Structural Analysis, *In Vitro* Anti-tubercular Activities, and In Silico ADMET Evaluation of Ethyl 7-Methoxy-3-(4-Substituted Benzoyl)indolizine-1-carboxylates

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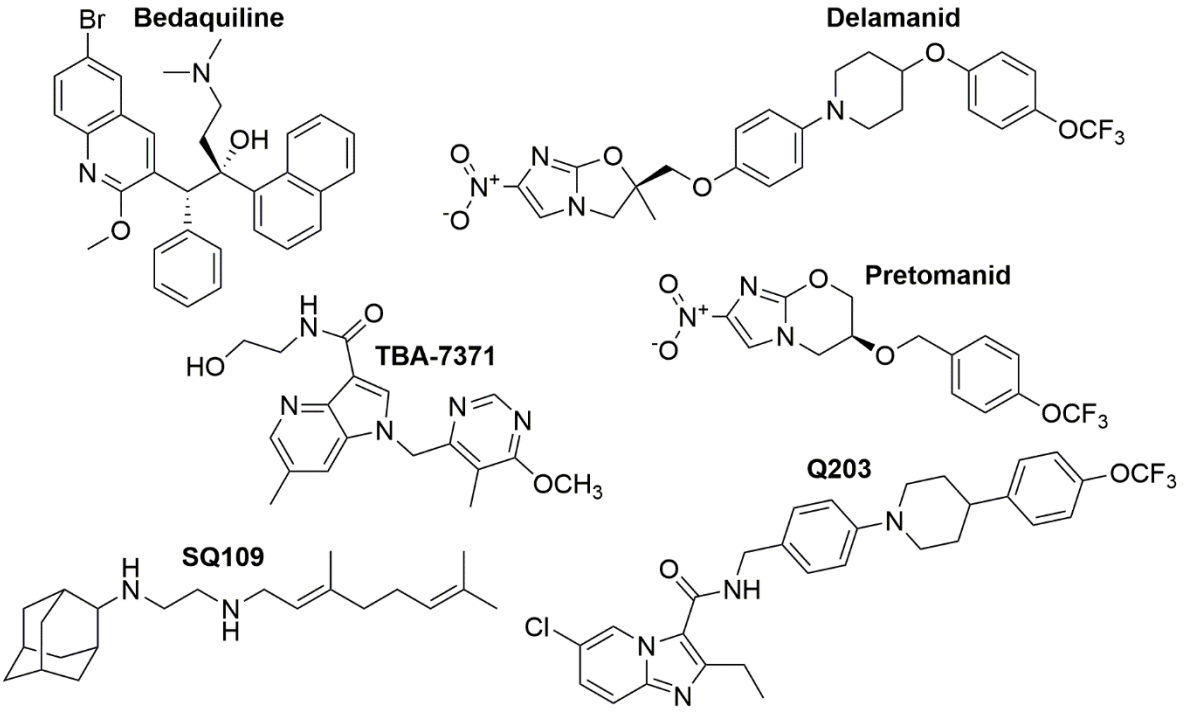


Figure S1- The approved anti-TB drugs (Bedaquiline, Delamanid, and Pretomanid) are undergoing clinical trial anti-Tb drugs (Q203, TBA-7371, and SQ109).[1, 2]

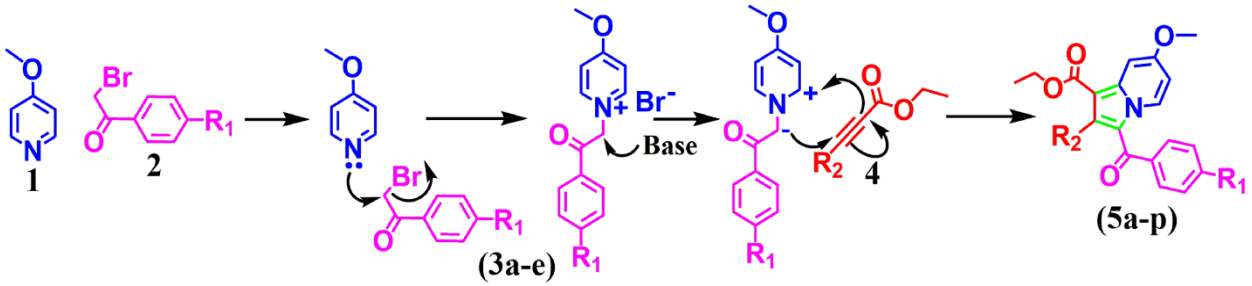


Figure S2- Plausible mechanism for Ethyl 7-Methoxy-3-(4-Substituted Benzoyl)indolizine-1-carboxylates.

Initially, the salt intermediate 4-methoxy-1-(2-oxo-2-phenylethyl)pyridin-1-ium bromide (**3a-d**) is synthesized by reacting 4-methoxypyridine with substituted phenacyl bromides (**2**) in acetone, a polar aprotic solvent, through an aromatic substitution type 2 reaction mechanism. These salts are then treated with reactive electron-deficient acetylenes (**4**) in DMF at room temperature to achieve positional specificity, followed by the base is added, leading to the formation of an indolizine nucleus (**5a-p**) by 3+2 cycloaddition reaction (**Figure S2**).[3, 4]

1. Characterization details

1.1 Ethyl 3-benzoyl-7-methoxyindolizine-1-carboxylate (5a)

Appearance; Light brown solid. FT-IR (KBr neat cm-1): 2189, 1735, 1699, 1618, 1609, 1230. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.85-9.79 (m, 1H), 7.82-7.78 (m, 2H), 7.75-7.71 (m, 2H), 7.55-7.50 (m, 3H), 6.76-6.80 (m, 1H), 4.36-4.32 (q, *J* = 7.2Hz, 2H), 3.99-3.96 (s, 3H), 1.40-1.35 (t, *J* = 7.2Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* = 185.06, 164.56, 159.95, 142.92, 140.19, 131.40, 130.76, 129.02, 128.49, 121.98, 109.25, 104.70, 97.65, 77.16, 56.35, 60.04, 55.87, 14.71.

1.2 Ethyl 3-benzoyl-7-methoxy-2-methylindolizine-1-carboxylate (5b)

Appearance; Brown solid. FT-IR (KBr neat cm^{-1}): 2190, 1736, 1696, 1620, 1605, 1226. ^{1}H NMR (400 MHz, DMSO-d_6) *δ* = 9.36-9.32 (m, 1H), 7.68-7.62 (m, 4H), 7.54-7.56 (m, 2H), 6.91 (s, 1H), 4.29-4.27 (q, *J* = 7.2Hz, 2H), 3.93 (s, 3H), 2.06 (s, 3H), 1.36-1.33 (t, *J* = 7.2Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) *δ* = 185.95, 163.92, 158.82, 141.06, 140.68, 137.03, 131.50, 129.43, 128.43, 121.25,107.82, 102.68, 97.00, 59.12, 55.43, 39.53, 14.25, 14.07.

1.3 Ethyl 3-benzoyl-2-ethyl-7-methoxyindolizine-1-carboxylate (5c)

Appearance; Brown solid. FT-IR (KBr neat cm^{-1}): 2188, 1732, 1698, 1617, 1606, 1226. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* = 9.30-9.19 (m, 1H), 7.65-7.60 (m, 4H), 7.53-7.51 (m, 2H), 6.87 (s, 1H), 4.30-4.25 (q, *J* = 7.2Hz, 2H), 3.90 (s, 3H), 2.55-2.52 (q, *J* = 7.2Hz, 2H), 1.34-1.31 (t, *J* = 7.2Hz, 3H), 0.90-0.86 (t, *J* = 7.2Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) *δ* = 186.52, 163.80, 158.94, 143.47, 141.49, 140.94, 131.63, 129.83, 128.50, 128.08, 120.83, 108.00, 101.69, 97.34, 59.30, 55.62, 39.52, 19.19, 15.76, 14.19.

1.4 Diethyl 3-benzoyl-7-methoxyindolizine-1,2-dicarboxylate (5d)

Appearance; Light green solid. FT-IR (KBr neat cm^{-1}): 2187, 1734, 1696, 1619, 1608, 1229. ^{1}H NMR (400 MHz, DMSO-d_6) *δ* = 9.48-9.29 (m, 1H), 7.62-7.56 (m, 4H), 7.46-7.48 (m, 2H), 7.03-6.98 (s, 1H), 4.25-4.20 (q, *J* = 7.2Hz, 2H), 3.94 (s, 3H), 3.65-3.59 (q, *J* = 7.2Hz, 2H), 1.25-1.21 (t, *J* = 7.2Hz, 3H), 1.02-0.98 (t, *J* = 7.2Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) *δ* = 185.42, 164.01, 162.36, 159.62, 140.23, 139.19, 131.85, 131.51,128.46, 127.99,119.51, 109.87, 101.08, 97.13, 61.12, 59.89, 39.52, 14.04, 13.29.

1.5 Ethyl 7-methoxy-3-(4-nitrobenzoyl)indolizine-1-carboxylate (5e)

Appearance; Brown colour solid. FT-IR (KBr neat cm^{-1}): 2985, 1733, 1685, 1633, 1604, 1225. ^1H NMR (400 MHz, $CDCl_3$) δ = 9.70-9.65 (m, 1H), 8.35-8.30 (m, 2H), 7.95-7.92 (m, 2H), 7.63-7.61 (m, 1H), 7.49-7.47 (m, 1H), 7.03-7.01 (m, 1H), 4.24-4.20 (q, *J* = 7.2Hz, 2H), 3.92-3.90 (s, 3H), 1.27-1.23 (t, *J* = 7.2Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 182.26, 163.56, 160.54, 149.39, 145.47, 142.76, 131.12, 130.29, 129.67, 124.25, 121.44, 110.08, 104.89, 98.01, 60.24, 56.46, 40.18, 39.98, 39.77, 14.86.

1.6 Ethyl 7-methoxy-2-methyl-3-(4-nitrobenzoyl)indolizine-1-carboxylate (5f)

Appearance; Brown solid. FT-IR (KBr neat cm^{-1}): 2188, 1739, 1699, 1621, 1607, 1228. ^1H NMR (400 MHz, $CDCl_3$) δ = 9.48-9.43 (m, 1H), 8.77-8.72 (m, 4H), 7.84-7.81 (m, 2H), 6.93-6.91 (m, 1H), 4.26-4.21 (q, *J* = 7.2Hz, 2H), 3.90(s, 3H), 2.05 (s, 3H), 1.32-1.27 (t, *J* = 7.2Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 183.92, 164.42, 157.32, 140.60, 139.79, 137.23, 131.45, 129.75, 128.63, 120.89,107.47, 102.55, 97.14, 59.21, 55.66, 39.24, 14.74, 14.04.

1.7 Ethyl 2-ethyl-7-methoxy-3-(4-nitrobenzoyl)indolizine-1-carboxylate (5g)

Appearance; Brown solid. FT-IR (KBr neat cm^{-1}): 2183, 1734, 1699, 1616, 1605, 1231. ^1H NMR (400 MHz, $CDCl_3$) δ = 9.38-9.32 (m, 1H), 8.73-8.70 (m, 2H), 7.85-7.81 (m, 2H), 6.92-6.90 (s, 1H), 4.27-4.23 (q, *J* = 7.2Hz, 2H), 3.90 (s, 3H), 2.49-2.46 (q, *J* = 7.2Hz, 2H), 1.32-1.27 (t, *J* = 7.2Hz, 3H), 0.86-0.82 (t, *J* = 7.2Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 185.42, 164.79, 158.45, 143.77, 141.21, 140.49, 131.36, 129.38, 128.05, 128.80, 120.38, 107.31, 101.96, 97.43, 59.08, 55.26, 39.25, 19.91, 15.67, 14.84.

