Supplementary Information

Biocompatible *de novo* Indolylchalcones as Platelet Aggregation Inhibition and Diabetic Wound Healing Agents

Sumit Kumar,[a,b#] Radhika Chaurasia,[c#] Gaurav Kumar,[a#] Arun K. Sharma,[d] Ijaz Ahmed,[e] Alam Nur-E-Kamal,[e] Monalisa Mukherjee,[c*] Brajendra K. Singh,[a*] and Virinder S. Parmar[a,b,c,f*]

[a]*Bioorganic Laboratory, Department of Chemistry, University of Delhi, Delhi 110007, India*

[b]*Department of Chemistry and Environmental Science, Medgar Evers College, The City University of New York, 1638 Bedford Avenue, Brooklyn, New York 11225, USA*

[c]*Molecular Science and Engineering Laboratory, Amity Institute of Click Chemistry and Research Studies, Amity University, Noida, Sector 125, Uttar Pradesh 201 313, India*

[d]*Department of Cardiovascular Pharmacology, Amity Institute of Pharmacy, Amity University, Haryana, Gurugram-122413, India*

[e]*Department of Biology, Medgar Evers College, The City University of New York, 1638 Bedford Avenue, Brooklyn, New York 11225, USA*

[f]*Nanoscience Program, CUNY Graduate Center, and Departments of Chemistry, Medgar Evers College and City College, 160 Convent Avenue, New York, NY 10031, USA*

[#]***: All authors have equal contributions*** *(SK, RC and GK)*

***Corresponding Authors:** Professor Virinder S. Parmar (vparmar@mec.cuny.edu); Professor Brajendra K. Singh (singhbk@chemistry.du.ac.in)*

Professor Monalisa Mukherjee (mmukherjee@amity.edu)

Experimental Part and NMR

Table of Contents

1. Experimental

The IR spectra were recorded either on a Perkin–Elmer model 2000 FT-IR or RXI FT-IR spectrometer. Using tetramethylsilane (TMS) as an internal standard, the ^{1}H, and ^{13}C NMR spectra were recorded on the JEOL alpha-400 and or Bruker-Avance Neo 400 FT-NMR spectrometers. The coupling constant (*J*) is expressed in Hz while the chemical shift values are on the δ scale. The FAB-HRMS spectra of all the compounds to measure their accurate masses were recorded on a micro TOF-Q instrument from Bruker Daltonics, Bremen high resolution mass spectrometer in positive mode using the matrix HEDS (bishydroxyethylsulfide) doped with sodium acetate. Indole 3-carboxaldehyde **1**, barium hydroxide $Ba(OH)_2$, acetic, propanic, butyric, and valeric anhydrides **16-19** and different substituted acetophenones **2-8** were purchased from Sigma Aldrich Chemical Co. (USA). Ethanol and dichloromethane (DCM) were distilled over activated molecular sieves (4 A°) prior to use. Analytical TLCs were performed on pre-coated Merck silica gel 60F254 plates; the spots were detected under UV light. Silica gel (100–200 mesh) was used for column chromatography. Melting points were recorded in a sulfuric acid bath and are uncorrected. DMEM (Gibco TM, cat. No. 11-965-118), FBS (Gibco TM, Cat. No. A5256801), Pen/Strep (Gibco TM, Cat. No. 10-378-016), Dimethyl Sulfoxide (Sigma Cat. No. 317275), Thiazolyl Blue Tetrazolium Bromide (Sigma Cat.o 475989).

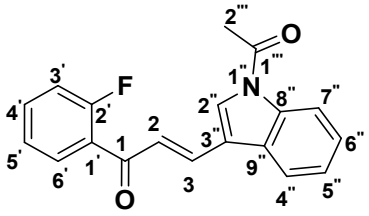
1.1. General procedure for the synthesis of novel indole-based chalcones (9-15):

Different substituted indole-based chalcones (**9-15**) were prepared by magnetic stirring of different substituted acetophenones (**2-8**) (0.0378 mol) in dry distilled ethanol and fused barium hydroxide (0.05 mol) for 10-15 minutes and then indole 3-carboxaldehyde **1** (500 mg, 0.0056 mol) was added at room temperature. The progress of the reaction was monitored by thin layer chromatography (TLC). Reaction was completed after 24 hours. After completion of reaction, excess of ethanol was evaporated off and then reaction mixture was poured over crushed ice and extracted with ethyl acetate. The organic layer was then evaporated under reduced pressure and the crude product obtained was purified by column chromatography (30:70, ethyl acetate:hexane) to afford indole-based chalcones (**9-15**) as dark yellow solid in 73 and 86 % yields. The structures of the known compounds **9-15** were further confirmed by comparison of their spectral data with those reported in the literature.[1,2,3]

1.2. General procedure for *N*-acylated novel indolylfluorochalcones (20-27):

The *N*-acylated novel indolylfluorochalcones **20-23** and **24-27** were synthesized by using indolylfluorochalcones **10** and **11** (500 mg, 0.00188 mol) with different acid anhydrides **16-19** (0.00188 mol) in dichloromethane (DCM) and dimethylaminopyridine (DMAP) as catalyst for overnight stirring at room temperature. After completion of reaction, excess of DCM was evaporated off and then reaction mixture was poured over crushed ice and extracted with ethyl acetate. The organic layer was then evaporated under reduced pressure and the crude product obtained was purified by column chromatography (10:90, ethyl acetate:hexane) to afford *N*-acylated novel indole-based chalcones (**20-23** and **24-27**) as a light yellow solid in 80-91 % yields.

1.2.1. 1-(2-Fluoro-phenyl)-3-(1-acetyl-1*H*-indol-3-yl)-propenone (20)



It was obtained as a light yellow solid (518 mg) in 89 % yield.

Melting Point (M. Pt.): 126-128 ˚C.

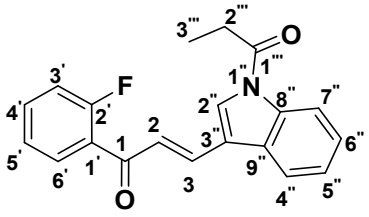
IR (KBr): 1715 (N-*C*=*O*), 1658 (C=O), 1611, 1595, 1453, 1020, 818, 623, 424 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 2.69 (3H, s, C-2'''H), 7.17-7.22 (1H, m, C-6''H), 7.26-7.30 (1H, m, C-5''H), 7.38-7.46 (2H, m, C-4''H, & C-7''H), 7.52-7.61 (2H, m, C-5'H & C-3H), 7.76 (1H, brs, C-2H), 7.85-7.94 (3H, m, C-3'H, C-4'H & C-6'H) and 8.48-8.50 (1H, m, C-2''H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 24.04 (C-2'''), 116.63 (d, *J* = 23.2 Hz, C-3'), 116.99 (C-4''), 118.92 (C-3''), 120.40 (C-5''), 124.64 (d, *J* = 3.7 Hz, C-5'), 124.71 (C-6''), 125.73 (d, *J* = 7.3 Hz, C-6'), 126.27 (C-7''), 127.03 (C-9''), 127.16 & 127.79 (C-2'' & C-8''), 129.01 (C-2), 131.11 (d, *J* = 2.8 Hz, C-3), 134.6 (d, *J* = 9.0 Hz, C-4'), 136.45 (d, *J* = 69.9 Hz, C-1'), 161.38 (d, *J* = 252.9 Hz, C-2'), 168.43 (C-1''') and 188.72 (d, *J* = 2.9 Hz, C-1).

FAB-HRMS: Calcd. for $[M+Na]^+$ $C_{19}H_{14}FNO_2Na$; 330.0901. Found: 330.0887.

1.2.2. 1-(2-Fluoro-phenyl)-3-(1-propionyl-1*H*-indol-3-yl)-propenone (21)



It was obtained as a light yellow solid (509 mg) in 84 % yield.

Melting Point (M. Pt.): 114-116 ˚C.

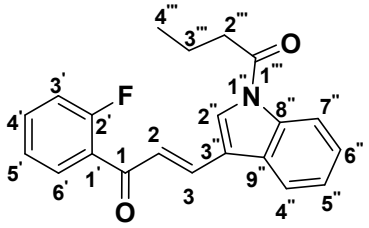
IR (KBr): 1719 (N-*C*=*O*), 1661 (C=O), 1611, 1595, 1542, 1327, 1266, 903, 743, 424 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.34-1.38 (3H, t, C-3'''H), 2.96-3.01 (3H, q, C-2'''H), 7.16-7.21 (1H, m, C-6''H), 7.26-7.30 (1H, m, C-5''H), 7.36-7.45 (2H, m, C-4''H, & C-7''H), 7.51-7.60 (2H, m, C-5'H & C-3H), 7.80 (1H, brs, C-2H), 7.84-7.93 (3H, m, C-3'H, C-4'H & C-6'H) and 8.50-8.52 (1H, m, C-2''H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 8.60 (C-3'''), 29.28 (C-2'''), 116.62 (d, *J* = 23.6 Hz, C-3'), 116.99 (C-4''), 118.76 (C-3''), 120.36 (C-5''), 124.59 (C-6''), 124.63 (d, *J* = 3.6 Hz, C-5'), 125.74 (d, *J* = 7.3 Hz, C-6'), 126.22 (C-7''), 127.06 (C-9''), 127.19 & 127.65 (C-2'' & C-8''), 128.45 (C-2), 131.10 (d, *J* = 2.7 Hz, C-3), 134.02 (d, *J* = 9.1 Hz, C-4'), 136.58 (d, *J* = 65.9 Hz, C-1'), 161.37 (d, *J* = 252.8 Hz, C-2'), 171.99 (C-1''') and 188.61 (d, *J* = 2.7 Hz, C-1).

FAB-HRMS: Calcd. for $[M+Na]^+$ $C_{20}H_{16}FNO_2Na$; 344.1057. Found: 344.1047.

1.2.3. 1-(2-Fluoro-phenyl)-3-(1-butionyl-1*H*-indol-3-yl)-propenone (22)



It was obtained as a light yellow solid (530 mg) in 84 % yield.

Melting Point (M. Pt.): 94-97 ˚C.

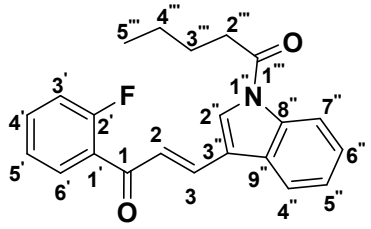
IR (KBr): 1711 (N-*C*=*O*), 1670 (C=O), 1594, 1545, 1202, 1021, 767, 416 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.09-1.12 (3H, t, C-4'''H), 1.90-1.92 (3H, m, C-3'''H), 2.94-2.98 (3H, t, C-2'''H), 7.28-7.33 (1H, m, C-6''H), 7.43-7.52 (3H, m, C-5''H, C-4''H, & C-7''H), 7.61-7.65 (1H, m, C-3H), 7.72-7.75 (1H, m, C-5'H), 7.83-7.86 (2H, m, C-2H & C-3'H), 7.93-8.02 (2H, m, C-4'H & C-6'H) and 8.54-8.56 (1H, m, C-2''H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 13.75 (C-4'''), 18.04 (C-3'''), 37.78 (C-2'''), 115.28 (d, *J* = 21.9 Hz, C-3'), 117.17 (C-4''), 118.69 (C-5''), 119.79 (d, *J* = 3.7 Hz, C-5'), 120.25 (C-3''), 121.37 (C-6''), 124.13 (d, *J* = 2.9 Hz, C-6'), 124.15 (C-7''), 124.63 (C-9''), 126.31 (C-2''), 127.68 (C-8''), 128.53 (C-2), 130.33 (C-3), 130.38 (d, *J* = 7.4 Hz, C-4'), 137.03 (d, *J* = 58.4 Hz, C-1'), 161.85 (d, *J* = 242.7 Hz, C-2'), 171.24 (C-1''') and 188.98 (C-1).

FAB-HRMS: Calcd. for $[M+Na]^+$ $C_{21}H_{18}FNO_2Na$; 358.1214. Found: 358.1206.

1.2.4. 1-(2-Fluoro-phenyl)-3-(1-pentionyl-1*H*-indol-3-yl)-propenone (23)



It was obtained as a light yellow solid (574 mg) in 87 % yield.

Melting Point (M. Pt.): 103-105 ˚C.

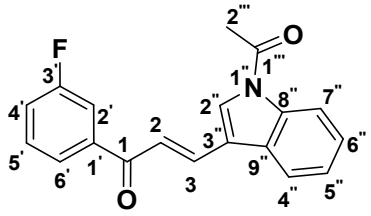
IR (KBr): 1723 (N-*C*=*O*), 1655 (C=O), 1570, 1451, 1380, 1194, 1051, 748, 623, 527 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.99-1.03 (3H, t, C-5'''H), 1.48-1.53 (3H, m, C-4'''H), 1.84-1.87 (3H, m, C-3'''H), 2.95-2.99 (3H, t, C-2'''H), 7.28-7.33 (1H, m, C-6''H), 7.41-7.54 (3H, m, C-5''H, C-4''H, & C-7''H), 7.60-7.64 (1H, m, C-3H), 7.72-7.75 (1H, m, C-5'H), 7.82-7.85 (2H, m, C-2H & C-3'H), 7.93-8.01 (2H, m, C-4'H & C-6'H) and 8.53-8.55 (1H, m, C-2''H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 13.85 (C-5'''), 22.32 (C-4'''), 26.61 (C-3'''), 35.66 (C-2'''), 115.28 (d, *J* = 22.0 Hz, C-3'), 117.17 (C-4''), 118.68 (C-3''), 119.78 (d, *J* = 21.3 Hz, C-5'), 120.25 (C-5''), 121.36 (C-6''), 124.13 (d, *J* = 3.2 Hz, C-6'), 124.62 (C-7''), 126.30 (C-9''), 127.68 & 128.57 (C-2'' & C-8''), 130.32 (C-2), 130.40 (C-3), 137.03 (d, *J* = 18.3 Hz, C-4'), 140.45 (d, *J* = 6.9 Hz, C-1'), 162.96 (d, *J* = 247.8 Hz, C-2'), 171.41 (C-1''') and 188.95 (C-1).

FAB-HRMS: Calcd. for $[M+Na]^+$ $C_{22}H_{20}FNO_2Na$; 372.1370. Found: 372.1375.

1.2.5. 1-(3-Fluoro-phenyl)-3-(1-acetyl-1*H*-indol-3-yl)-propenone (24)



It was obtained as a light yellow solid (489 mg) in 84 % yield.

Melting Point (M. Pt.): 148-150 ˚C.

IR (KBr): 1712 (N-*C*=*O*), 1665 (C=O), 1582, 1383, 1356, 1222, 1016, 746, 527 cm^{-1}.

