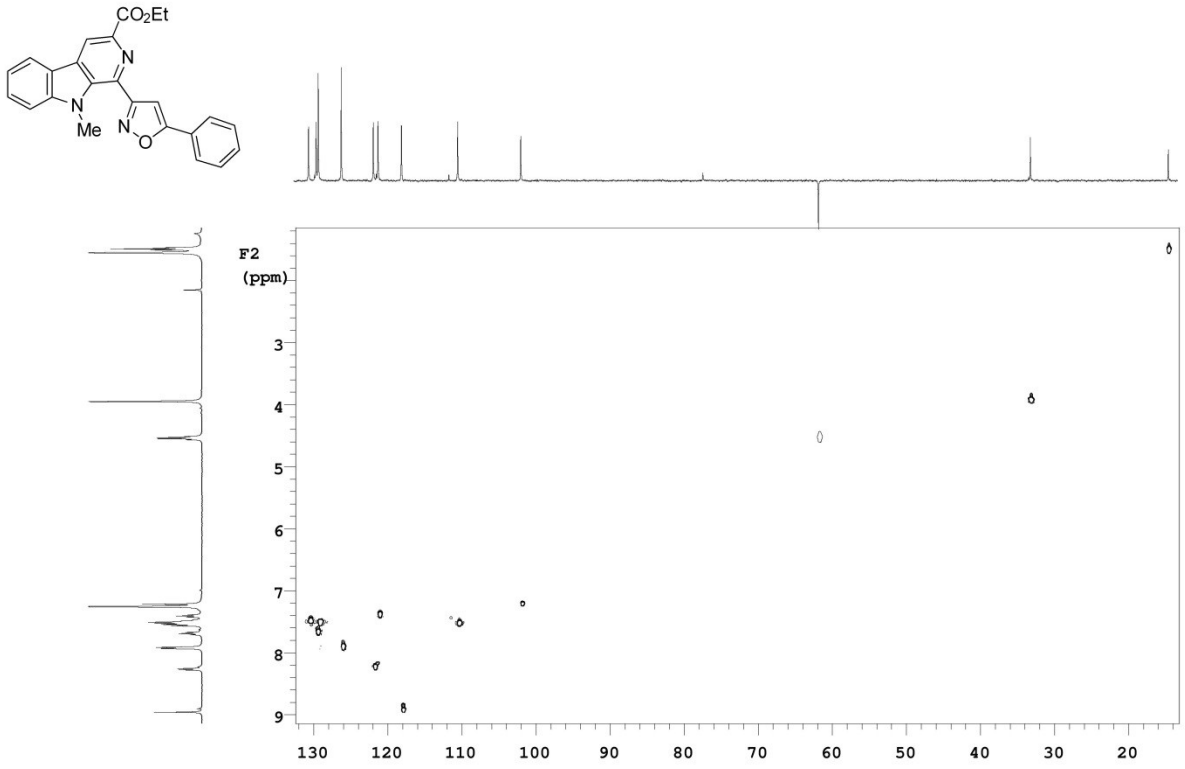


Figure S-70:-HSQC-NMR spectrum of ethyl 9-methyl-1-(5-phenylisoxazol-3-yl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(20Z)**