1.8 Diethyl 7-methoxy-3-(4-nitrobenzoyl)indolizine-1,2-dicarboxylate (5h)

Appearance; Yellow solid. FT-IR (KBr neat cm^{-1}): 2986, 1736, 1699, 1633, 1609, 1227. ^1H NMR (400 MHz, DMSO-d_6) δ = 9.48-9.39 (m, 1H), 8.32-8.29 (m, 2H), 7.83-7.81 (m, 2H), 7.10-6.98 (s, 1H), 4.25-4.20 (q, *J* = 7.2Hz, 2H), 3.95 (s, 3H), 3.55-3.52 (q, *J* = 7.2Hz, 2H), 1.25-1.20 (t, *J* = 7.2Hz, 3H), 1.03-1.00 (t, *J* = 7.2Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ = 185.21, 163.80, 162.15, 159.42, 140.02, 138.98, 131.64, 131.30,128.25, 127.78,119.30, 109.66, 100.87, 96.92, 60.91, 59.69, 55.67, 39.52, 13.84, 13.08.

1.9 Ethyl 3-(4-chlorobenzoyl)-7-methoxyindolizine-1-carboxylate (5i)

Appearance; Brown colour solid. FT-IR (KBr neat cm^{-1}): 2983, 1731, 1697, 1634, 1604, 1223. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.69-9.58 (m, 1H), 7.78-7.72(m, 2H), 7.65-7.50 (m, 3H), 7.52-7.50 (m, 1H), 7.04-6.99 (m, 1H), 4.27-4.25 (q, J = 7.2Hz, 2H), 3.94 (s, 3H), 1.30-1.27 (t, J = 7.2Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ = 182.90, 163.56, 160.12, 142.38, 138.54, 136.70, 132.86, 130.65, 129.06, 128.97, 121.48, 109.77, 104.25, 97.76, 60.05, 56.30, 39.52, 14.77.

1.10 Ethyl 3-(4-chlorobenzoyl)-7-methoxy-2-methylindolizine-1-carboxylate (5j)

Appearance; Brown colour solid. FT-IR (KBr neat cm^{-1}): 2981, 1737, 1693, 1636, 1607, 1226. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.30-9.27 (m, 1H), 7.63-7.60(m, 3H), 7.56-7.53 (m, 2H), 6.87-7.85 (m, 1H), 4.25-4.20 (q, J = 7.2Hz, 2H), 2.06-2.04 (s, 3H), 1.31-1.28 (t, J = 7.2Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 185.24, 164.59, 159.68, 151.41, 141.92, 140.07, 137.92, 136.98, 132.86, 131.67, 130.99, 130.22, 129.28, 121.80, 110.55, 108.62, 103.57, 97.76, 59.89, 56.19, 40.24, 40.03, 39.82, 15.13, 14.90.

1.11 Ethyl 3-(4-chlorobenzoyl)-2-ethyl-7-methoxyindolizine-1-carboxylate (5k)

Appearance; Brown colour solid. FT-IR (KBr neat cm^{-1}): 2984, 1734, 1696, 1636, 1607, 1229. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.20-9.15 (m, 1H), 7.94-7.89 (m, 2H), 7.60-7.55 (m, 3H), 6.87-7.84 (m, 1H), 4.28-4.25 (q, J = 7.2Hz, 2H), 3.90 (s, 3H), 2.54-2.51 (q, J = 7.2Hz, 2H), 1.34-1.30 (t, J = 7.2Hz, 3H), 0.90-0.87 (t, J = 7.2Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ = 185.11, 163.77, 159.10, 143.69, 141.92, 141.63, 139.64, 136.34, 131.18, 130.11, 128.66, 120.65, 108.09, 101.87, 97.37, 59.37, 55.68, 39.52, 19.28 15.74, 14.19.

1.12 Diethyl 3-(4-chlorobenzoyl)-7-methoxyindolizine-1,2-dicarboxylate (5l)

Appearance; Yellow solid. FT-IR (KBr neat cm^{-1}): 2985, 1731, 1695, 1635, 1608, 1228. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.35-9.29 (m, 1H), 7.65-7.60(m, 3H), 7.55-7.51 (m, 2H), 7.05-6.99 (s, 1H), 4.25-4.20 (q, J = 7.2Hz, 2H), 3.94 (s, 3H), 3.65-3.60 (q, J = 7.2Hz, 2H), 1.25-1.21 (t, J = 7.2Hz, 3H), 1.05-1.01 (t, J = 7.2Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ = 184.12, 164.05, 162.31, 159.80, 140.36, 137.94, 136.65, 132.41, 131.63, 130.36, 128.13, 119.31, 109.98, 101.27, 97.21, 61.30, 59.97, 55.92, 39.52, 14.06, 13.28.

1.13 Ethyl 7-methoxy-3-(4-methylbenzoyl)indolizine-1-carboxylate (5m)

Appearance; Brown colour. FT-IR (KBr neat cm^{-1}): 2983, 1737, 1695, 1632, 1604, 1224. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.67-9.55 (m, 1H), 7.66-7.62(m, 3H), 7.55-7.50 (m, 1H), 7.36-7.33 (s, 2H), 7.03-6.99 (m, 1H) 4.26-4.20 (q, *J* = 7.2Hz, 2H), 3.93 (s, 3H), 2.40 (s, 3H), 1.29-1.26(t, *J* = 7.2Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ = 183.92, 163.43, 159.69, 141.93, 141.88, 136.93, 130.59, 129.27, 128.90, 121.55, 109.39, 103.65, 97.43, 59.78, 56.04, 39.52, 21.30, 14.57.

1.14 Ethyl 7-methoxy-2-methyl-3-(4-methylbenzoyl)indolizine-1-carboxylate (5n)

Appearance; Brown colour. FT-IR (KBr neat cm^{-1}): 2984, 1736, 1697, 1635, 1606, 1227. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.33-9.20 (m, 1H), 7.62(m, 1H), 7.55-7.51 (m, 2H), 7.35-7.31 (m, 2H), 6.89-6.85 (m, 1H) 4.26-4.21 (q, *J* = 7.2Hz, 2H), 3.90 (s, 3H), 2.38 (s, 3H), 2.07 (s, 3H), 1.35-1.30 (t, *J* = 7.2Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ = 186.43, 164.58, 159.28, 142.49, 141.52, 138.45, 137.04, 129.93, 129.22, 122.01, 108.34, 103.06, 97.55, 59.70, 56.05, 39.52, 21.57, 14.70.

1.15 Ethyl 2-ethyl-7-methoxy-3-(4-methylbenzoyl)indolizine-1-carboxylate (5o)

Appearance; Brown colour. FT-IR (KBr neat cm^{-1}): 2989, 1737, 1699, 1639, 1609, 1229. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.05-9.01 (m, 1H), 7.63(m, 1H), 7.55-7.52 (m, 2H), 7.35-7.30 (m, 3H), 6.85-6.81 (m, 1H) 4.27-4.23 (q, *J* = 7.2Hz, 2H), 3.92-3.85 (s, 3H), 2.59-2.54 (q, *J* = 7.2Hz, 2H), 2.38 (s, 3H), 1.34-1.30 (t, *J* = 7.2Hz, 3H). 0.91-0.88(t, *J* = 7.2Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ = 186.82, 164.29, 159.17, 143.20, 142.47, 141.70, 138.44, 130.06, 129.50, 128.91, 121.42, 108.30, 101.86, 97.68, 59.69, 56.04, 39.52, 21.59, 19.67, 16.25, 14.63.

1.16 Diethyl 7-methoxy-3-(4-methylbenzoyl)indolizine-1,2-dicarboxylate (5p)

Appearance; Yellow solid. FT-IR (KBr neat cm^{-1}): 2987, 1733, 1696, 1636, 1607, 1225. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.35-9.29 (m, 1H), 7.65-7.60(m, 3H), 7.55-7.51 (m, 2H), 7.05-6.99 (s, 1H), 4.25-4.20 (q, *J* = 7.2Hz, 2H), 3.94 (s, 3H), 3.65-3.60 (q, *J* = 7.2Hz, 2H), 1.25-1.21 (t, *J* = 7.2Hz, 3H), 1.05-1.01 (t, *J* = 7.2Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ = 185.27, 164.10, 162.43, 159.49, 142.27, 140.10, 136.49, 131.08, 130.11, 128.69, 128.55, 119.77, 109.78, 100.88, 97.06, 61.15, 59.88, 55.89, 39.52, 21.13, 14.07, 13.30.