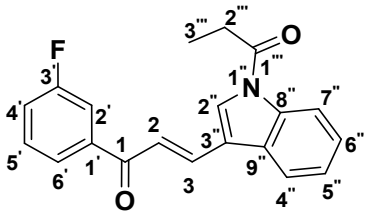
^{1}H NMR (400 MHz, $CDCl_3$): δ 2.70 (3H, s, C-2'''H), 7.27-7.32 (1H, m, C-6''H), 7.41-7.46 (2H, m, C-5''H & C-7''H), 7.48-7.53 (1H, m, C-4''H), 7.60-7.64 (1H, m, C-3H), 7.71-7.74 (1H, m, C-5'H), 7.80 (1H, brs, C-2H), 7.82-8.84 (1H, m, C-2'H) 7.91-8.00 (2H, m, C-4'H & C-6'H) and 8.49-8.51 (1H, m, C-2''H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 24.04 (C-2'''), 115.27 (d, *J* = 22.0 Hz, C-2'), 117.08 (C-4''), 118.85 (C-3''), 119.82 (d, *J* = 21.7 Hz, C-5'), 120.29 (C-5''), 121.47 (C-6''), 124.13 (d, *J* = 3.0 Hz, C-6'), 124.72 (C-7''), 126.35 (C-9''), 127.78 & 128.99 (C-2'' & C-8''), 130.33 (C-2), 130.41

(C-3), 136.87 (d, *J* = 13.3 Hz, C-4'), 140.39 (d, *J* = 6.3 Hz, C-1'), 162.95 (d, *J* = 247.8 Hz, C-3'), 168.41 (C-1''') and 188.90 (d, *J* = 2.5 Hz, C1).

FAB-HRMS: Calcd. for $[M+Na]^+$ $C_{19}H_{14}FNO_2Na$; 330.0901. Found: 330.0883.

1.2.6. 1-(3-Fluoro-phenyl)-3-(1-propionyl-1*H*-indol-3-yl)-propenone (25)



It was obtained as a light yellow solid (531 mg) in 87 % yield.

Melting Point (M. Pt.): 138-140 ˚C.

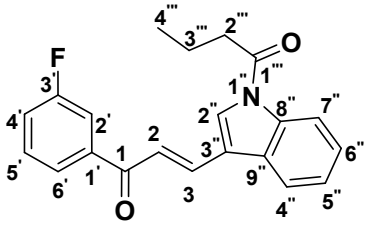
IR (KBr): 1721 (N-*C*=*O*), 1654 (C=O), 1378, 1383, 1342, 1218, 1034, 758, 730, 565 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 1.35-1.39 (3H, t, C-3'''H), 2.97-3.03 (3H, q, C-2'''H), 7.27-7.32 (1H, m, C-6''H), 7.41-7.45 (2H, m, C-5''H & C-7''H), 7.47-7.51 (1H, m, C-4''H), 7.59-7.62 (1H, m, C-3H), 7.70-7.74 (1H, m, C-2H), 7.81-7.83 (2H, m, C-2'H, C-5'H), 7.91-7.99 (2H, m, C-4'H & C-6'H) and 8.51-8.54 (1H, m, C-2''H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 8.60 (C-3'''), 29.31 (C-2'''), 115.26 (d, *J* = 22.0 Hz, C-2'), 117.09 (C-4''), 118.69 (C-3''), 119.78 (d, *J* = 21.7 Hz, C-5'), 120.25 (C-5''), 121.29 (C-6''), 124.12 (d, *J* = 2.9 Hz, C-6'), 124.60 (C-7''), 126.30 (C-9''), 127.64 & 128.45 (C-2'' & C-8''), 130.32 (C-2), 130.39 (C-3), 136.99 (d, *J* = 16.2 Hz, C-4'), 140.42 (d, *J* = 6.0 Hz, C-1'), 162.95 (d, *J* = 247.8 Hz, C-3'), 171.98 (C-1''') and 188.89 (d, *J* = 2.2 Hz, C1).

FAB-HRMS: Calcd. for $[M+Na]^+$ $C_{20}H_{16}FNO_2Na$; 344.1057. Found: 344.1047.

1.2.7. 1-(3-Fluoro-phenyl)-3-(1-butionyl-1*H*-indol-3-yl)-propenone (26)



It was obtained as a light yellow solid (574 mg) in 91 % yield.

Melting Point (M. Pt.): 104-106 ˚C.

IR (KBr): 1708 (N-*C*=*O*), 1652 (C=O), 1545, 1456, 1339, 1257, 1210, 1024, 761, 565 cm^{-1}.

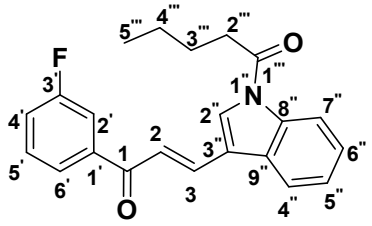
^1H NMR (400 MHz, $CDCl_3$): δ 1.09-1.12 (3H, t, C-4'''H), 1.86-1.96 (3H, m, C-3'''H), 2.94-2.97 (3H, t, C-2'''H), 7.28-7.33 (1H, m, C-6''H), 7.41-7.44 (1H, m, C-5''H), 7.45-7.49 (1H, m, C-

4"H), 7.49-7.54 (1H, m, C-7"H), 7.61-7.65 (1H, m, C-3H), 7.72-7.75 (1H, m, C-5'H), 7.83-7.86 (2H, m, C-2H & C-2'H), 7.93-7.95 (1H, m, C-4'H), 7.98-8.02 (1H, m, C-6'H) and 8.53-8.56 (1H, m, C-2"H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.94 (C-4'"), 19.23 (C-3'"), 38.97 (C-2'"), 116.48 (d, *J* = 21.9 Hz, C-2'), 118.36 (C-4"), 119.88 (C-3"), 120.98 (d, *J* = 3.9 Hz, C-5'), 121.45 (C-5"), 122.56 (C-6"), 125.32 (d, *J* = 2.9 Hz, C-6'), 125.82 (C-7"), 127.50 (C-9"), 128.88 (C-2), 129.72 (C-2"), 131.52 (C-8"), 131.59 (C-3), 138.22 (d, *J* = 18.4 Hz, C-4'), 141.65 (d, *J* = 6.9 Hz, C-1'), 164.15 (d, *J* = 247.9 Hz, C-3'), 172.43 (C-1'") and 190.17 (C-1).

FAB-HRMS: Calcd. for $[M+Na]^+$ $C_{21}H_{18}FNO_2Na$; 358.1214. Found: 358.1198.

1.2.8. 1-(3-Fluoro-phenyl)-3-(1-pentionyl-1*H*-indol-3-yl)-propenone (27)



It was obtained as a light yellow solid (550 mg) in 87 % yield.

Melting Point (M. Pt.): 114-116 ˚C.

IR (KBr): 1723 (N-*C*=*O*), 1648 (C=O), 1545, 1381, 1208, 1058, 823, 720, 648, 511 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.98-1.02 (3H, t, C-5'"H), 1.45-1.52 (3H, m, C-4'"H), 1.81-1.88 (3H, m, C-3'"H), 2.94-2.98 (3H, t, C-2'"H), 7.27-7.32 (1H, m, C-6"H), 7.40-7.48 (2H, m, C-5"H, & C-4"H), 7.49-7.53 (1H, m, C-7"H), 7.60-7.63 (1H, m, C-3H), 7.71-7.74 (1H, m, C-5'H), 7.81-7.85 (2H, m, C-2H & C-2'H), 7.92-7.96 (1H, m, C-4'H), 7.97-8.00 (1H, m, C-6'H) and 8.52-8.54 (1H, m, C-2"H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.29 (C-5'"), 22.76 (C-4'"), 27.05 (C-3'"), 36.10 (C-2'"), 115.72 (d, *J* = 22.0 Hz, C-2'), 117.61 (C-4"), 119.12 (C-3"), 120.22 (d, *J* = 21.3 Hz, C-5'), 120.69 (C-5"), 121.80 (C-6"), 124.57 (d, *J* = 3.2 Hz, C-6'), 125.06 (C-7"), 126.74 (C-9"), 128.12 & 129.01 (C-2" & C-8"), 130.76 (C-2), 130.80 (d, *J* = 7.9 Hz, C-3), 137.47 (d, *J* = 18.3 Hz, C-4'), 140.89 (d, *J* = 6.4 Hz, C-1'), 163.40 (d, *J* = 247.8 Hz, C-3'), 171.85 (C-1'") and 189.39 (C-1).

FAB-HRMS: Calcd. for $[M+Na]^+$ $C_{22}H_{20}FNO_2Na$; 372.1370. Found: 372.1364.

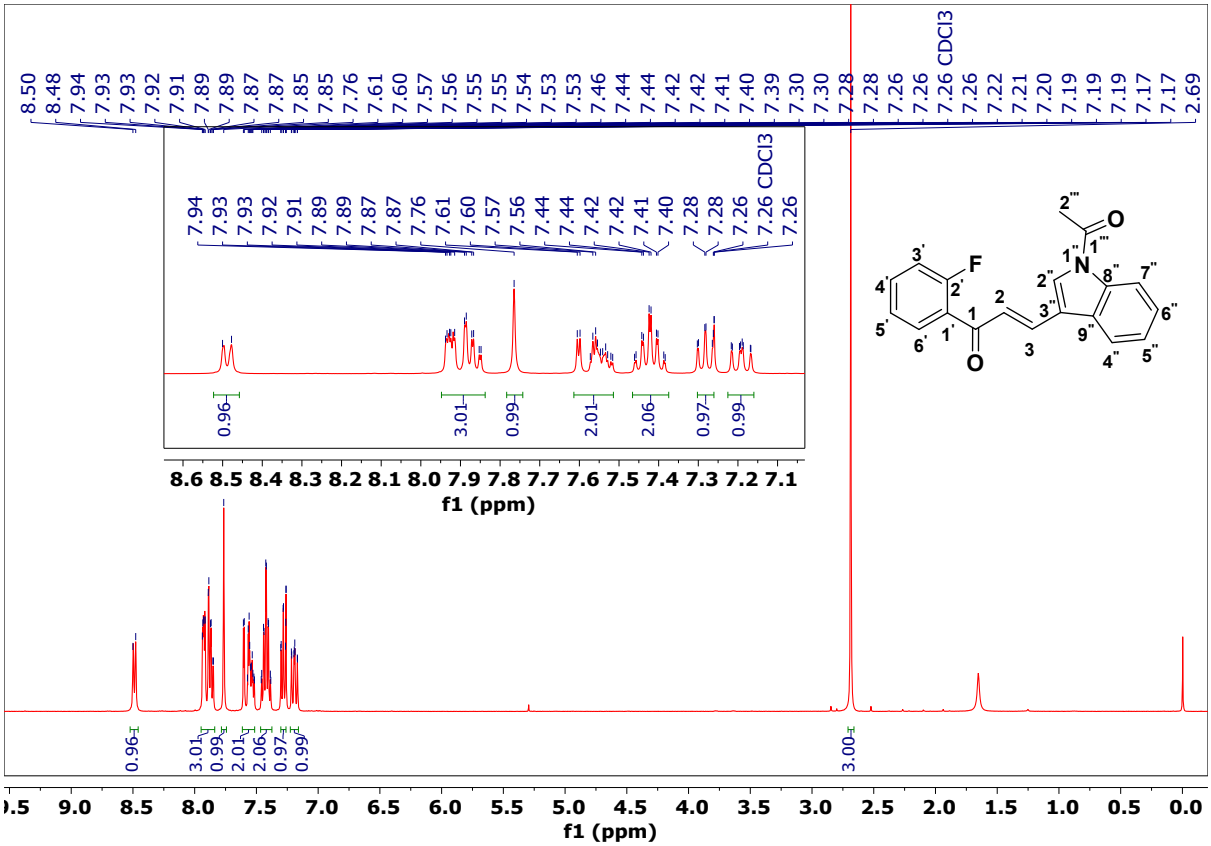


Figure S1: ^{1}H NMR spectrum of compound **20** (400 MHz, $CDCl_3$).

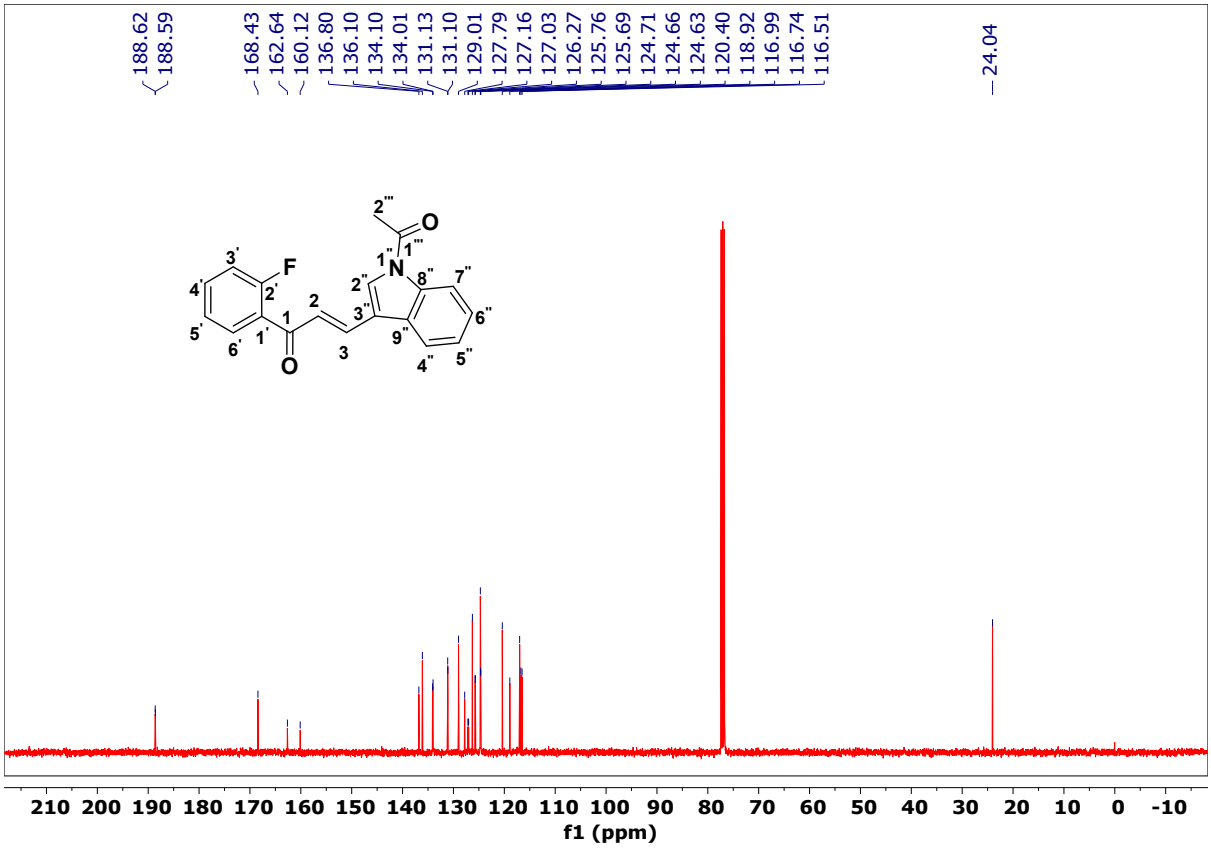


Figure S2: ^{13}C NMR spectrum of compound **20** (100 MHz, $CDCl_3$).