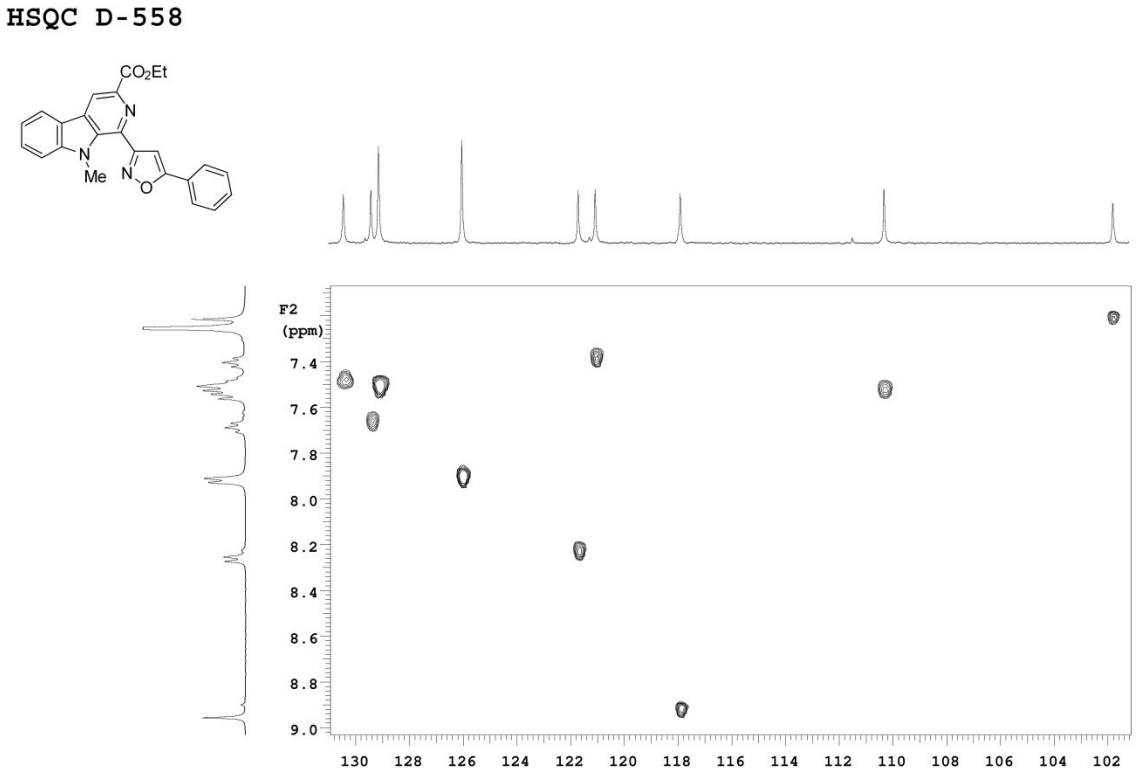


Figure S-71:- Expansion of HSQC-NMR spectrum of ethyl 9-methyl-1-(5-phenylisoxazol-3-yl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(20Z)**