2.1 Fourier Transform Infrared Spectroscopic (FT-IR) Data Analysis

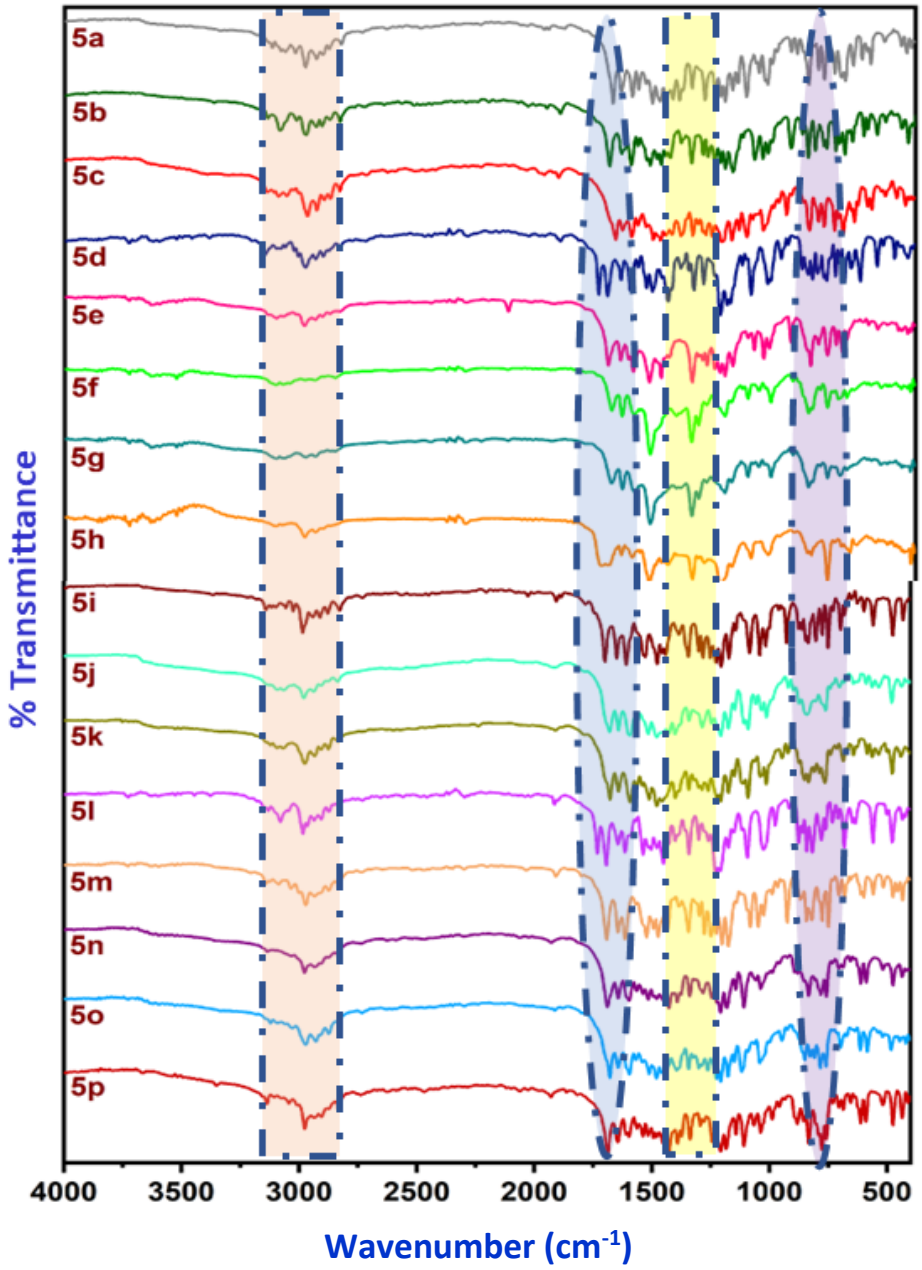


Figure S3- FT-IR spectra of the ethyl 3-(4-substitutedbenzoyl)-7-methoxyindolizine-1-carboxylate compounds (**5a-p**).

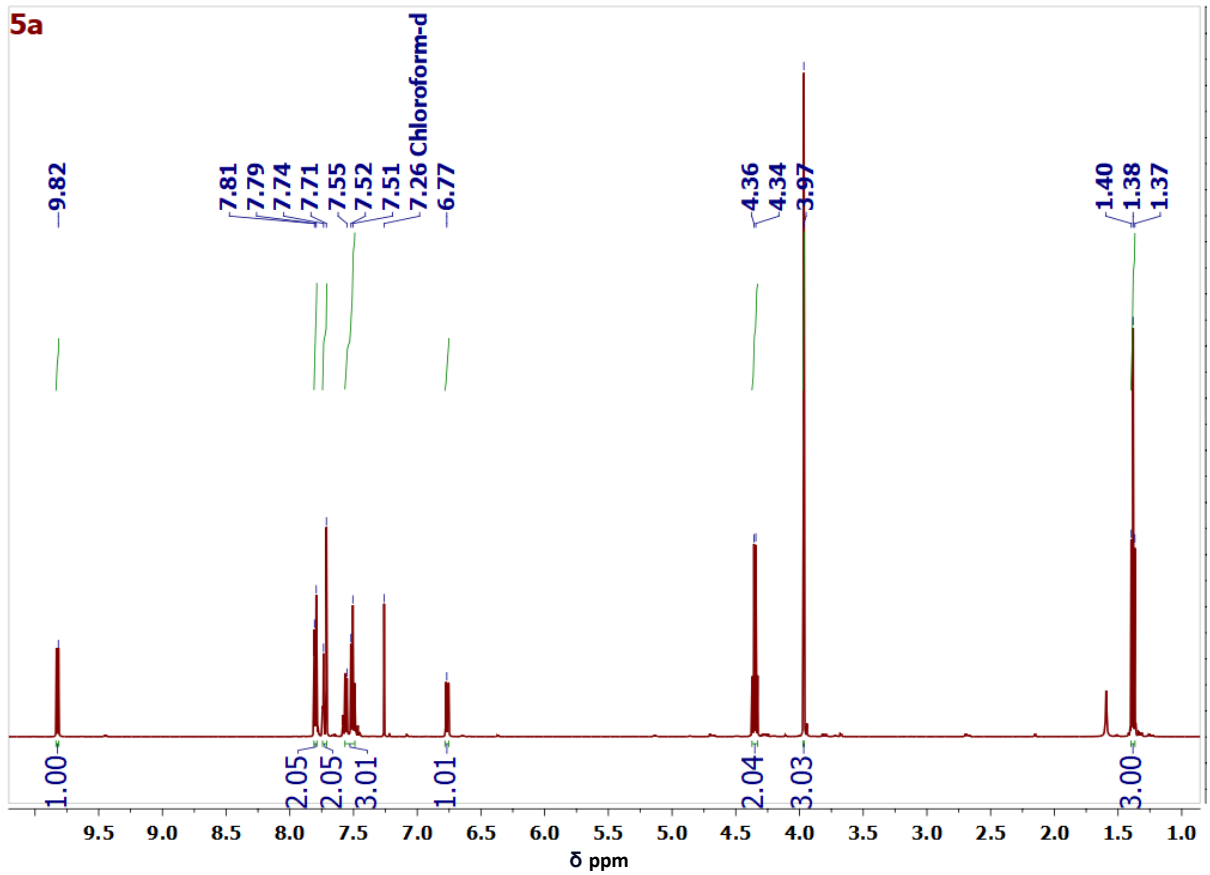


Figure S4- ^{1}H-NMR spectra of the ethyl 3-benzoyl-7-methoxyindolizine-1-carboxylate **(5a)**.

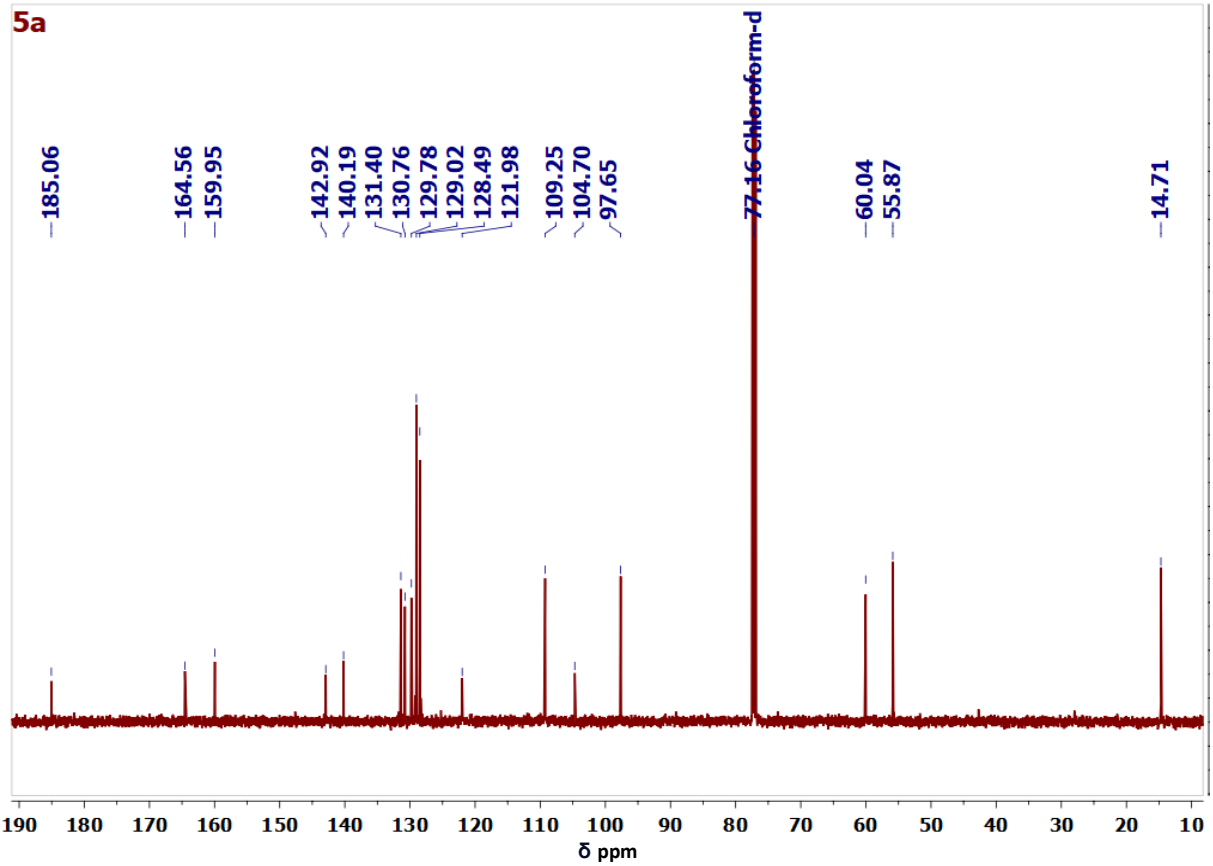


Figure S5- ^{13}C-NMR spectra of the ethyl 3-benzoyl-7-methoxyindolizine-1-carboxylate **(5a)**.

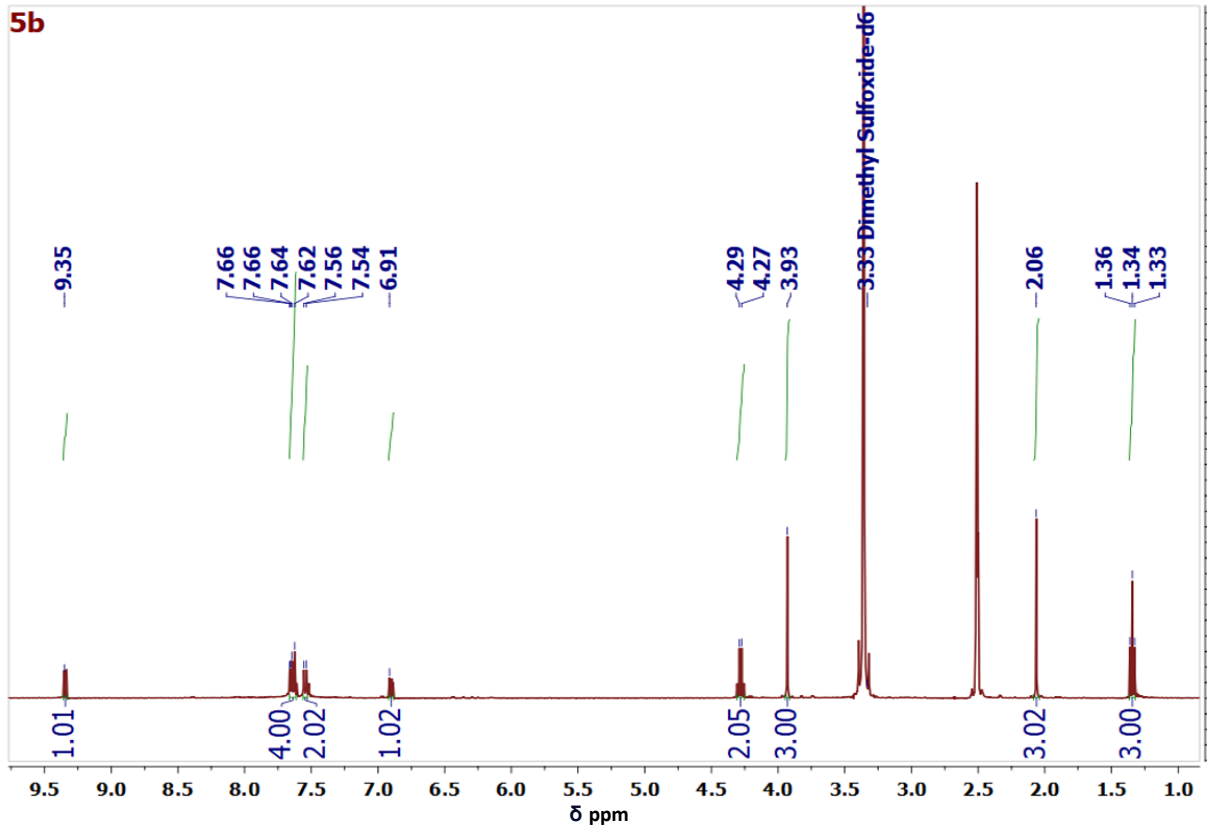


Figure S6- ^{1}H-NMR spectra of the ethyl 3-benzoyl-7-methoxy-2-methylindolizine-1-carboxylate **(5b)**.