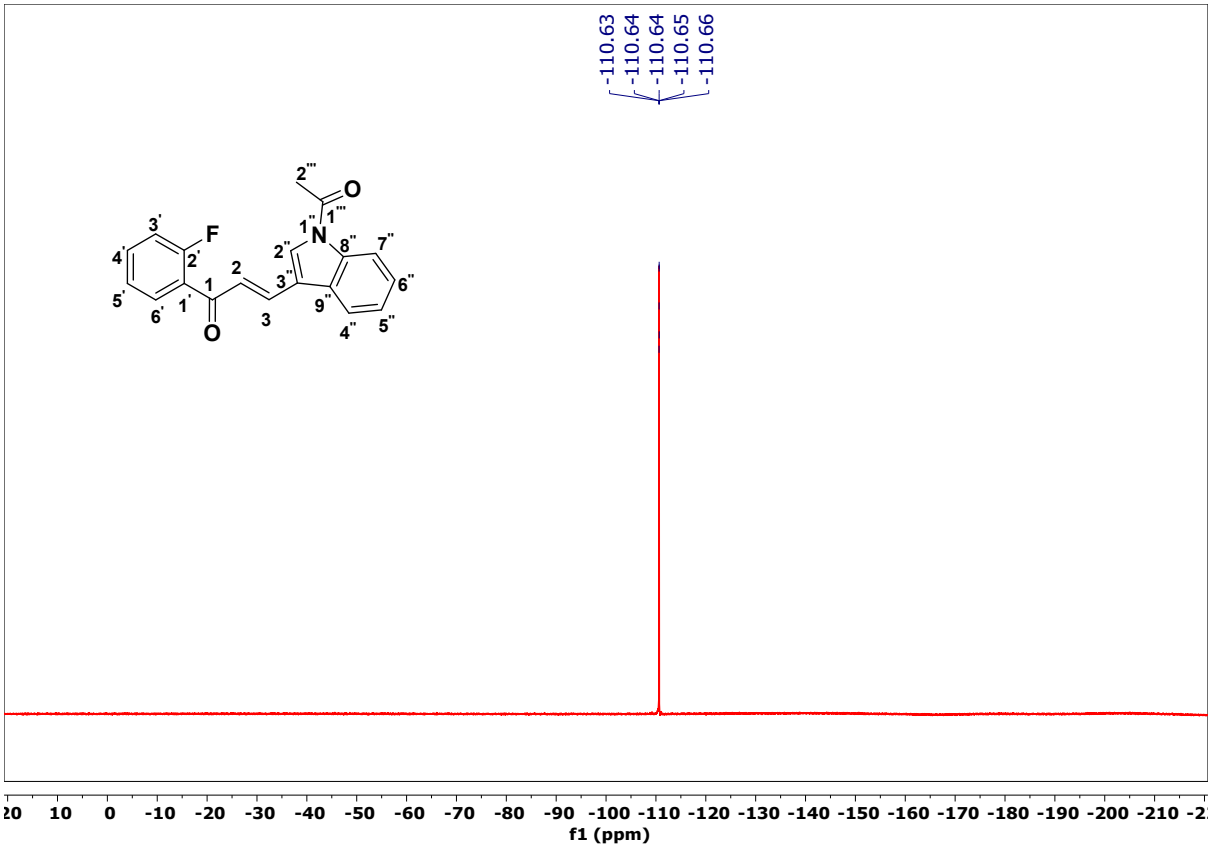


Figure S3: ^{19}F NMR spectrum of compound **20** (377 MHz, $CDCl_3$).

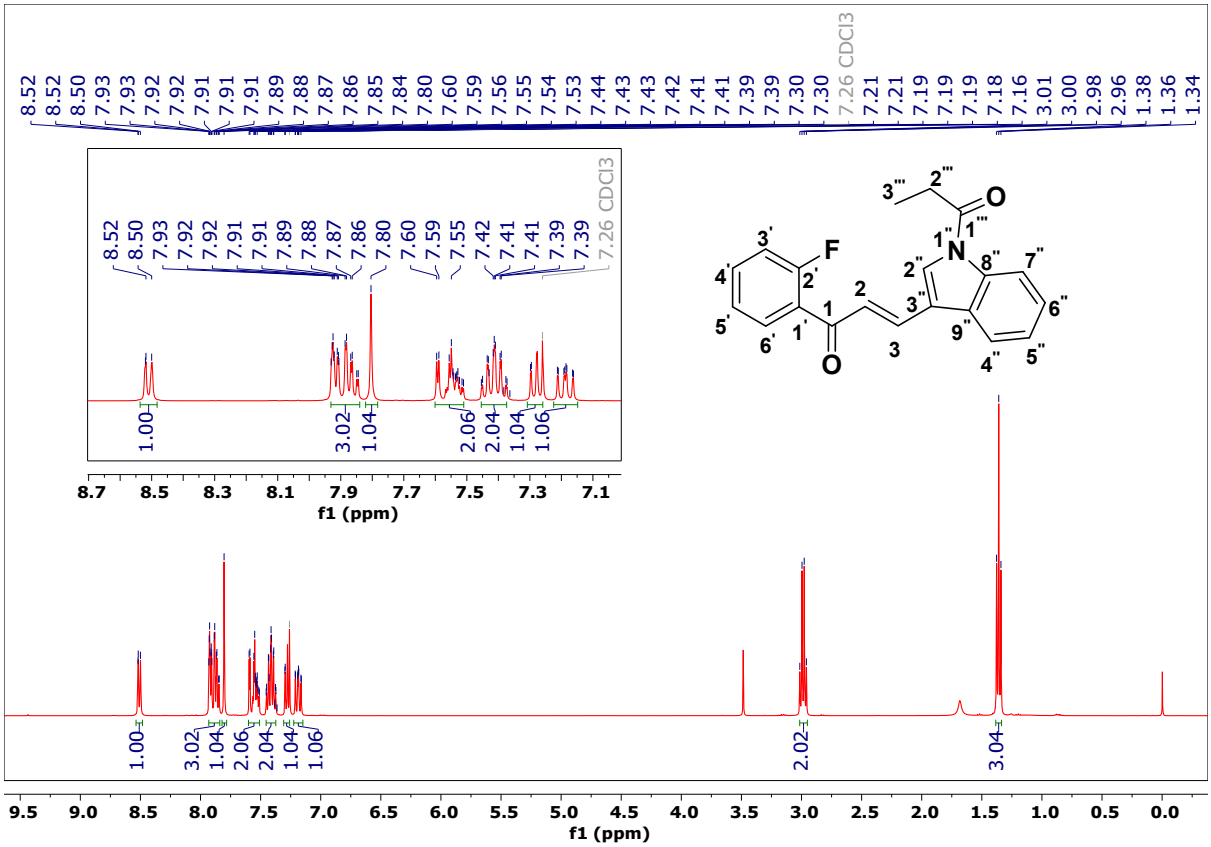


Figure S4: ^{1}H NMR spectrum of compound **21** (400 MHz, $CDCl_3$).

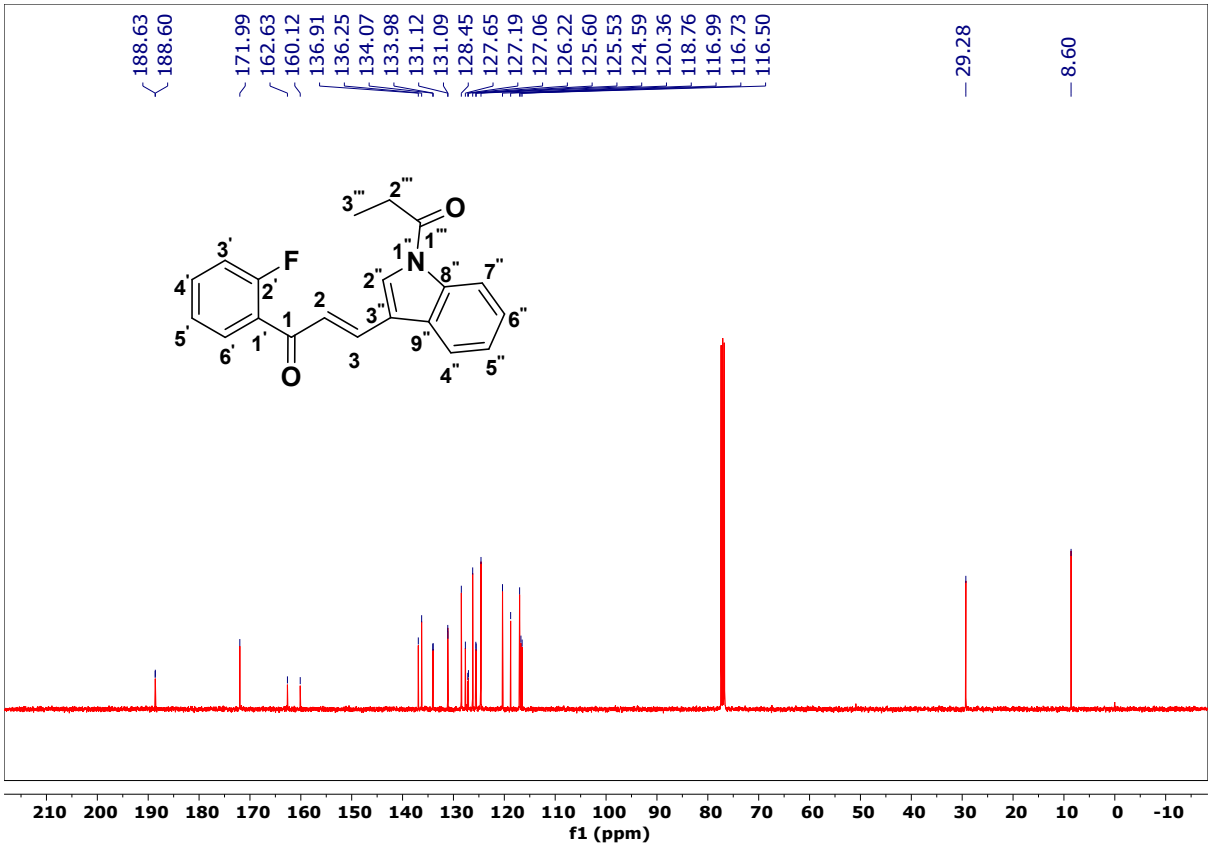


Figure S5: ^{13}C NMR spectrum of compound **21** (100 MHz, $CDCl_3$).

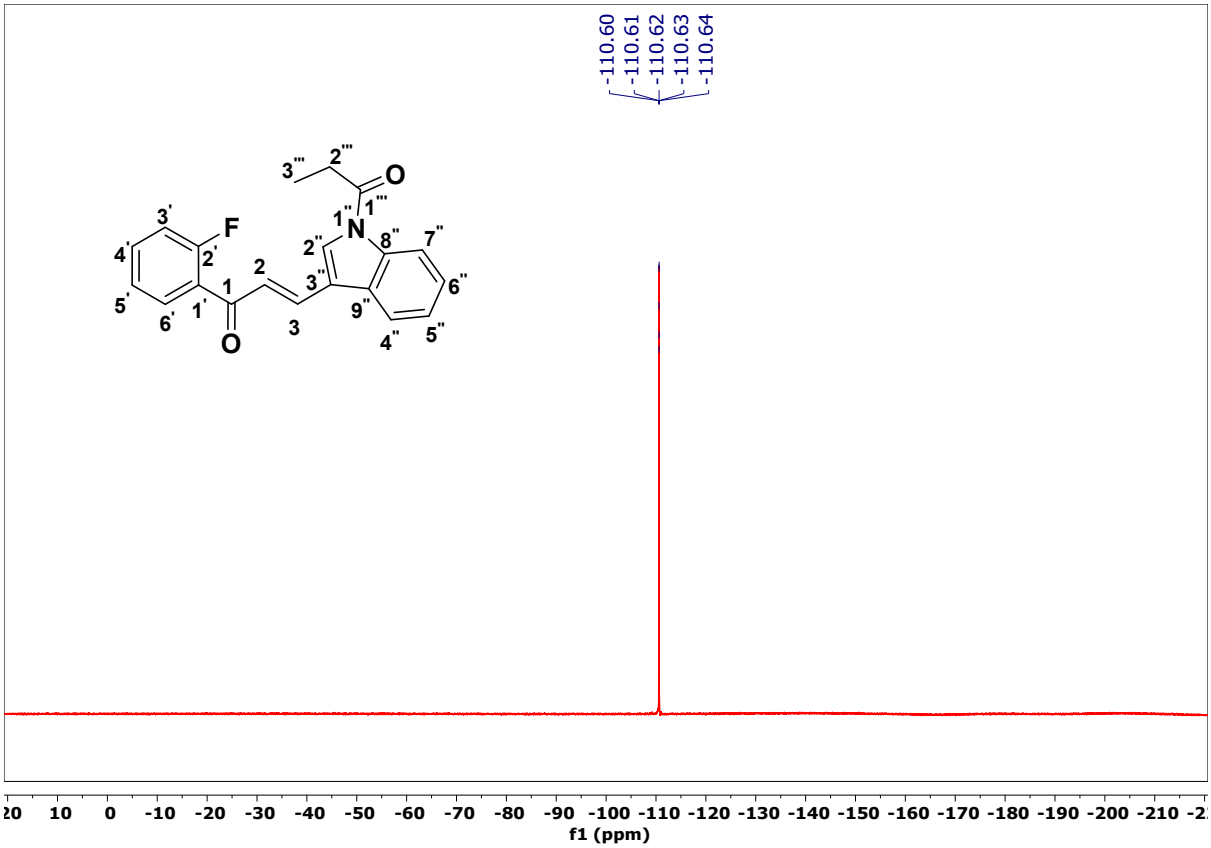


Figure S6: ^{19}F NMR spectrum of compound **21** (377 MHz, $CDCl_3$).

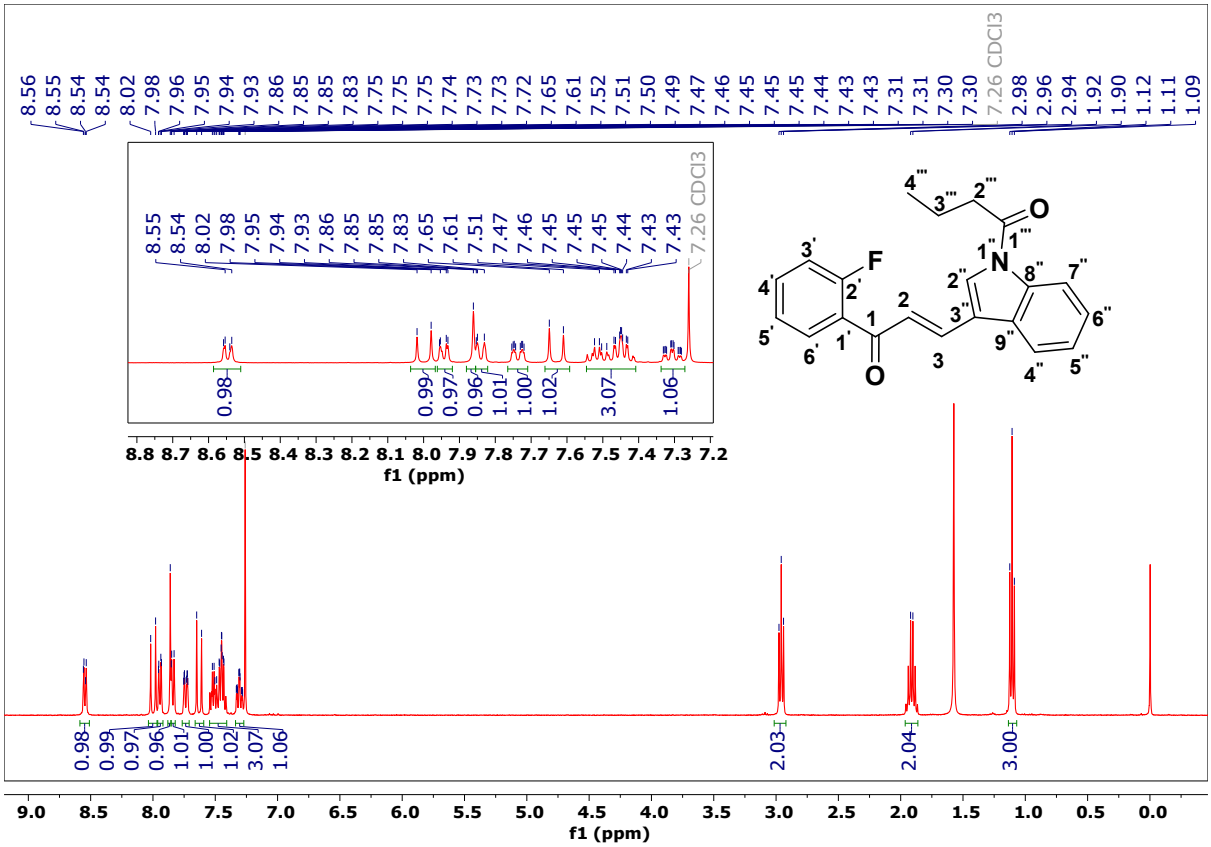


Figure S7: ^{1}H NMR spectrum of compound **22** (400 MHz, $CDCl_3$).