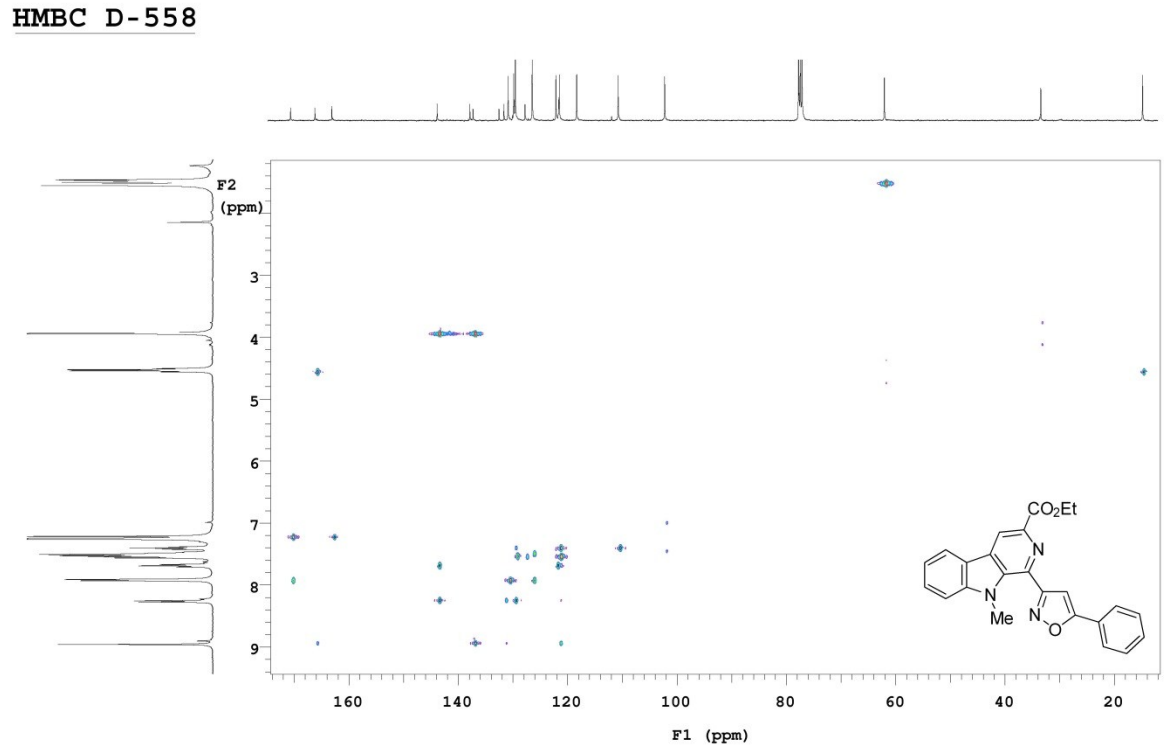


Figure S-72:- HMBC-NMR spectrum of ethyl 9-methyl-1-(5-phenylisoxazol-3-yl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(20Z)**

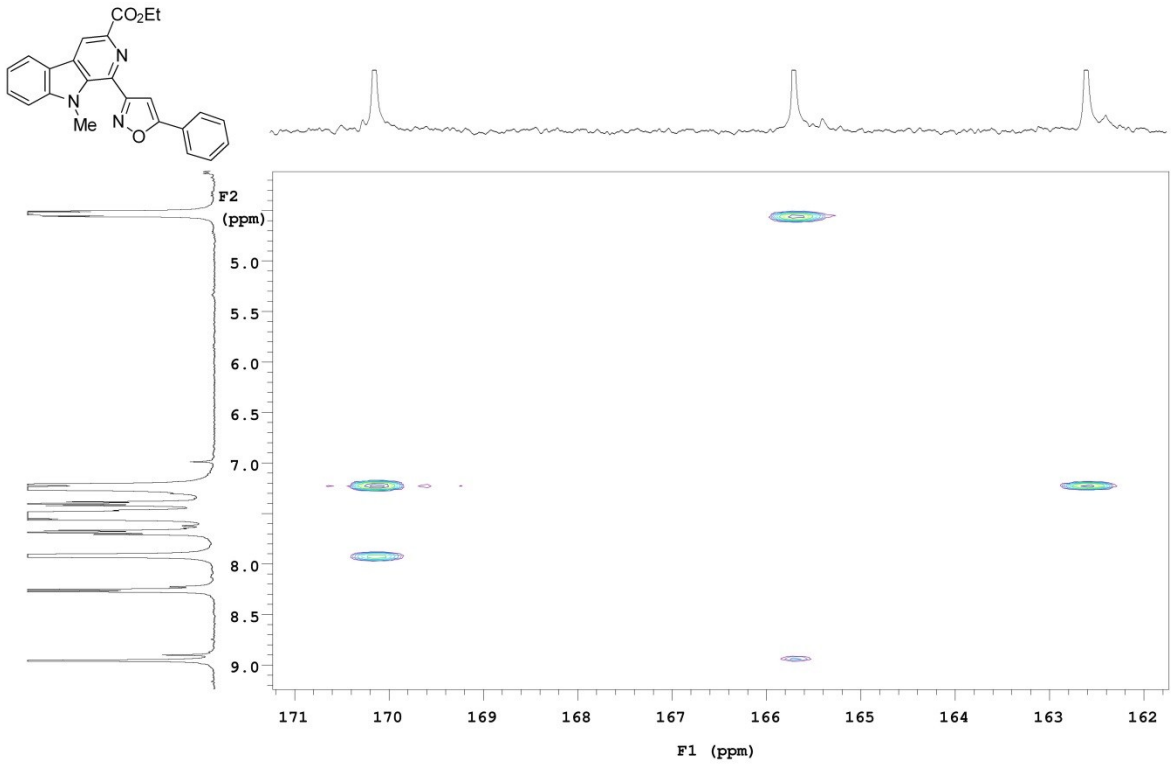


Figure S-73:- Expansion of HMBC-NMR spectrum of ethyl 9-methyl-1-(5-phenylisoxazol-3-yl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(20Z)**