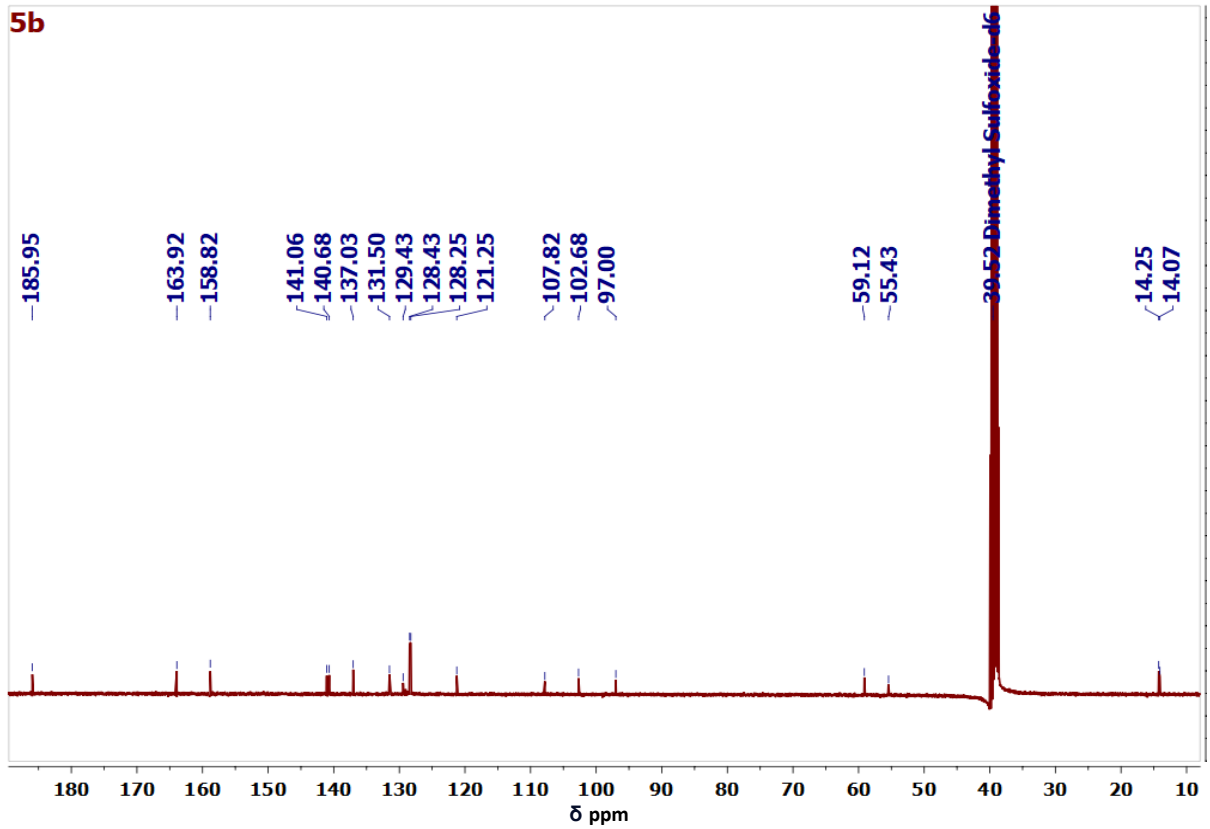


Figure S7- ^{13}C-NMR spectra of the ethyl 3-benzoyl-7-methoxy-2-methylindolizine-1-carboxylate **(5b)**.

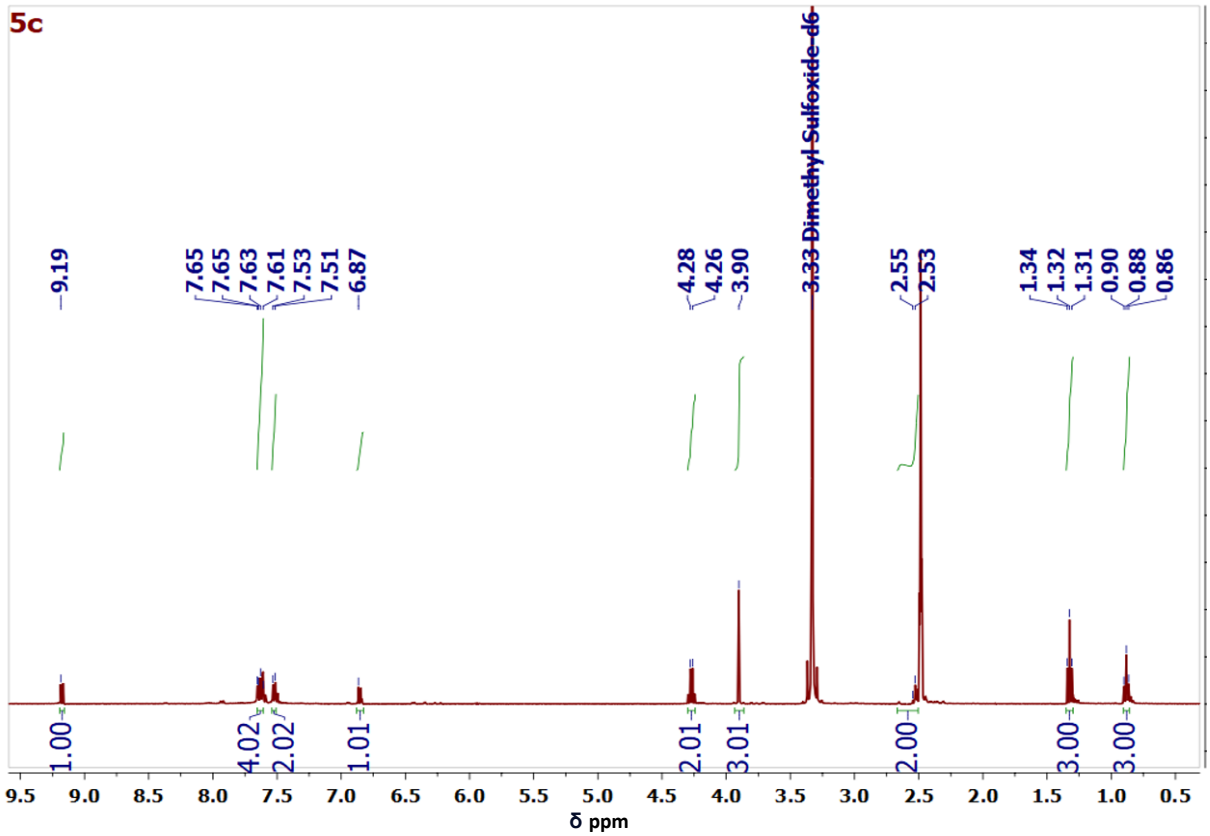


Figure S8- ^{1}H-NMR spectra of the ethyl 3-benzoyl-2-ethyl-7-methoxyindolizine-1-carboxylate **(5c)**.

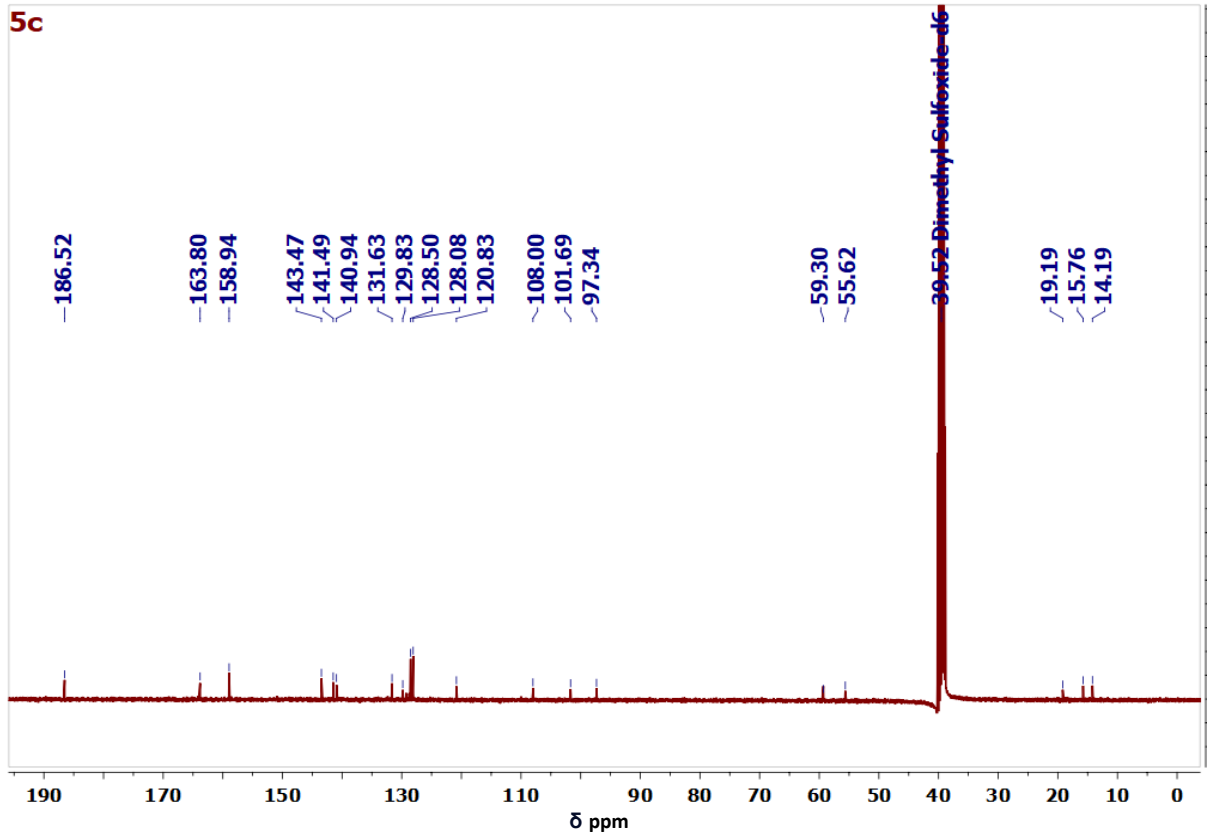


Figure S9- ^{13}C-NMR spectra of the ethyl 3-benzoyl-2-ethyl-7-methoxyindolizine-1-carboxylate **(5c)**.