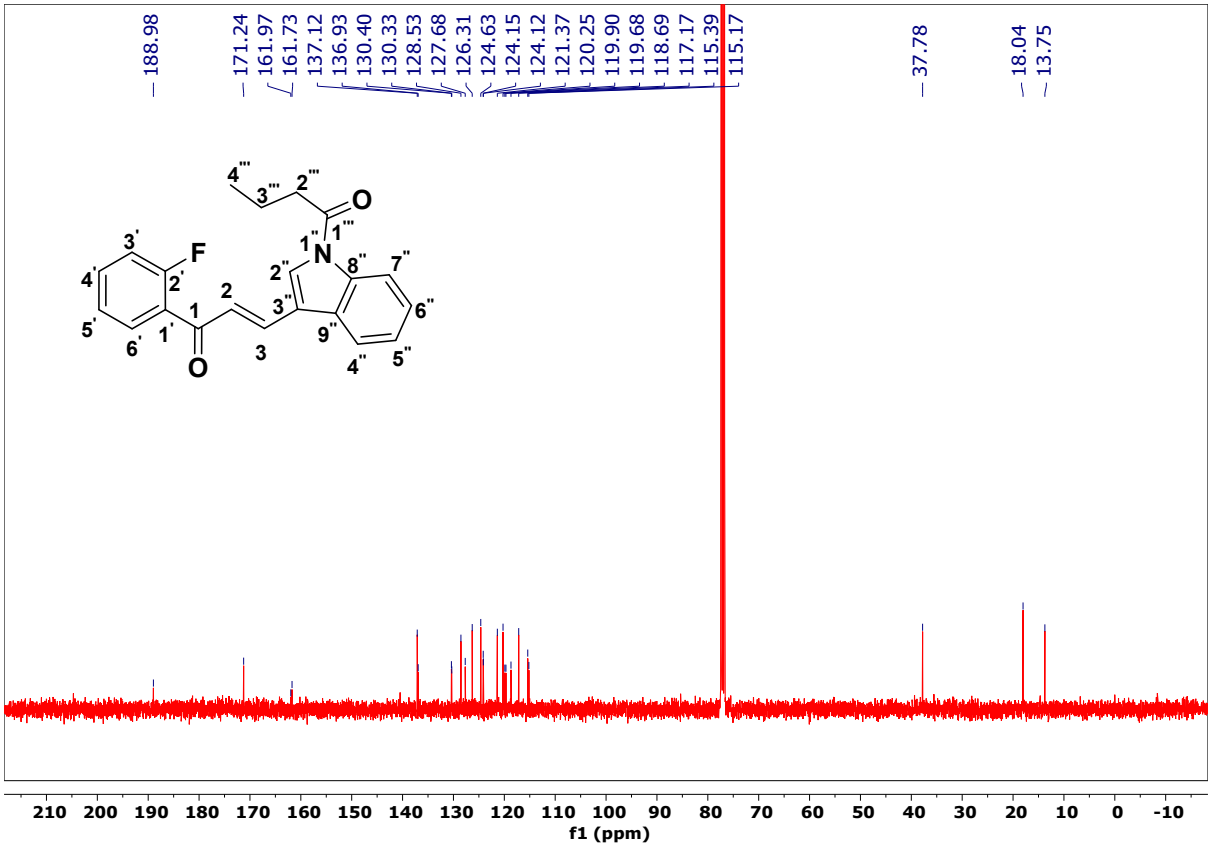


Figure S8: ^{13}C NMR spectrum of compound **22** (100 MHz, $CDCl_3$).

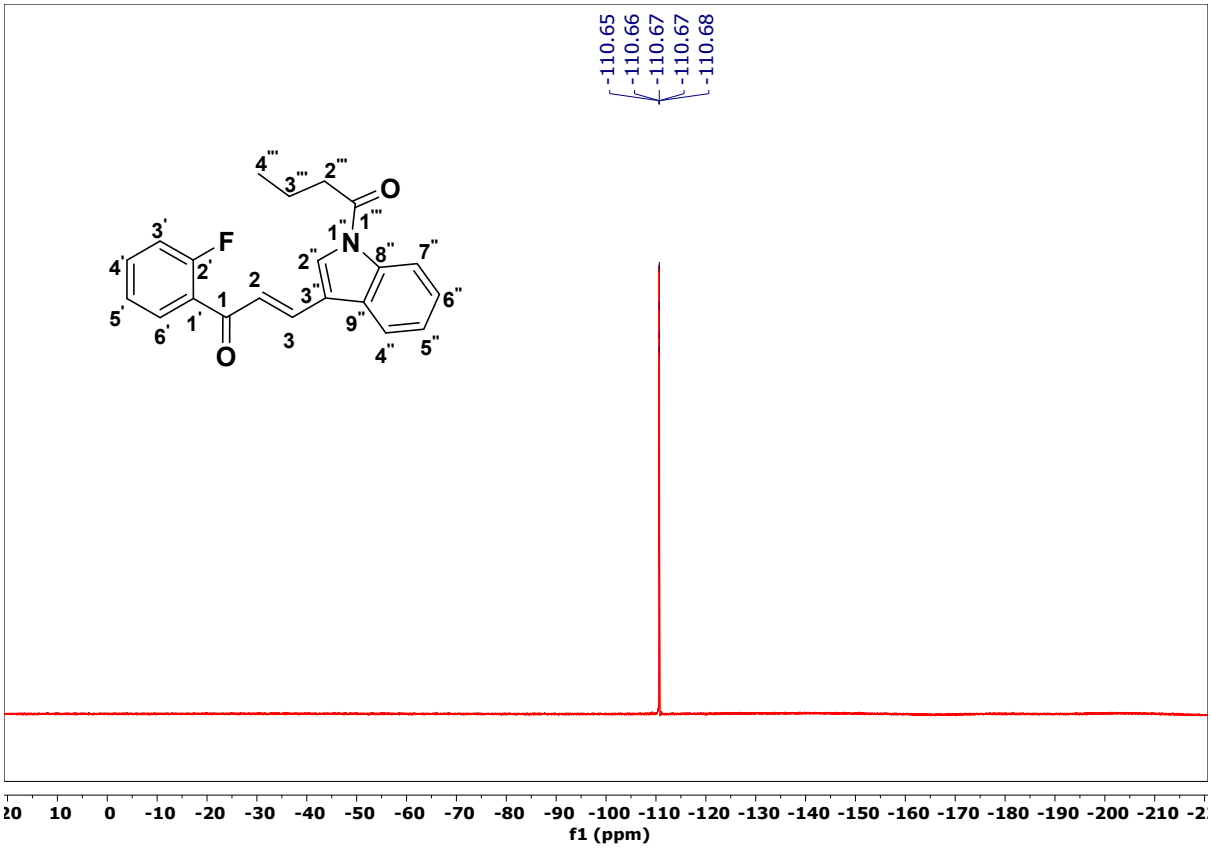


Figure S9: ^{19}F NMR spectrum of compound **22** (377 MHz, $CDCl_3$).

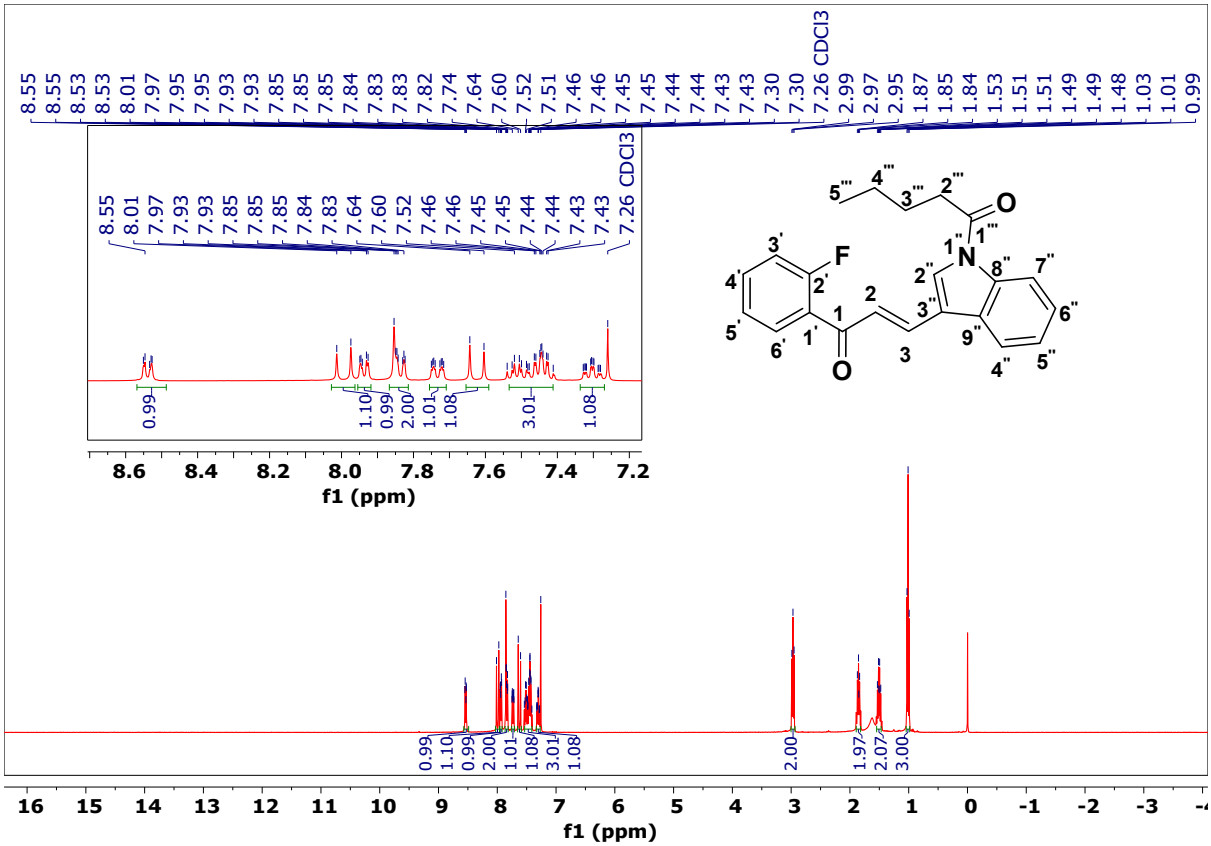


Figure S10: ^{1}H NMR spectrum of compound **23** (400 MHz, $CDCl_3$).

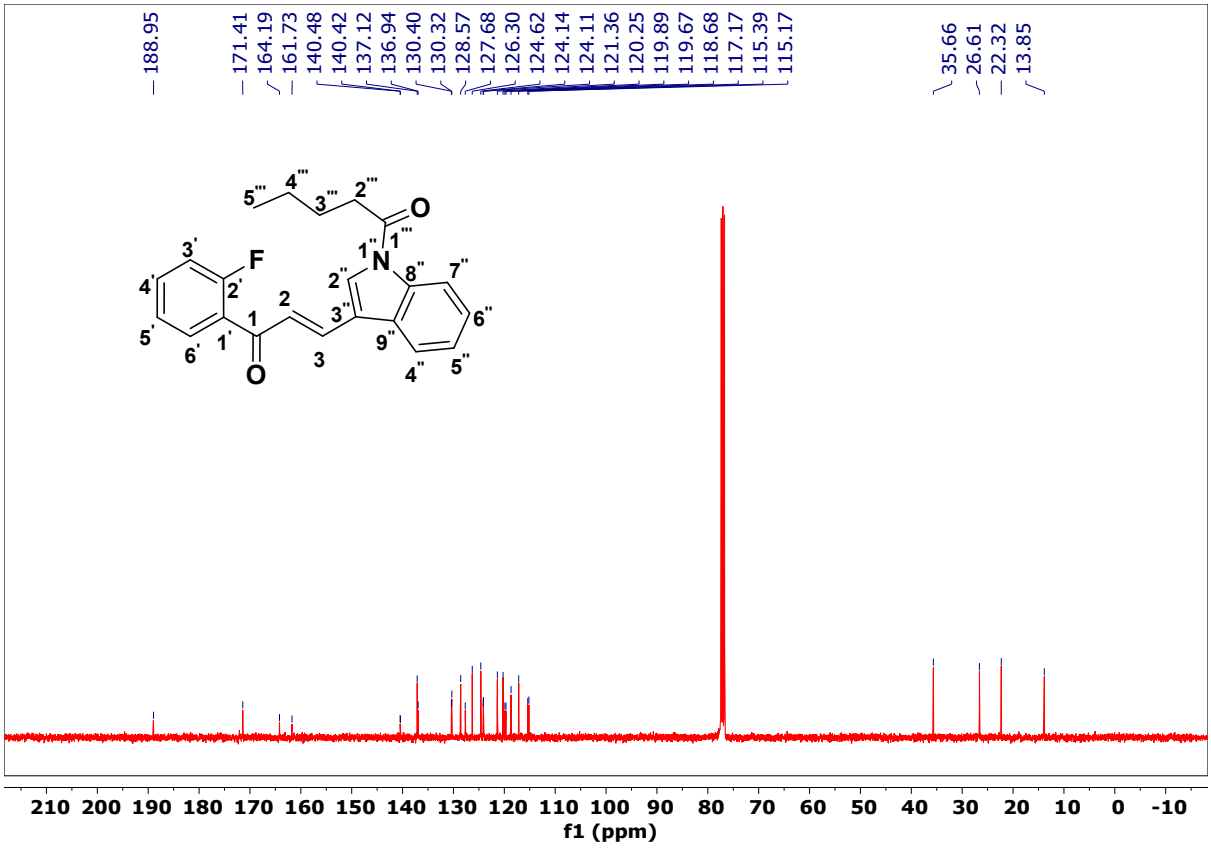


Figure S11: ^{13}C NMR spectrum of compound **23** (100 MHz, $CDCl_3$).