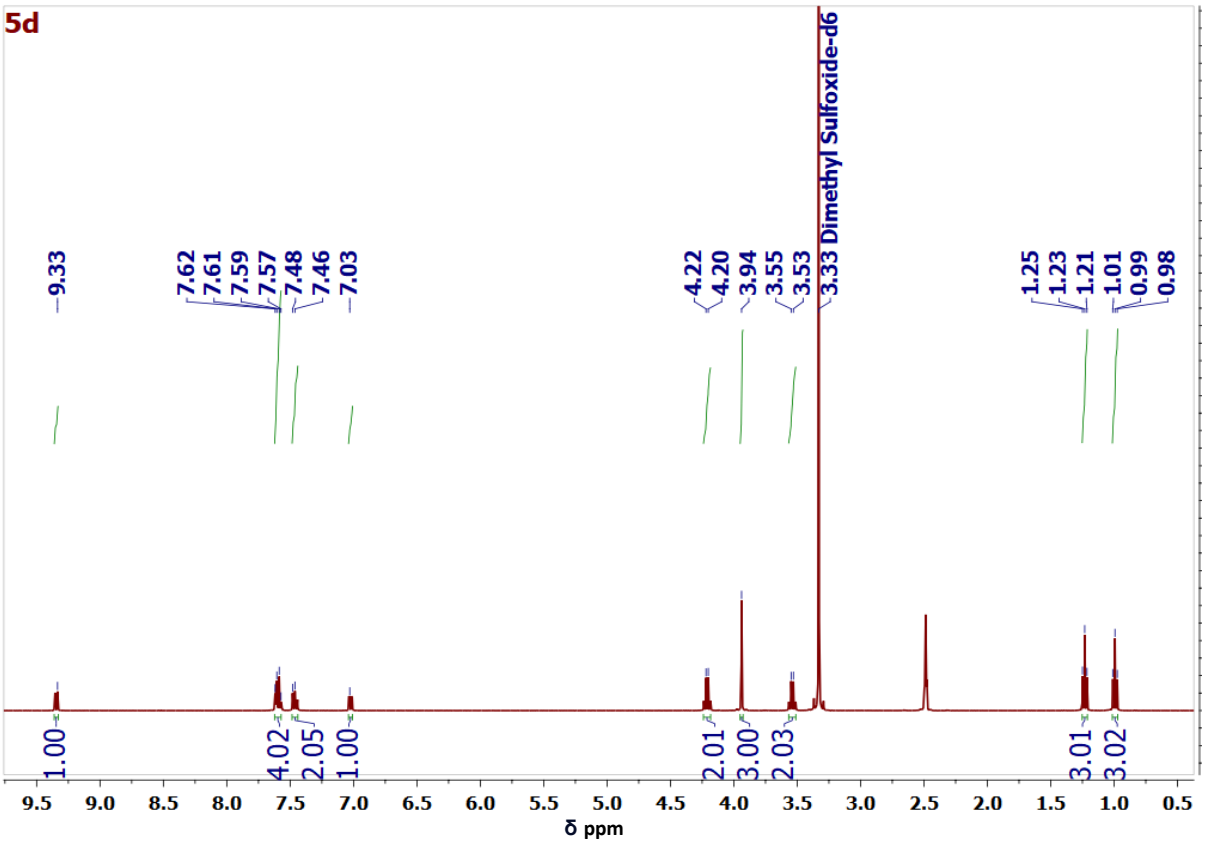


Figure S10- ^{1}H-NMR spectra of the diethyl 3-benzoyl-7-methoxyindolizine-1,2-dicarboxylate **(5d)**.

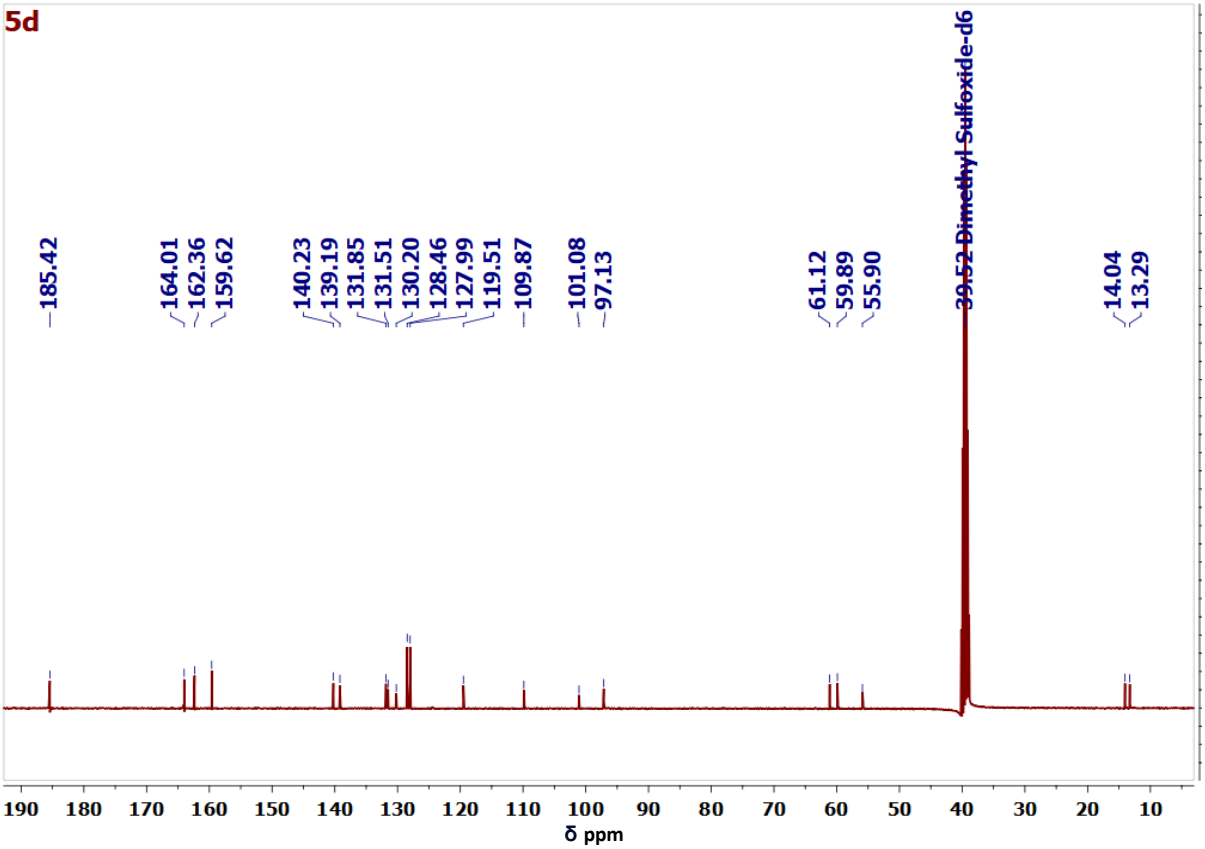


Figure S11- ^{13}C-NMR spectra of the diethyl 3-benzoyl-7-methoxyindolizine-1,2-dicarboxylate **(5d)**.

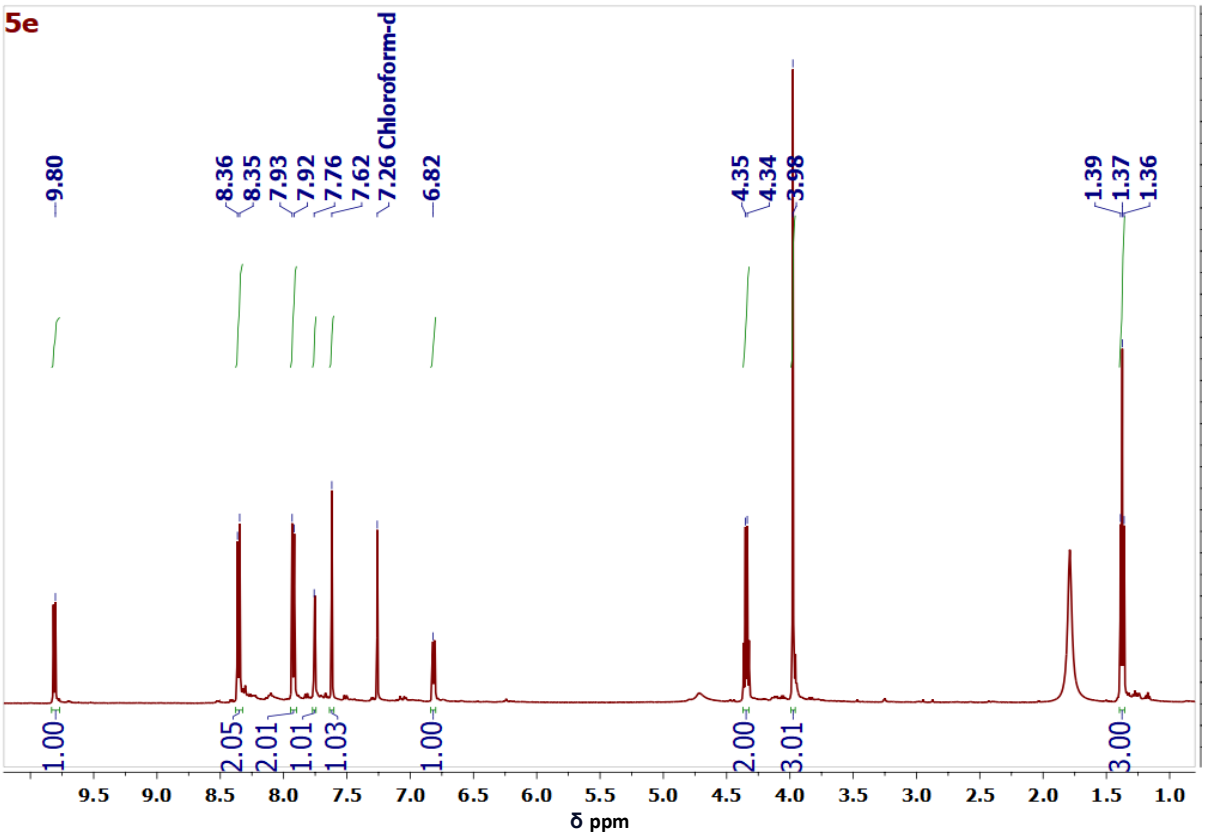


Figure S12- ^{1}H-NMR spectra of the ethyl 7-methoxy-3-(4-nitrobenzoyl)indolizine-1-carboxylate **(5e)**.