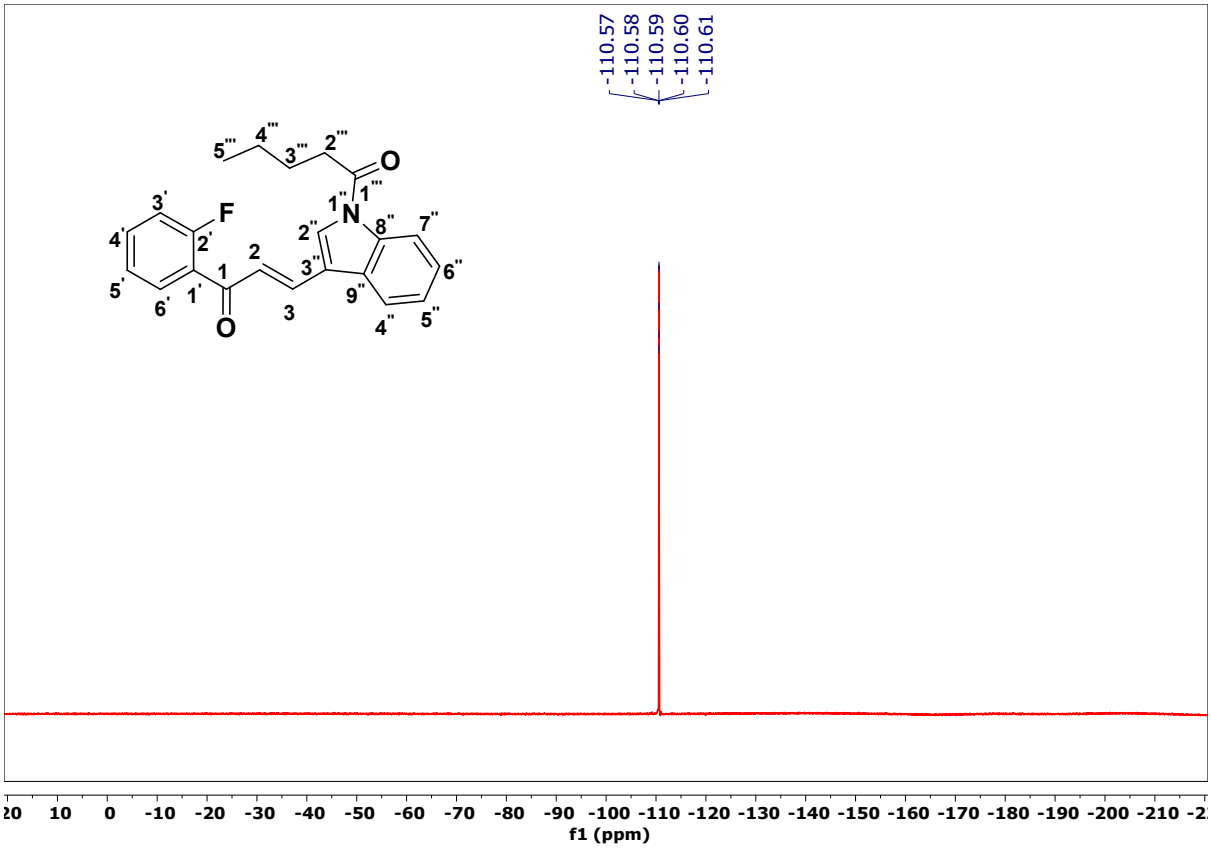


Figure S12: ^{19}F NMR spectrum of compound **23** (377 MHz, $CDCl_3$).

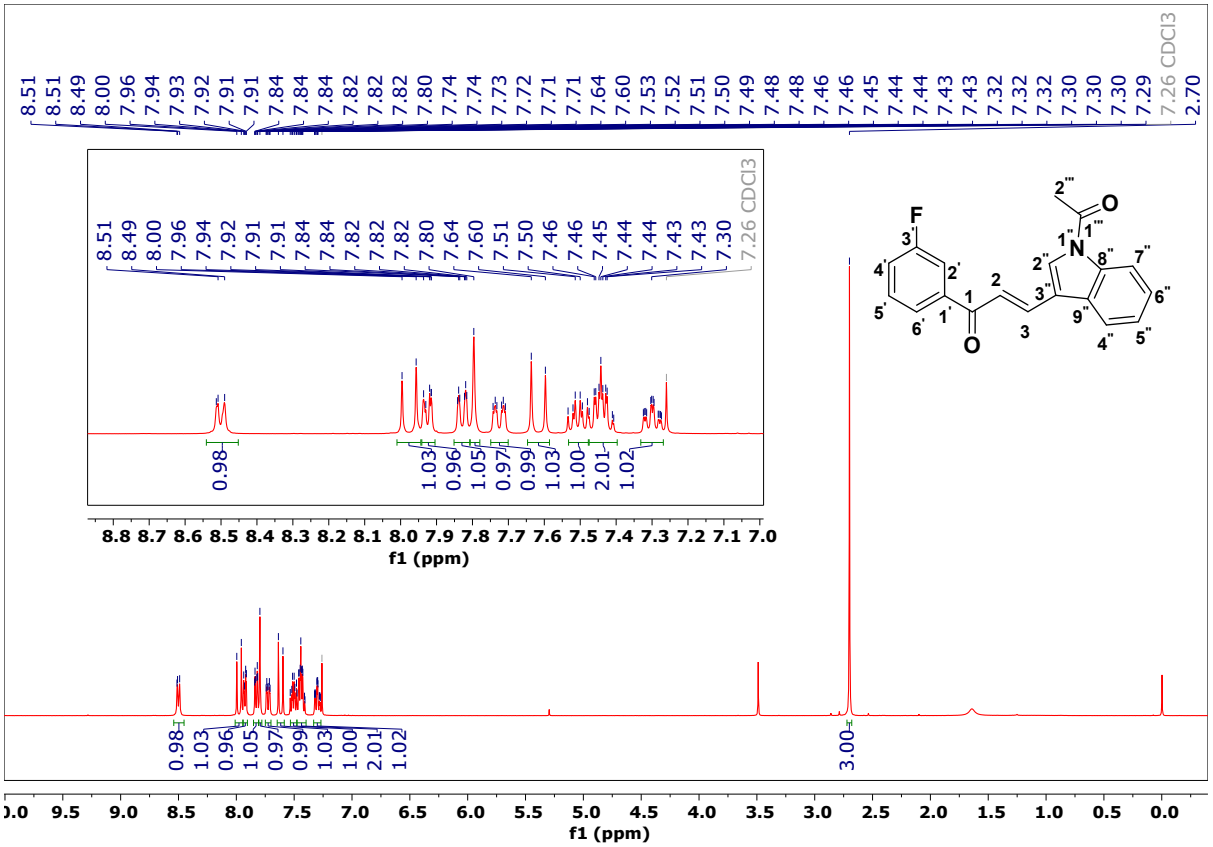


Figure S13: ^{1}H NMR spectrum of compound **24** (400 MHz, $CDCl_3$).

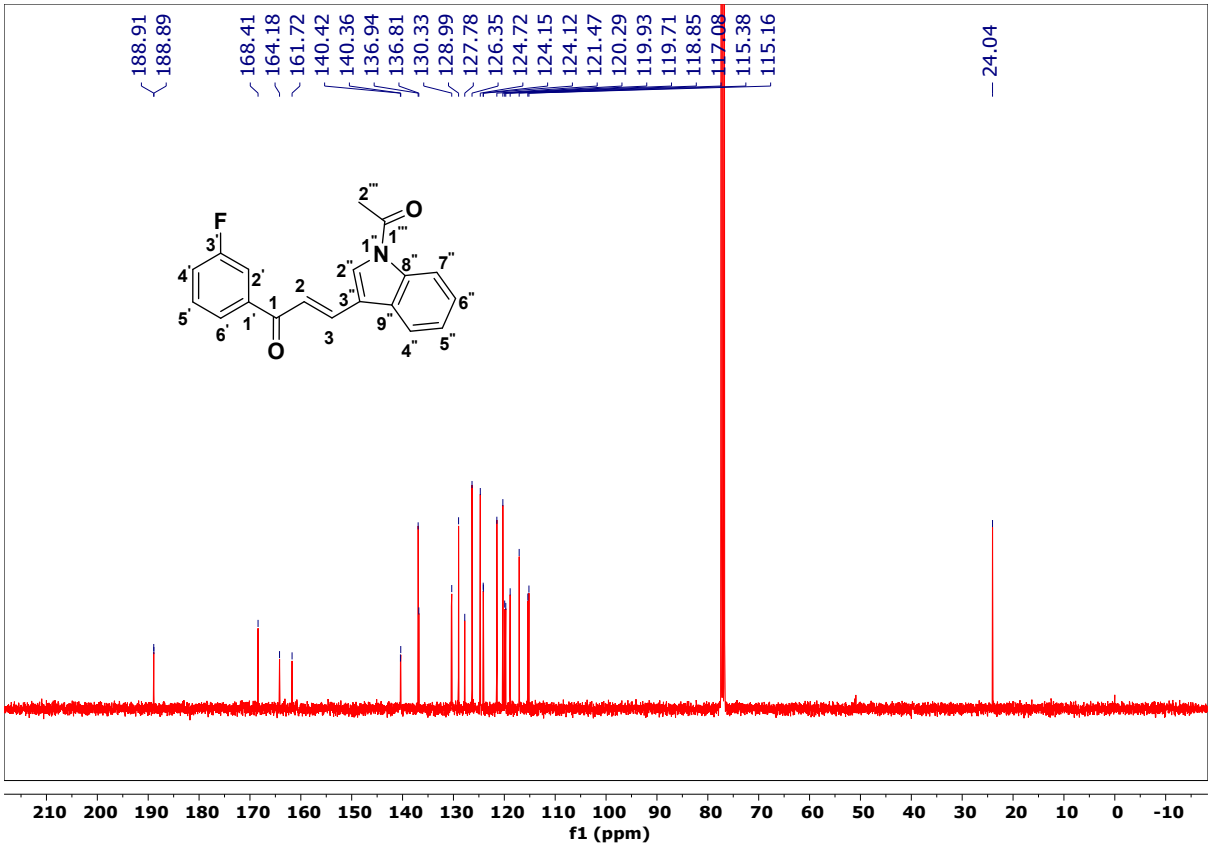


Figure S14: ^{13}C NMR spectrum of compound **24** (100 MHz, $CDCl_3$).

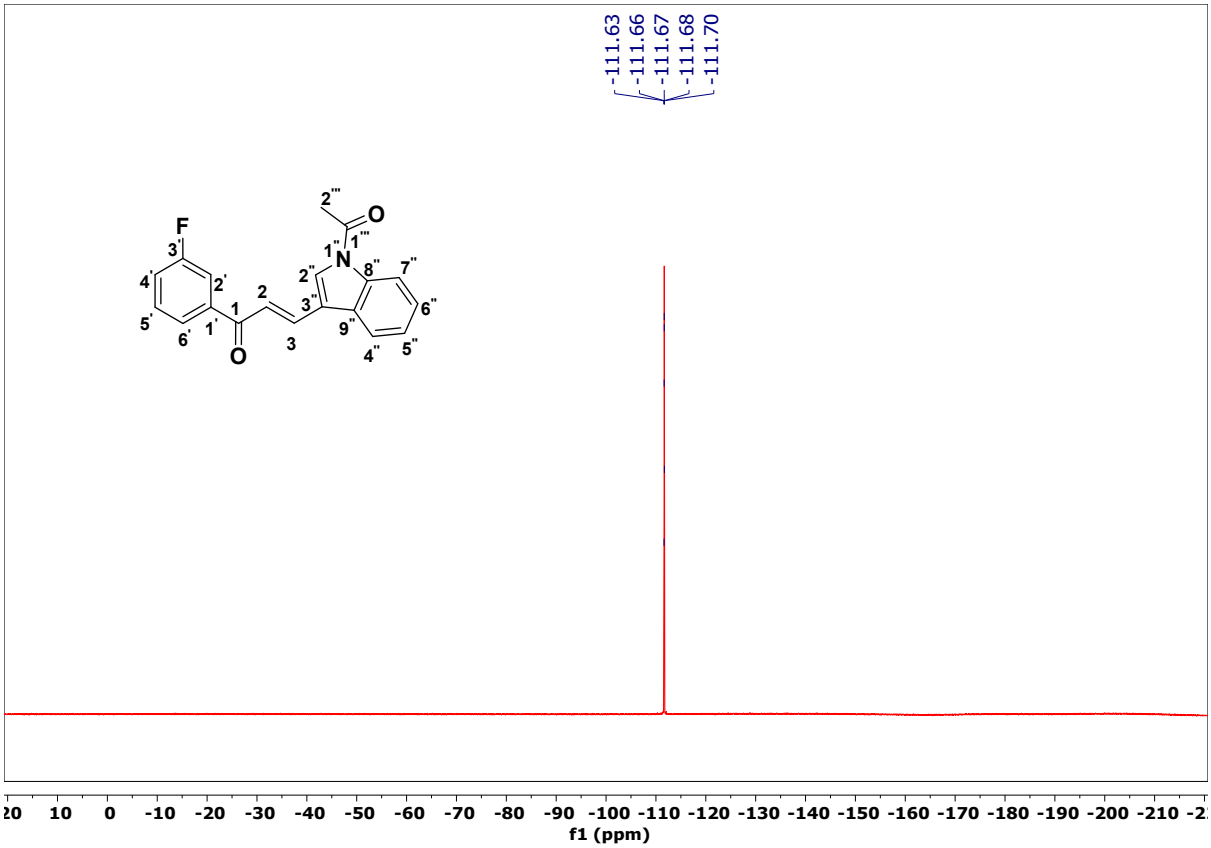


Figure S15: ^{19}F NMR spectrum of compound **24** (377 MHz, $CDCl_3$).

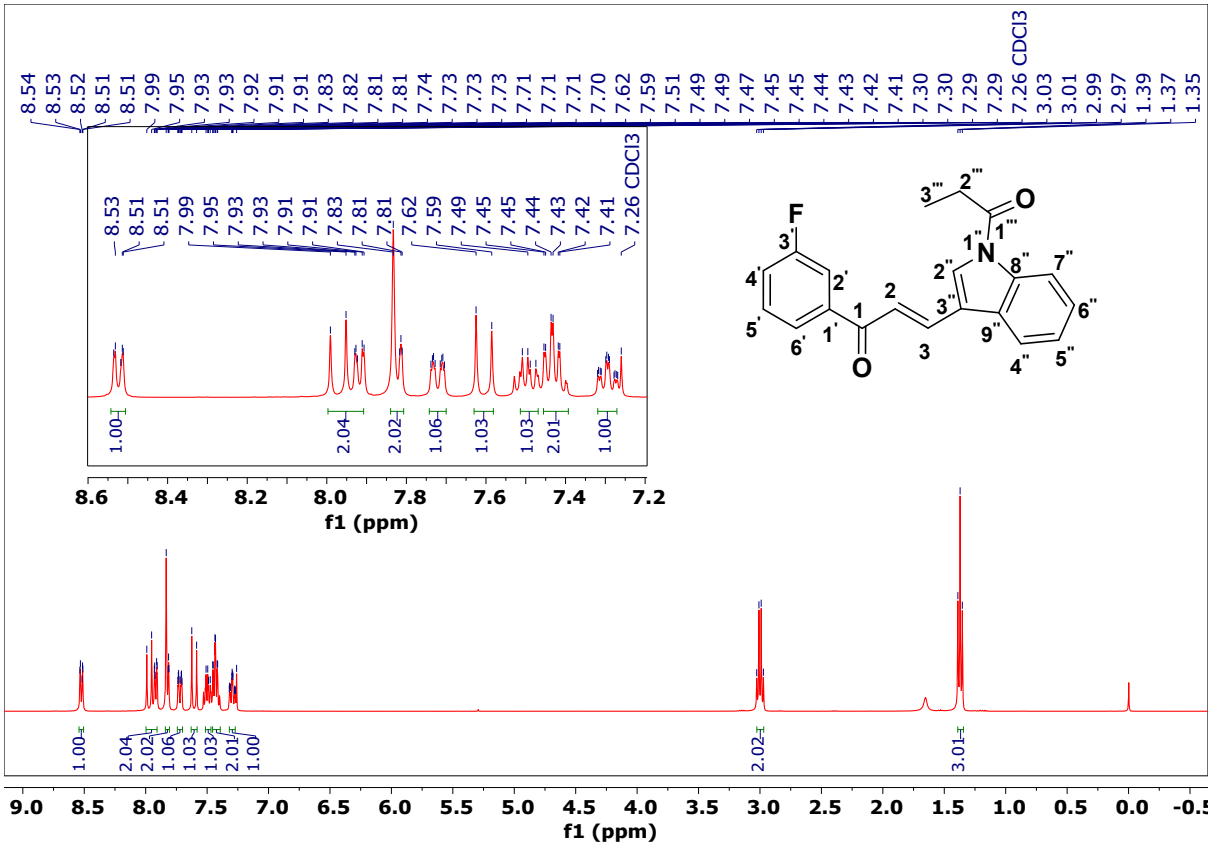


Figure S16: ^{1}H NMR spectrum of compound **25** (400 MHz, $CDCl_3$).

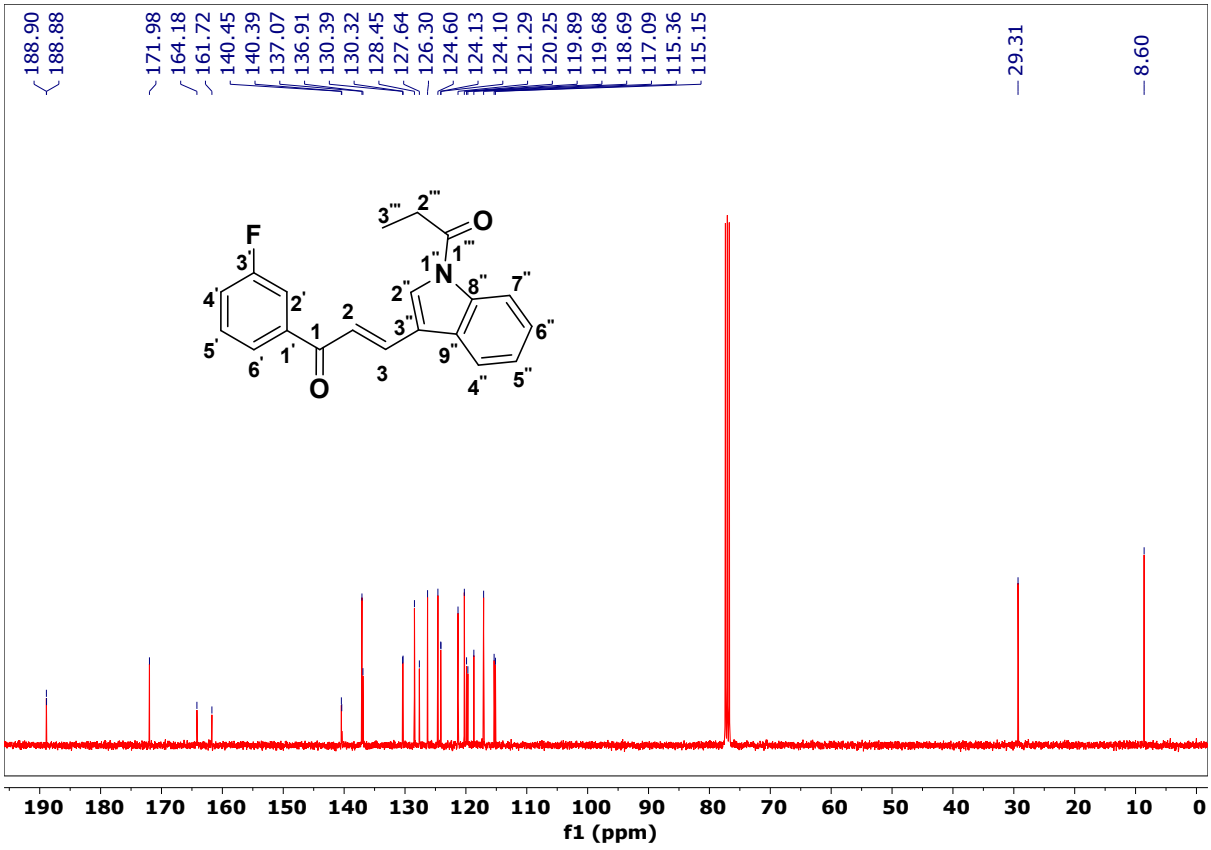


Figure S17: ^{13}C NMR spectrum of compound **25** (100 MHz, $CDCl_3$).

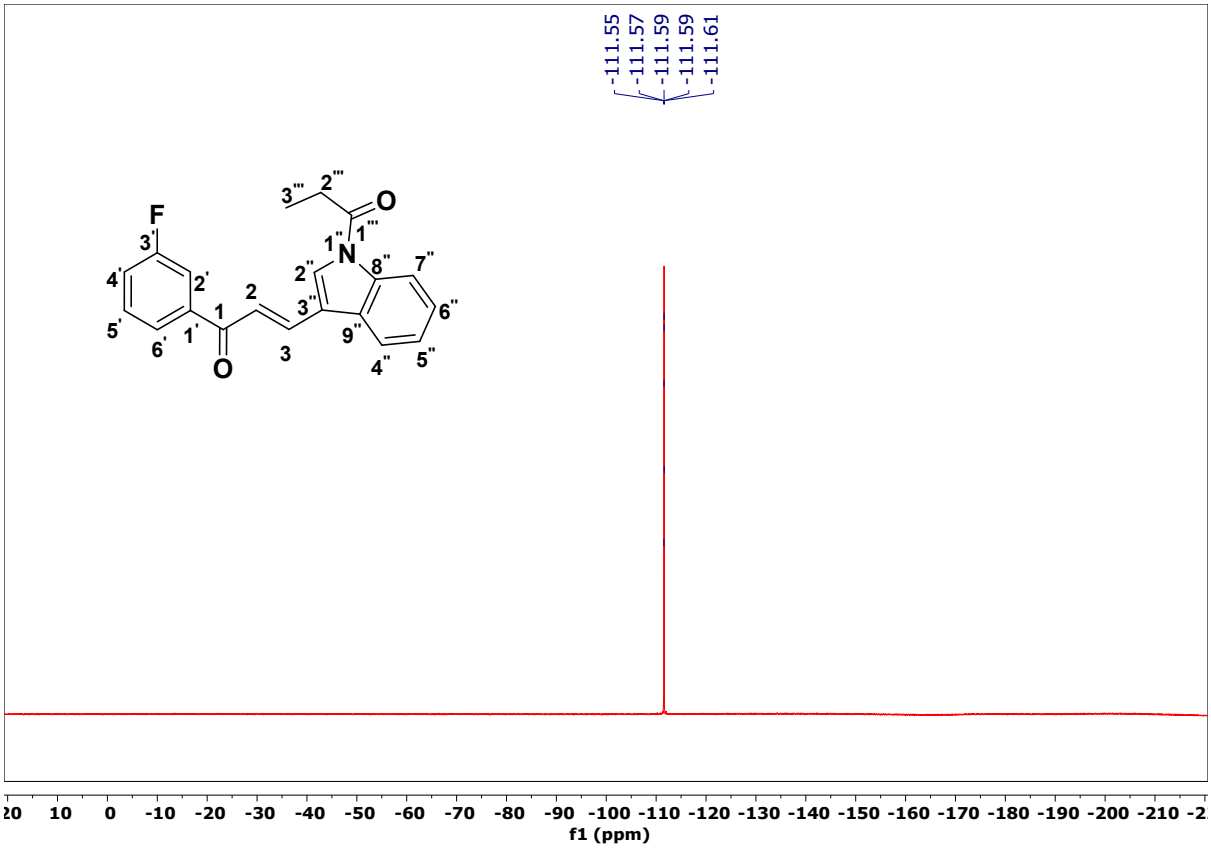


Figure S18: ^{19}F NMR spectrum of compound **25** (377 MHz, $CDCl_3$).

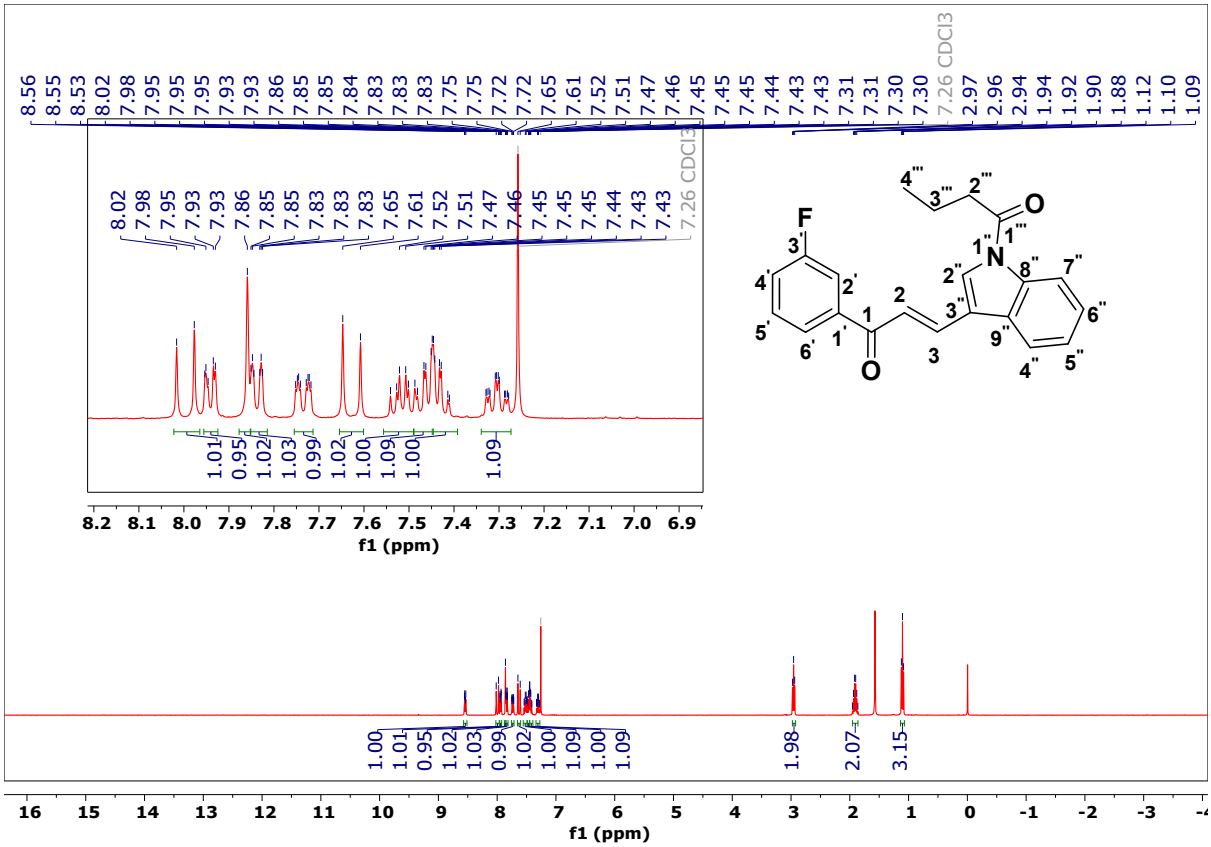


Figure S19: ^{1}H NMR spectrum of compound **26** (400 MHz, $CDCl_3$).

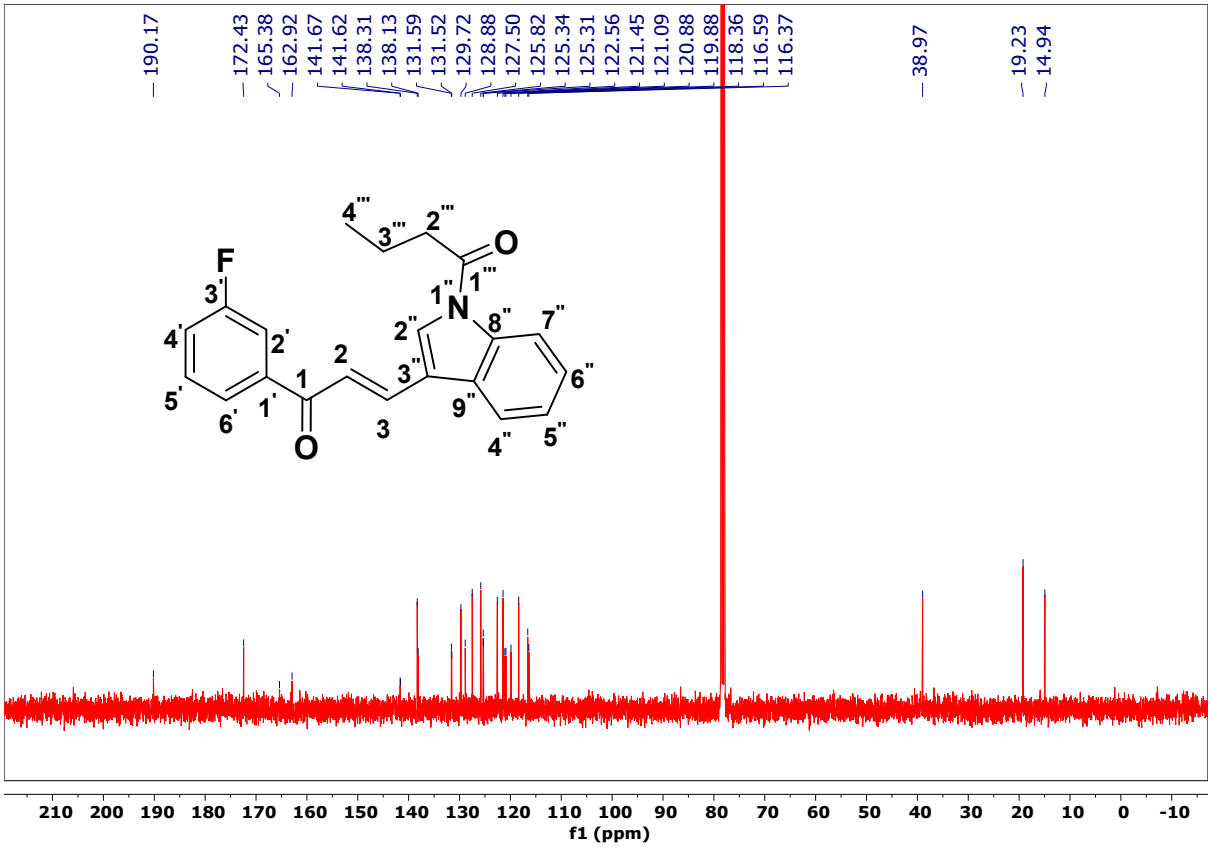


Figure S20: ^{13}C NMR spectrum of compound **26** (100 MHz, $CDCl_3$).