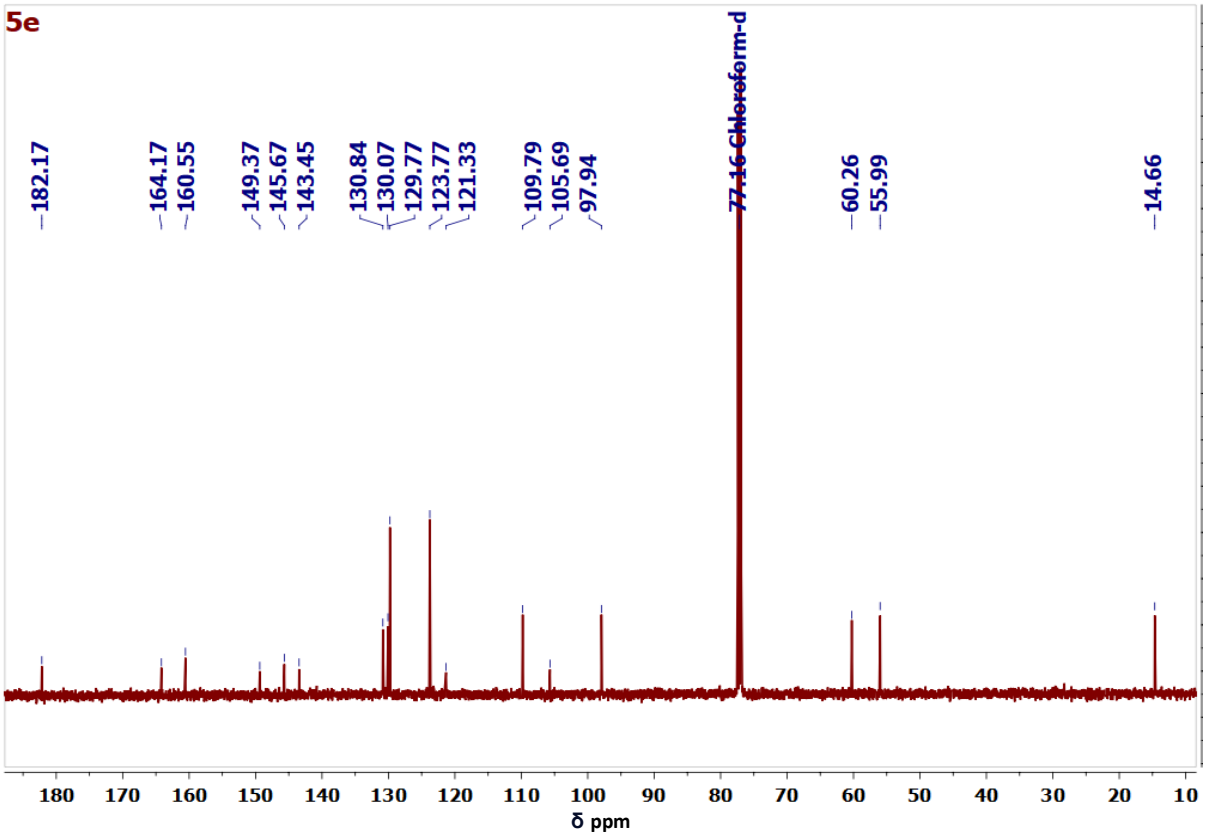


Figure S13- ^{13}C-NMR spectra of the ethyl 7-methoxy-3-(4-nitrobenzoyl)indolizine-1-carboxylate **(5e)**.

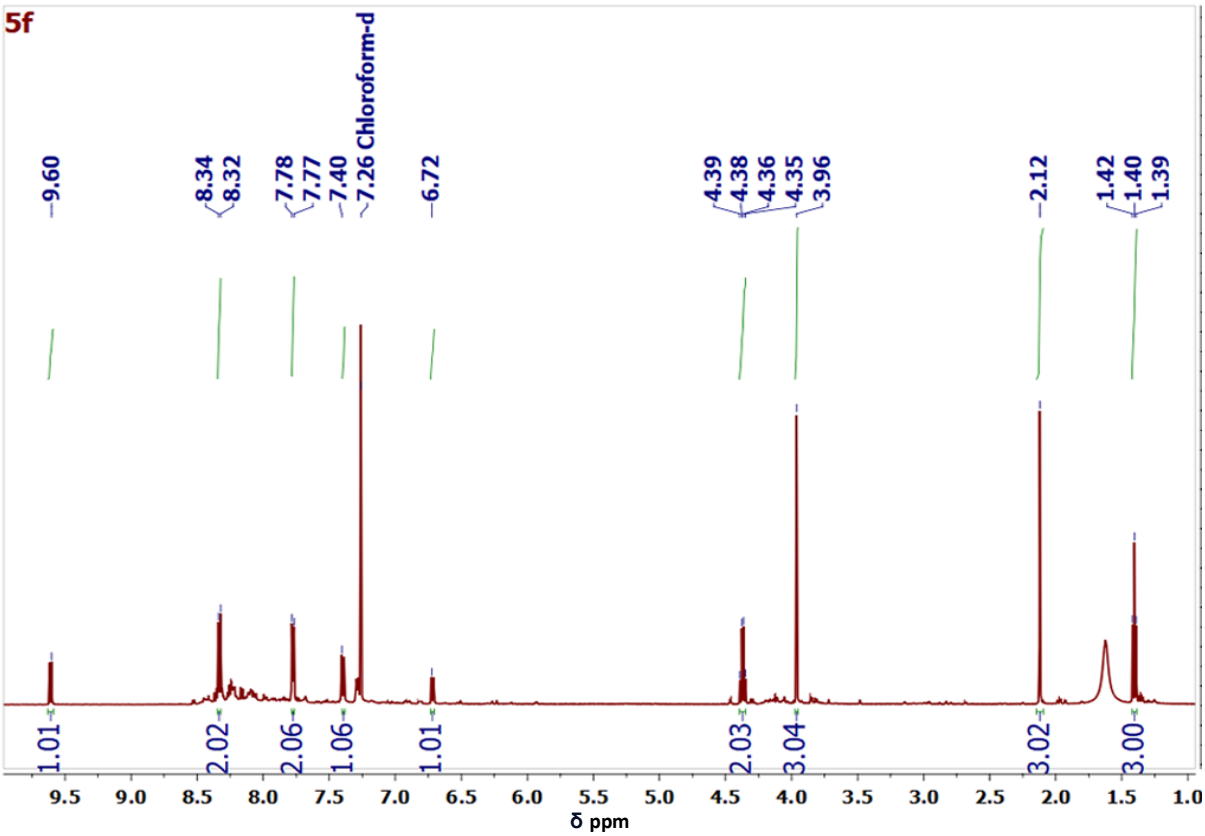


Figure S14- ^{1}H-NMR spectra of the ethyl 7-methoxy-3-(4-nitrobenzoyl)indolizine-1-carboxylate **(5f)**.

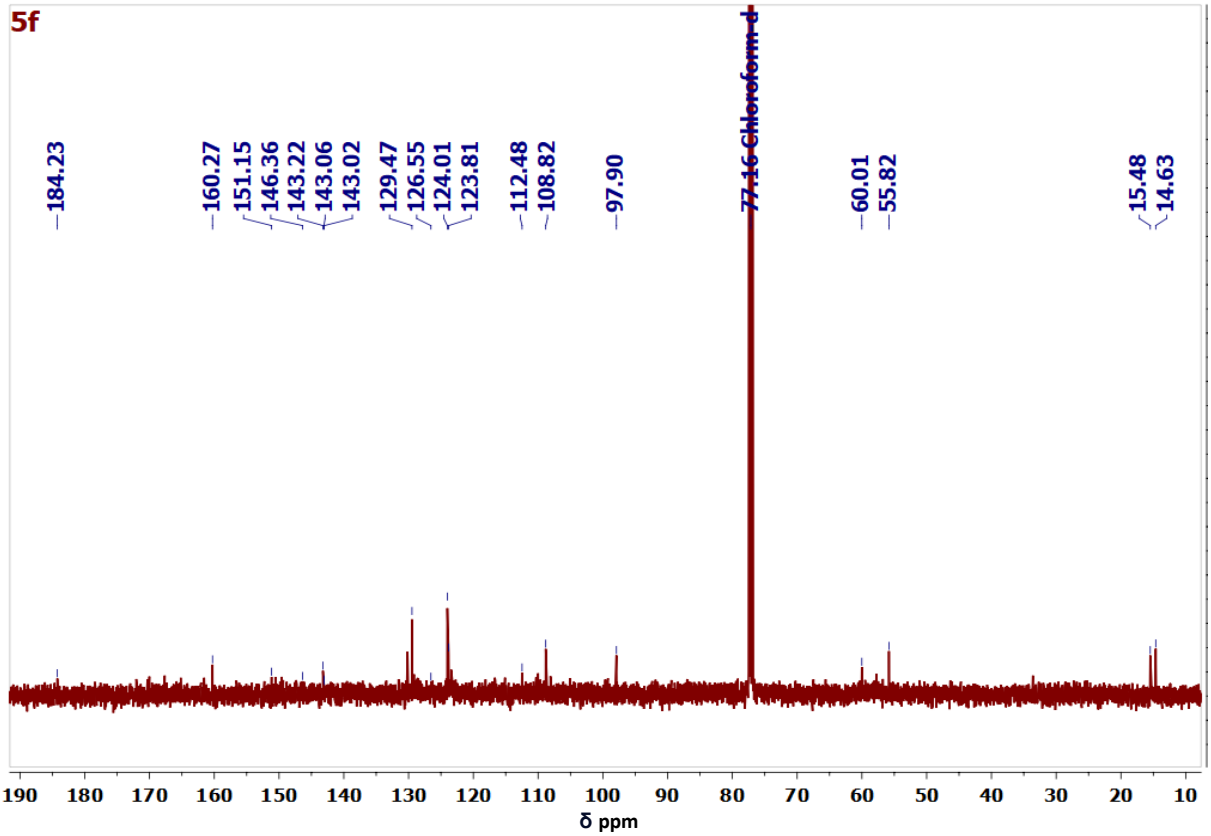


Figure S15- ^{13}C-NMR spectra of the ethyl 7-methoxy-3-(4-nitrobenzoyl)indolizine-1-carboxylate **(5f)**.