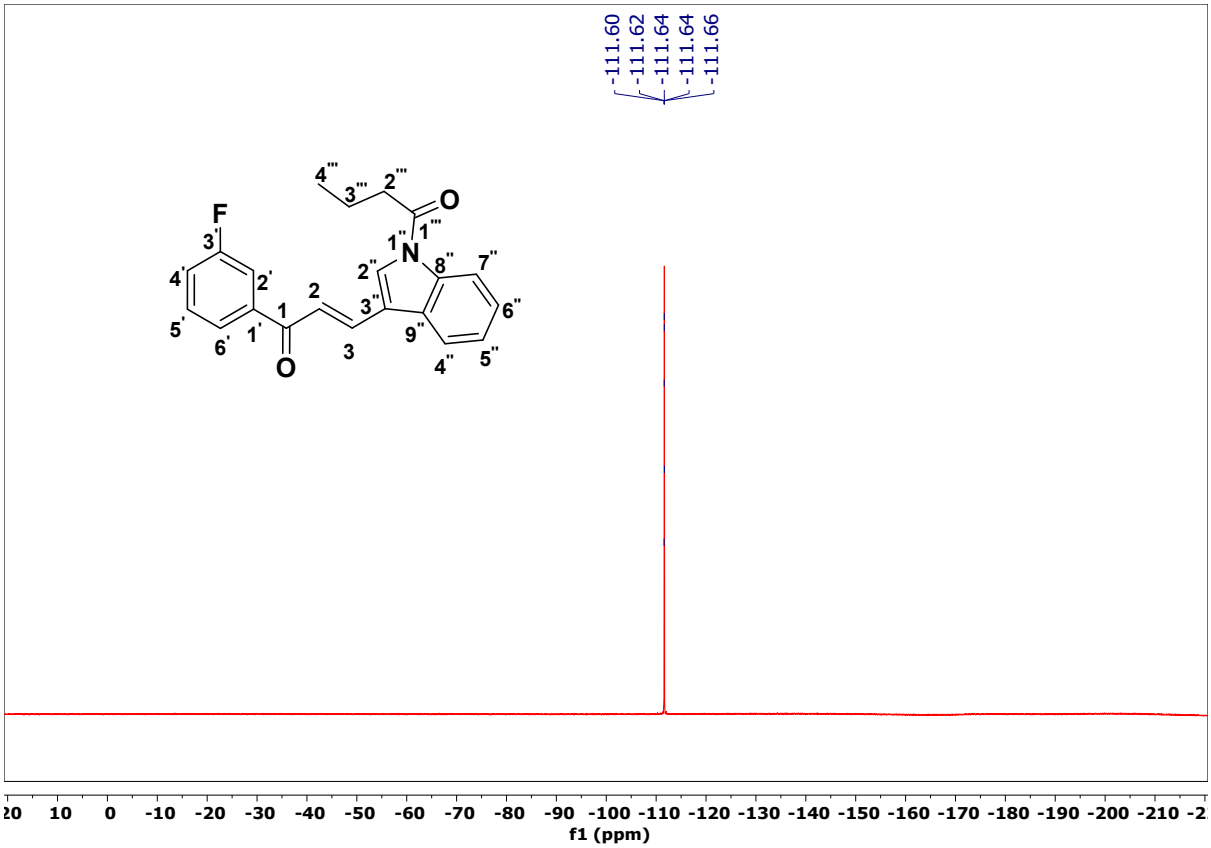


Figure S21: ^{19}F NMR spectrum of compound **26** (377 MHz, $CDCl_3$).

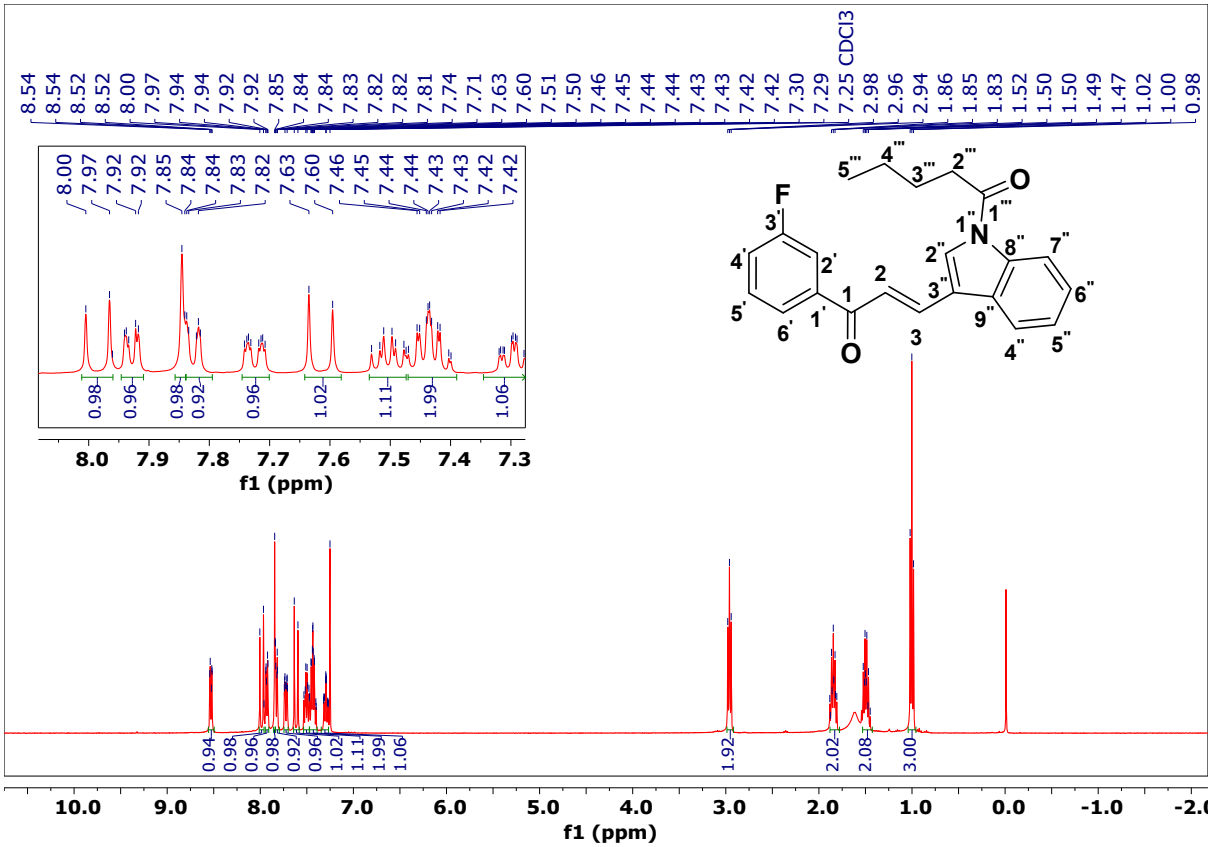


Figure S22: ^{1}H NMR spectrum of compound **27** (400 MHz, $CDCl_3$).

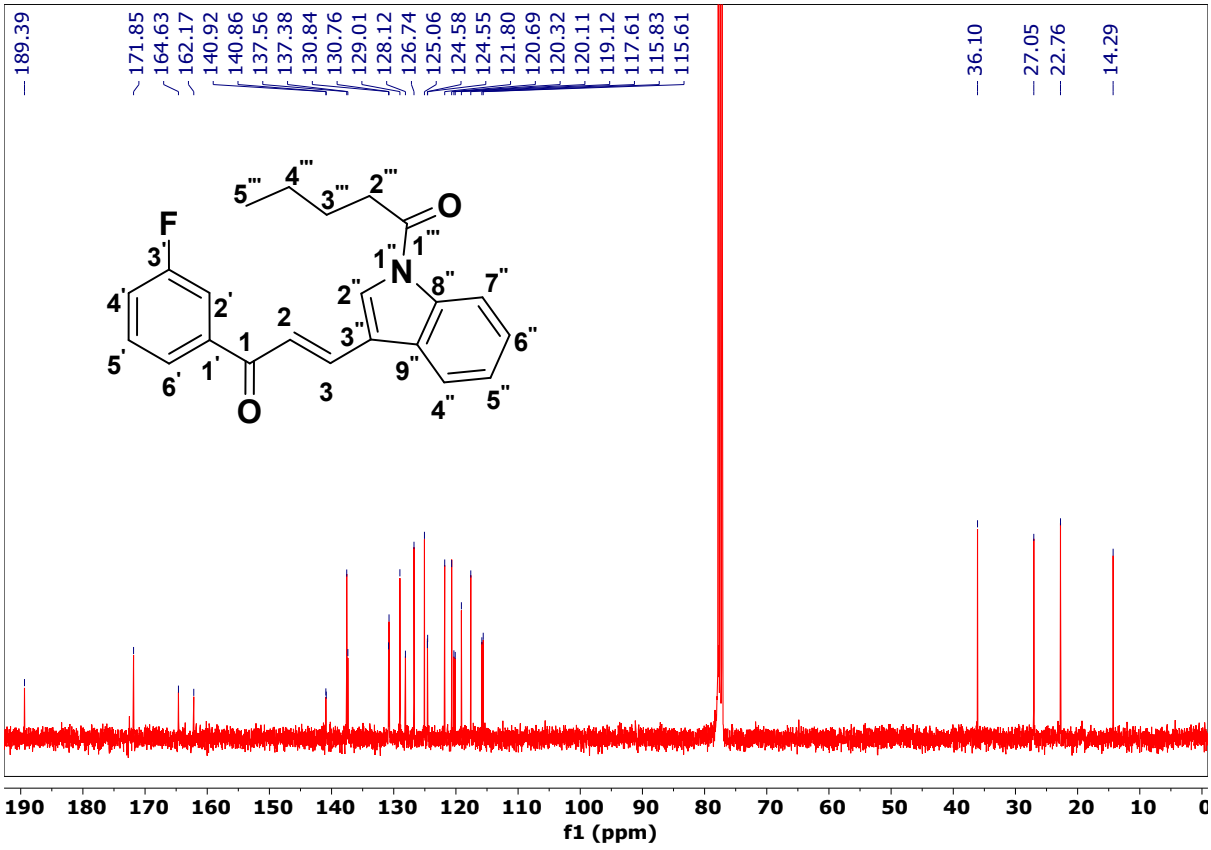


Figure S23: ^{13}C NMR spectrum of compound **27** (100 MHz, $CDCl_3$).

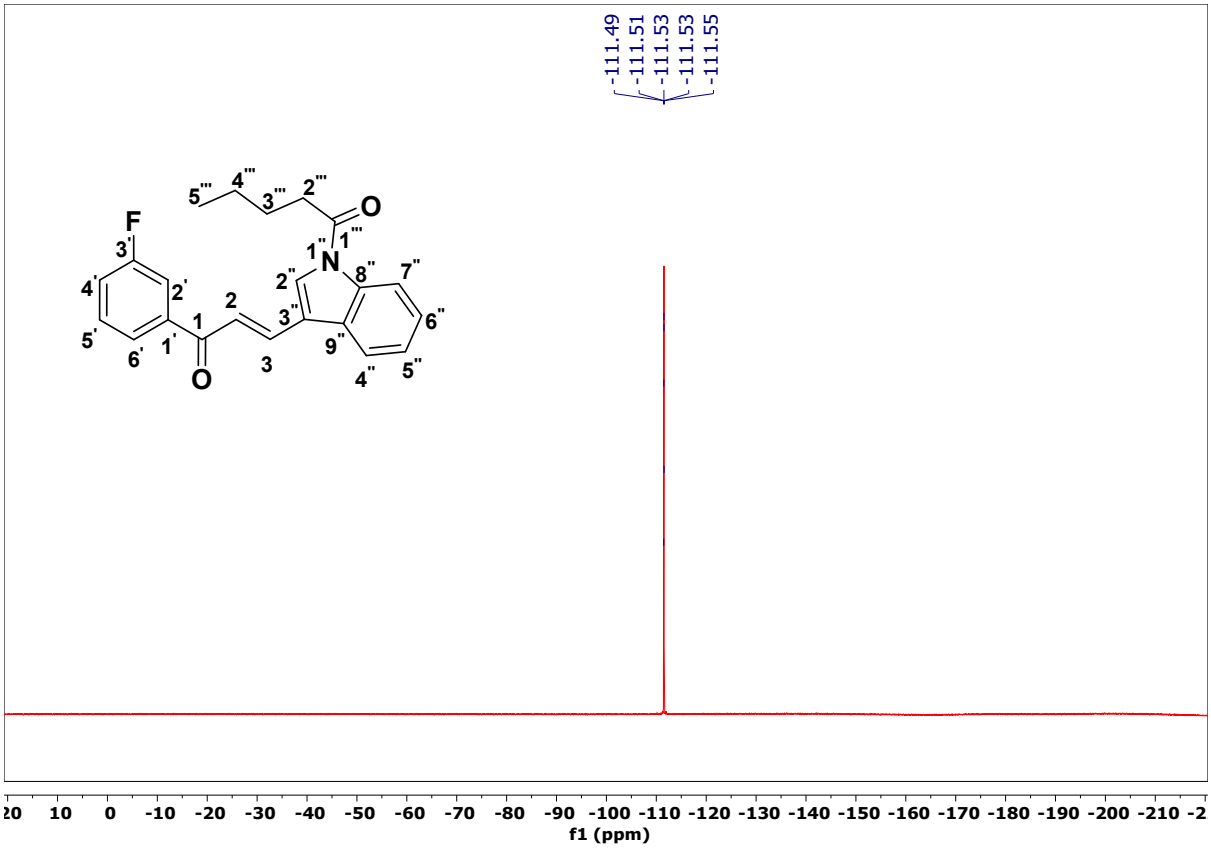


Figure S24: ^{19}F NMR spectrum of compound **27** (377 MHz, $CDCl_3$).

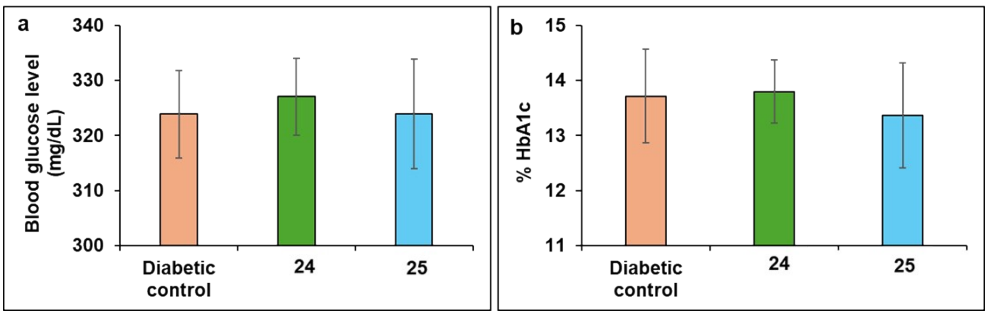


Figure S25: Graphs represent the effect of compound **24** and **25** on (a) blood glucose level and (b) % HbA1c in diabetic animals. All value represents in mean±SD. (@) showed significant difference (p <0.05) as compared with the diabetic control group.

Table S1: Effect of compound 24 and 25 on % wound closure in diabetic animals.

Average % Wound Closure			
Days	**Diabetic Control**	**Compound 24**	**Compound 25**
1	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
2	9.8 ± 7.6	6.3 ± 4.8	16.1 ± 4.3
3	19.0 ± 4.1	10.2 ± 4.6	25.8 ± 3.8
4	31.7 ± 3.5	12.1 ± 4.5	31.7 ± 3.5
5	36.6 ± 3.2	23.9 ± 3.9	45.3 ± 2.8
6	48.3 ± 2.6	45.3 ± 2.8	57.0 ± 2.2
7	56.1 ± 2.2	51.2 ± 2.5	61.9 ± 1.9
8	60.0 ± 2.0	60.0 ± 2.0	67.8 ± 1.6
9	63.9 ± 1.8	66.8 ± 1.7	73.6 ± 1.3
10	65.8 ± 1.7	72.7 ± 1.4	77.5 ± 1.1
11	69.7 ± 1.5	79.5 ± 1/0	82.4 ± 0.9
12	74.6 ± 1.3	83.4 ± 0.8	86.3 ± 0.7
13	77.5 ± 1.1	87.3 ± 0.6	90.2 ± 0.5
14	80.5 ± 1.0	90.2 ± 0.5	92.2 ± 0.4
15	85.4 ± 0.7	93.2 ± 0.3	96.1 ± 0.2
16	89.3 ± 0.5	98.0 ± 0.1	100.0 ± 0.0
17	94.54 ± 0.3	100 ± 0.2	100 ± 0.0

18	99.12 ± 0.5	100 ± 0.0	100 ± 0.0
19	100 ± 0.0	100 ± 0.0	100 ± 0.0

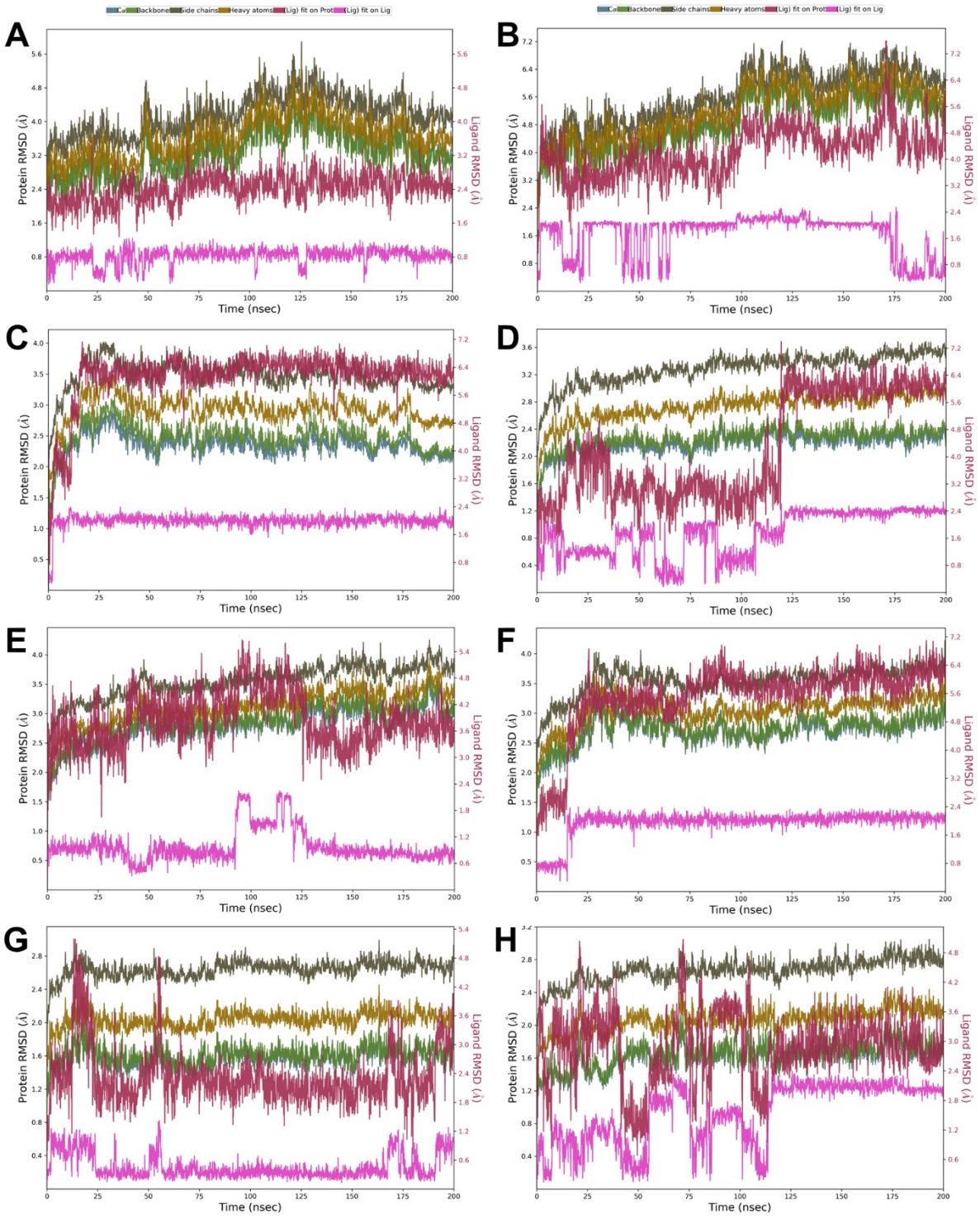


Figure S26. Root Mean Square Deviation (RMSD) analysis of protein and ligand complexes over a 200 ns molecular dynamics simulation: **A.** IL1R2-m24 **B.** IL1R2-m25 **C.** TNFalpha-m24 **D.** TNFalpha-m25 **E.** COX1-m24 **F.** COX1-m25 **G.** NOS-m24 **H.** NOS-m25. Protein RMSD values are shown for Cα atoms (blue), backbone atoms (green), side chains (brown),

and heavy atoms (gold) with reference to the left y-axis. Ligand RMSD values are shown for ligand fit on protein (red) and ligand fit on itself (magenta) with reference to the right y-axis.

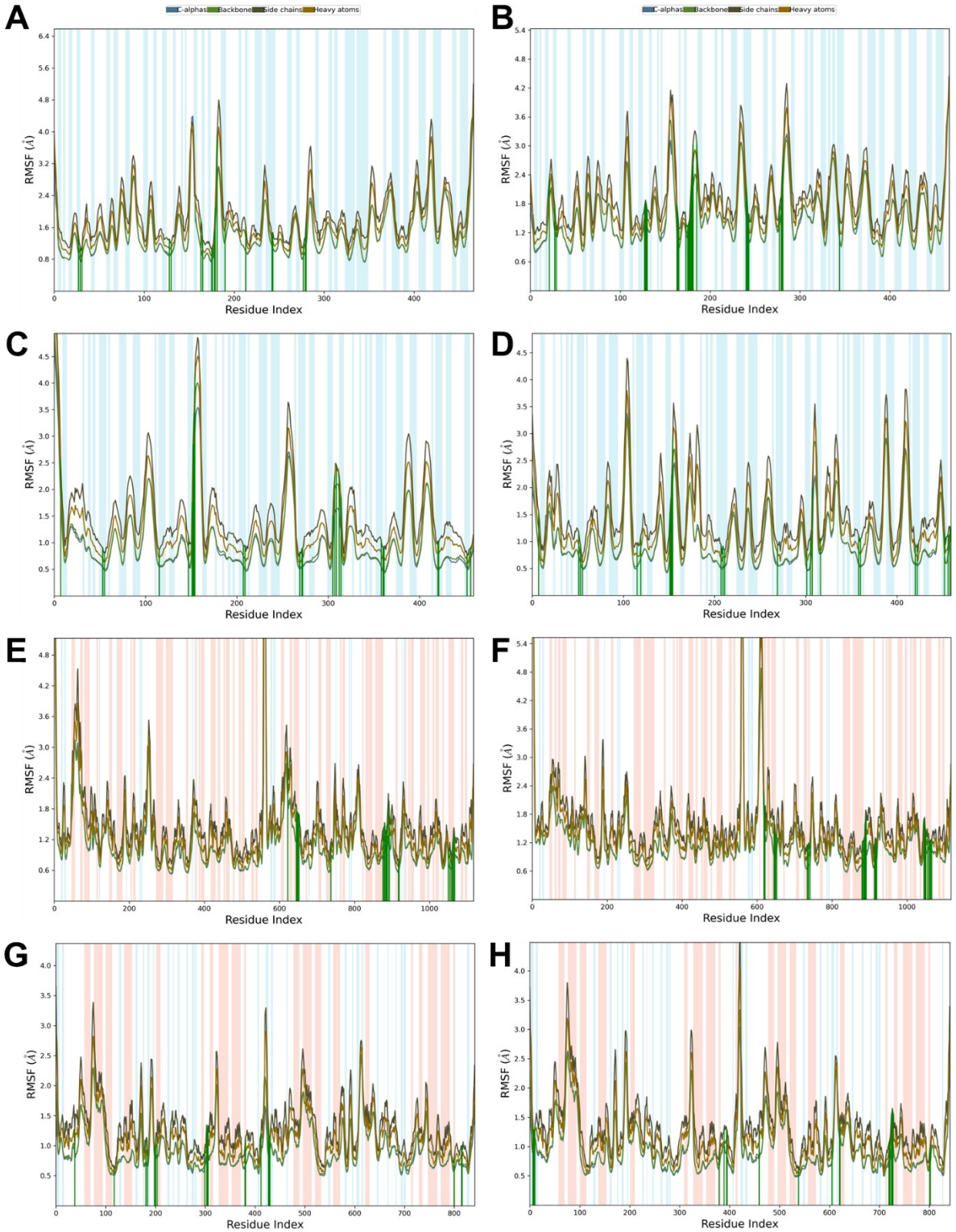


Figure S27. Root Mean Square Fluctuation (RMSF) profile of protein and ligand complexes: **A.** IL1R2-m24 **B.** IL1R2-m25 **C.** TNFalpha-m24 **D.** TNFalpha-m25 **E.** COX1-m24 **F.** COX1-m25 **G.** NOS-m24 **H.** NOS-m25.

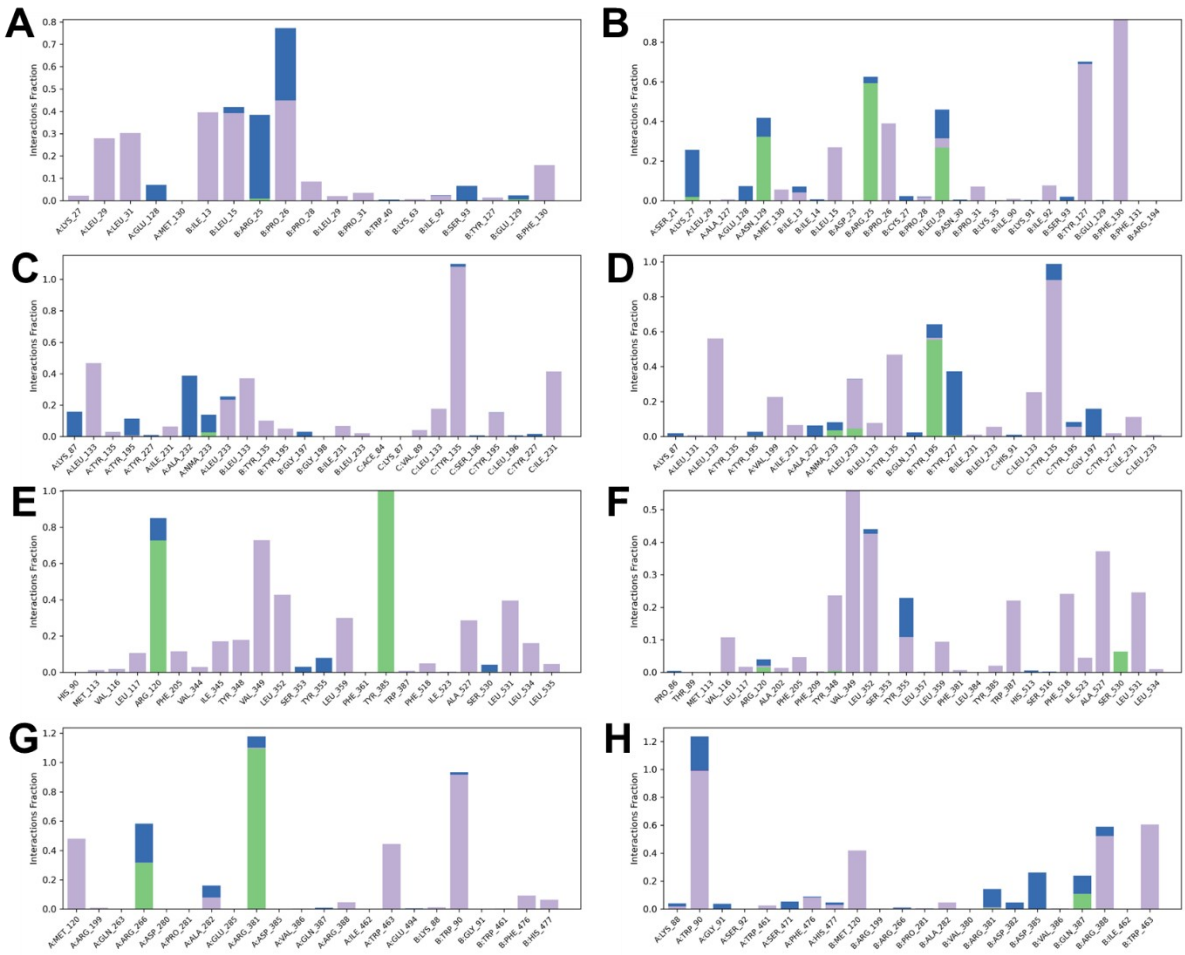


Figure S28. Protein–ligand interaction profile: **A.** IL1R2-m24 **B.** IL1R2-m25 **C.** TNFalpha-m24 **D.** TNFalpha-m25 **E.** COX1-m24 **F.** COX1-m25 **G.** NOS-m24 **H.** NOS-m25. The plot illustrates the fraction of simulation time during which specific protein residues maintain interactions with the ligand, categorized into hydrogen bonds (Green), hydrophobic contacts (Purple), and water bridges (Blue).

References:

1. Amir, M.; Javed, S. A.; Kumar, H. Synthesis and biological evaluation of some 4-(1-indol-3-yl)-6-phenyl-1, 2, 3, 4-tetrahydropyrimidin-2-ones/thiones as potent anti-inflammatory agents. *Acta Pharm*. **2008**, *58*, 467.

2. Singh, P.; Swain, B.; Thacker, P.S.; Sigalapalli, D.K.; Yadav, P.P.; Angeli, A.; Supuran, C.T.; Arifuddin, M. Synthesis and carbonic anhydrase inhibition studies of sulfonamide based indole-1, 2, 3-triazole chalcone hybrids. *Bioorg. Chem.* **2020**, *99*, 103839.

3. Kudličková, Z.; Michalková, R.; Salayová, A.; Ksiažek, M.; Vilková, M.; Bekešová, S.; Mojžiš, J. Design, synthesis, and evaluation of novel indole hybrid chalcones and their

antiproliferative and antioxidant activity. *Molecules*, **2023**, *28*, 6583.