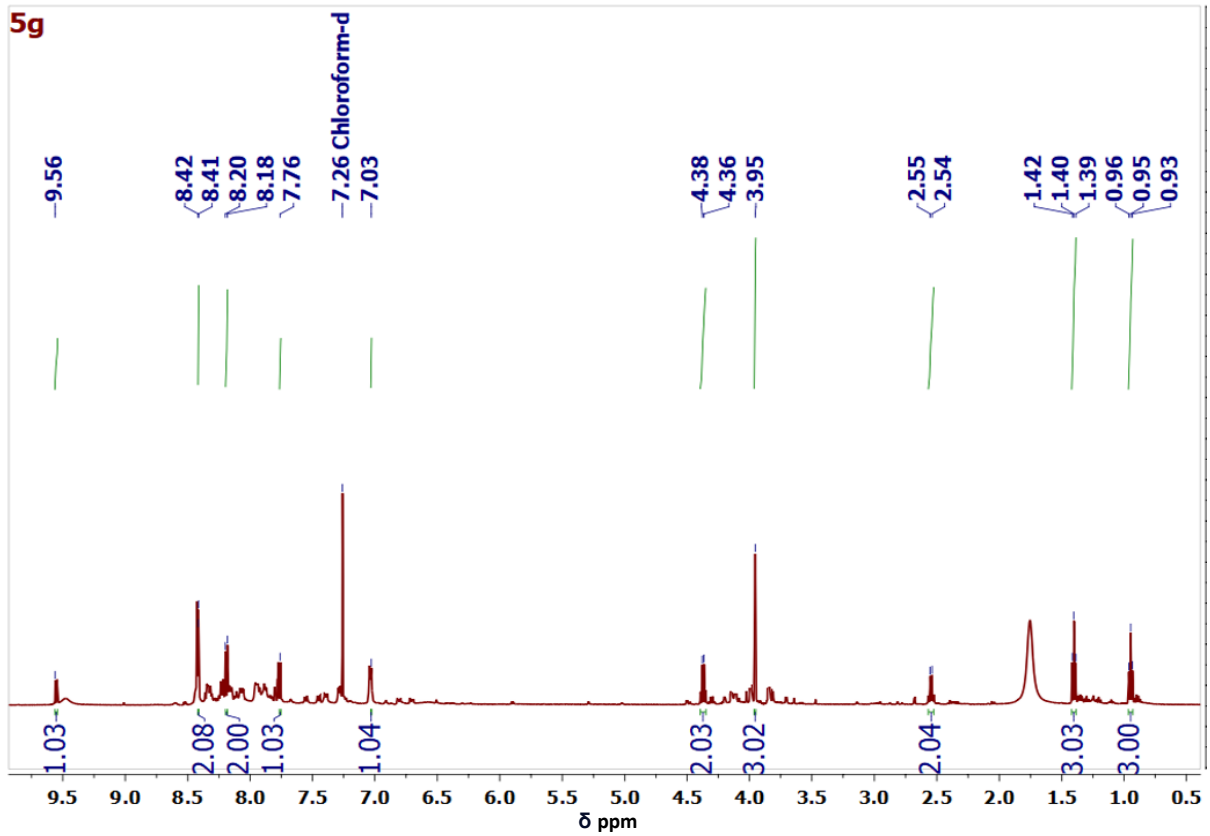


Figure S16- ^{1}H-NMR spectra of the ethyl 7-methoxy-3-(4-nitrobenzoyl)indolizine-1-carboxylate **(5g)**.

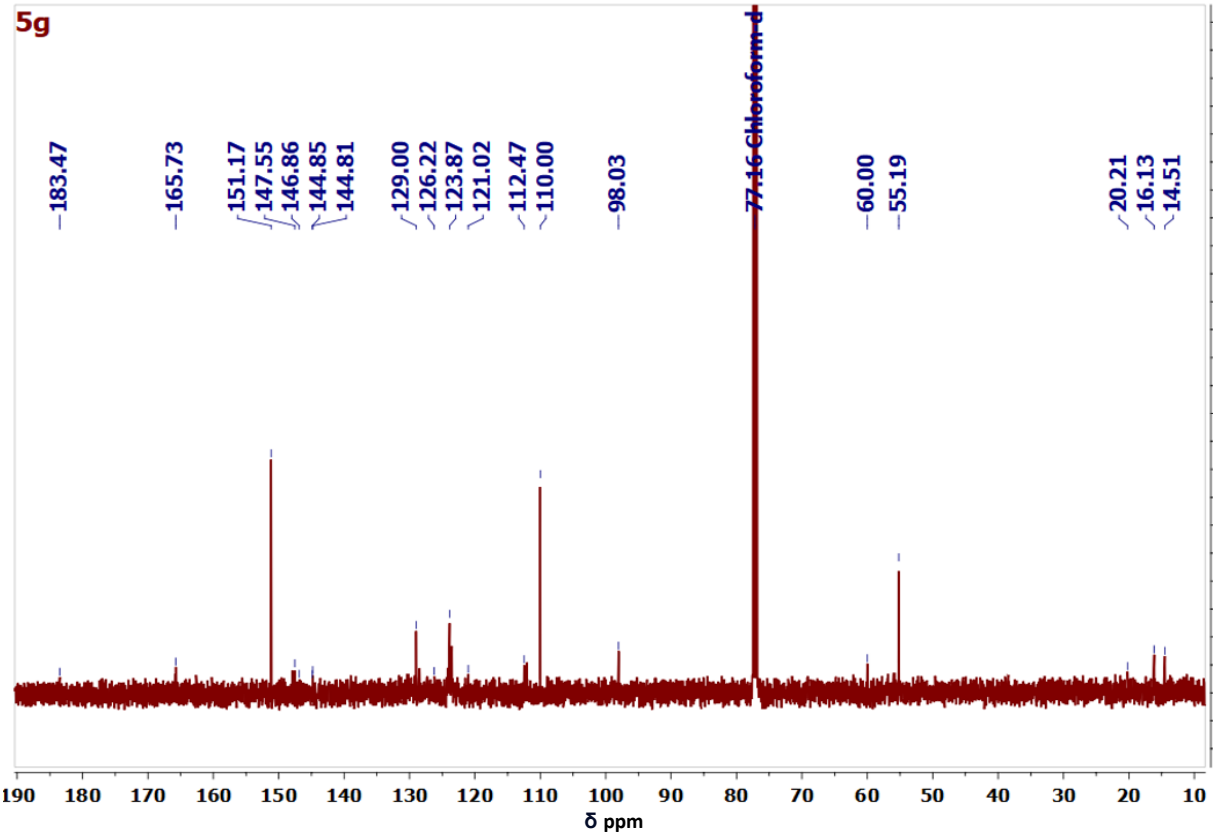


Figure S17- ^{13}C-NMR spectra of the ethyl 7-methoxy-3-(4-nitrobenzoyl)indolizine-1-carboxylate **(5g)**.

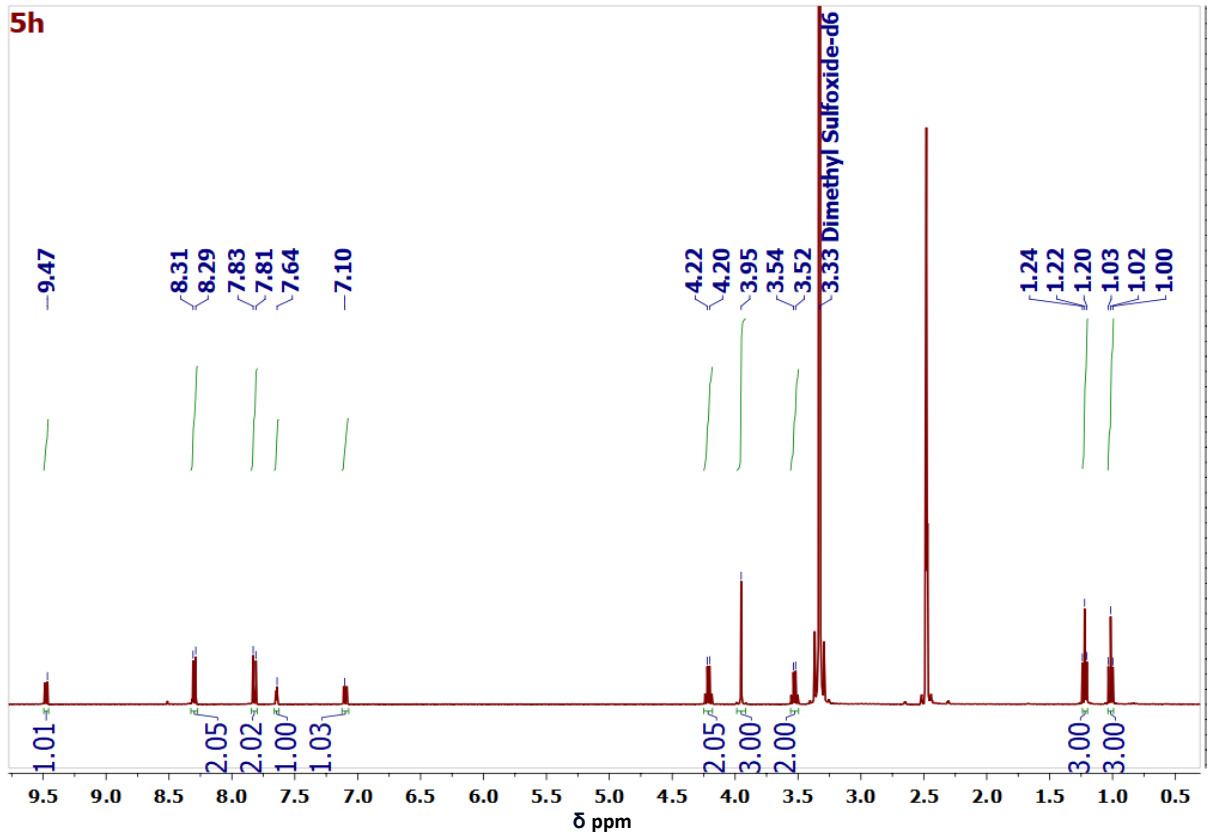


Figure S18- ^{1}H-NMR spectra of the diethyl 7-methoxy-3-(4-nitrobenzoyl)indolizine-1,2-dicarboxylate **(5h)**.

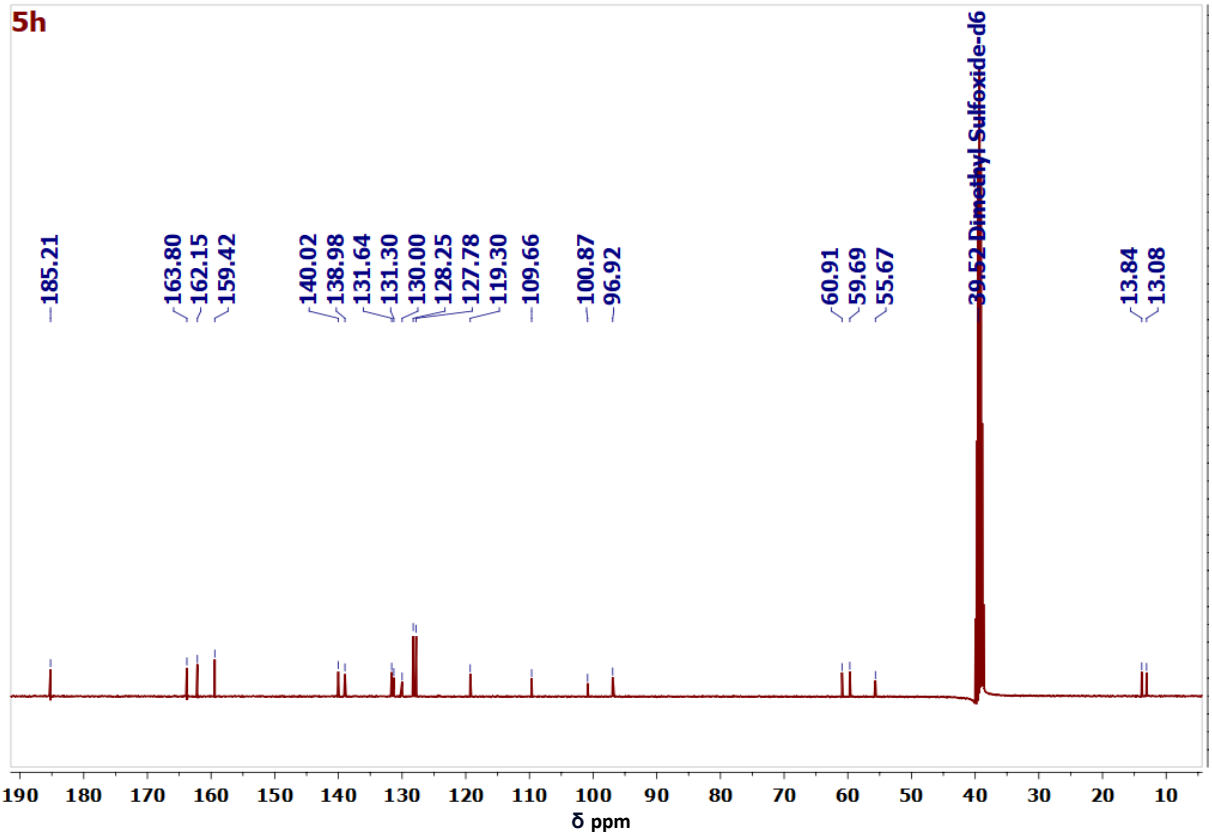


Figure S19- ^{13}C-NMR spectra of the diethyl 7-methoxy-3-(4-nitrobenzoyl)indolizine-1,2-dicarboxylate **(5h)**.

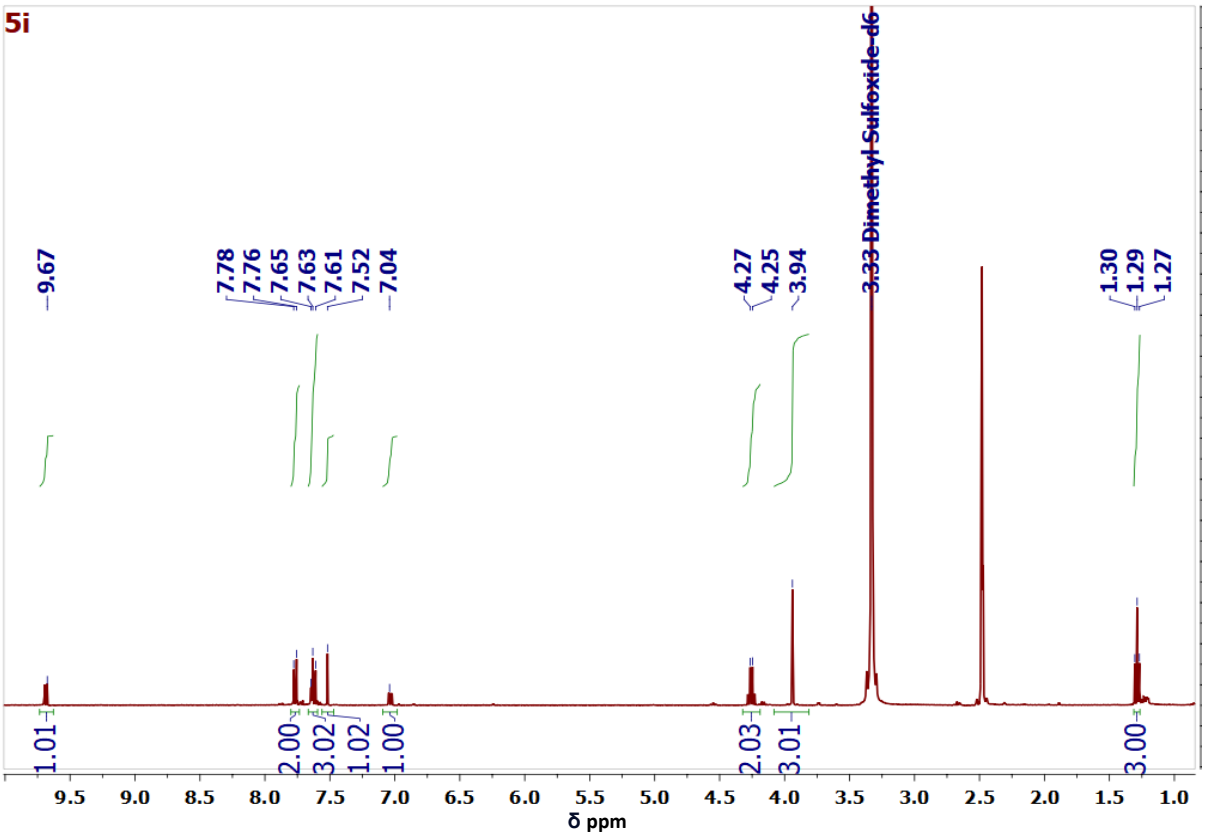


Figure S20- ^{1}H-NMR spectra of the ethyl 3-(4-chlorobenzoyl)-7-methoxyindolizine-1-carboxylate **(5i)**.

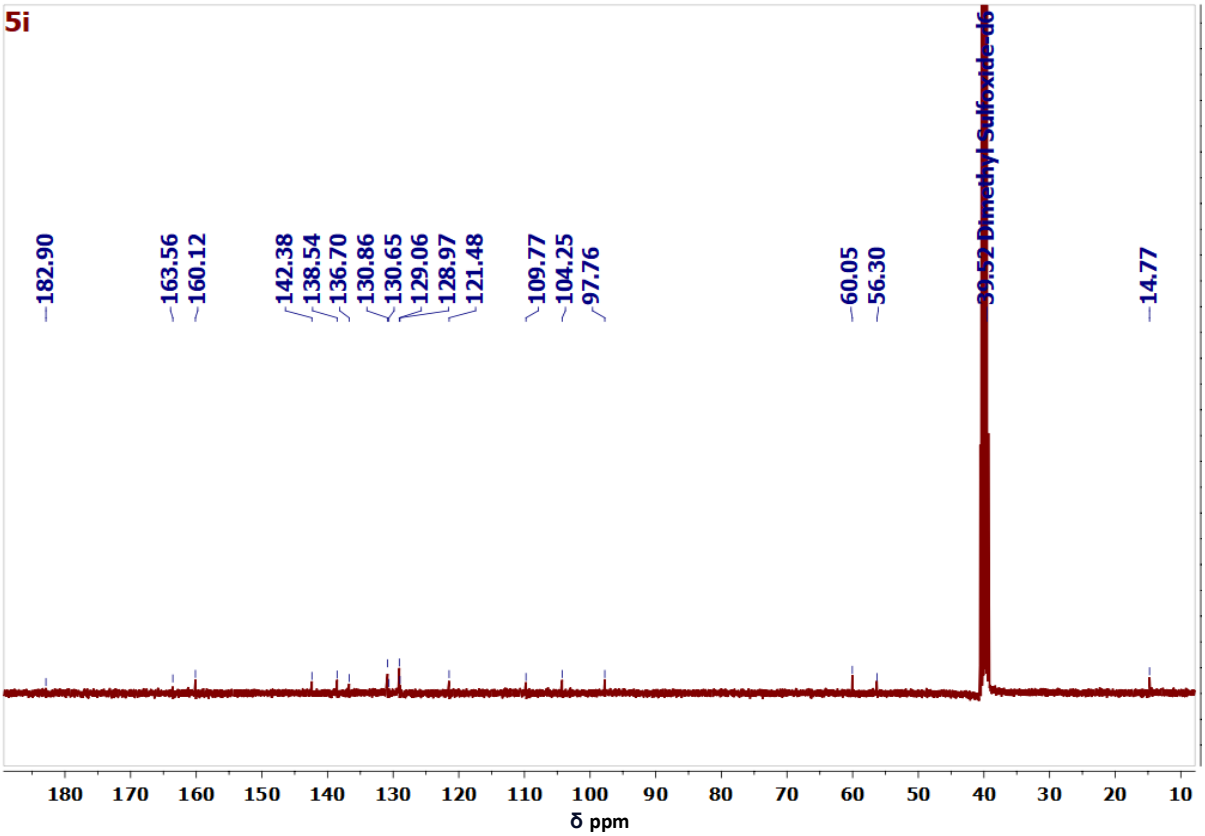


Figure S21- ^{13}C-NMR spectra of the ethyl 3-(4-chlorobenzoyl)-7-methoxyindolizine-1-carboxylate **(5i)**.

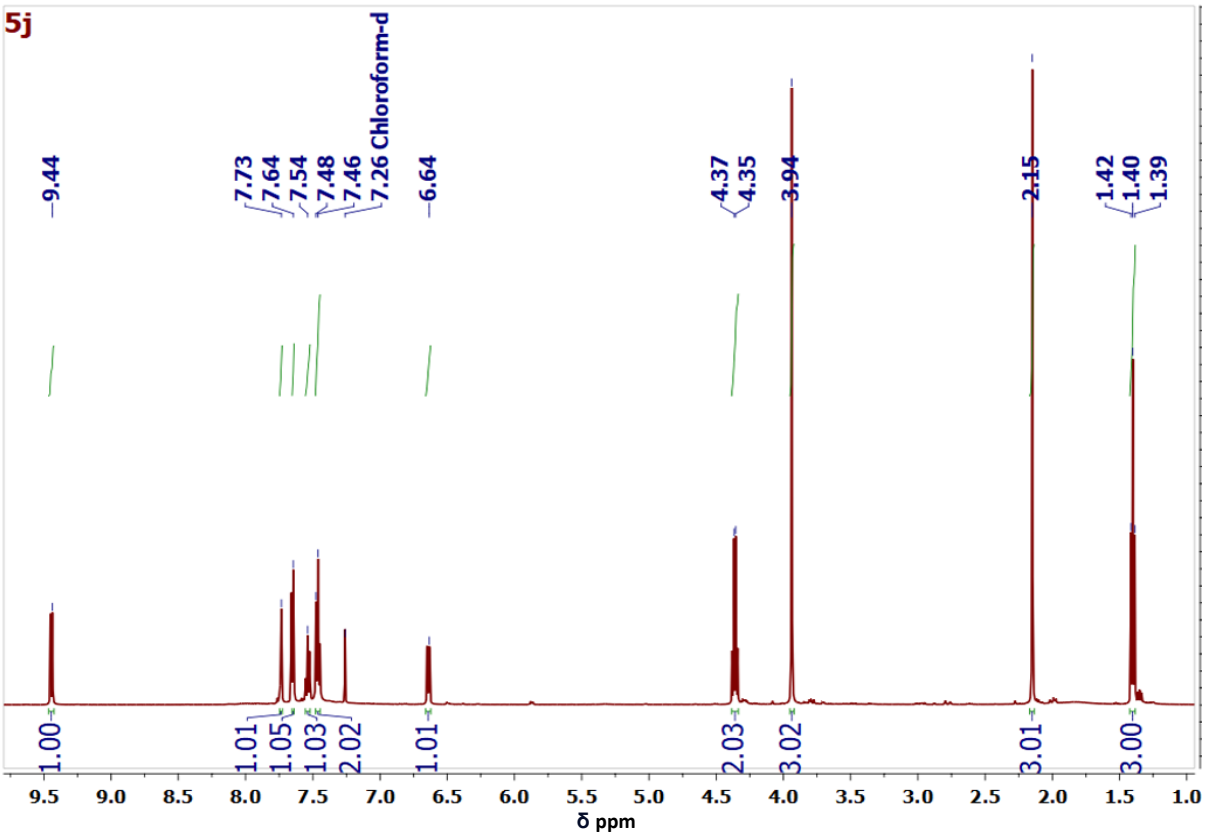


Figure S22- ^{1}H-NMR spectra of the diethyl 7-methoxy-3-(4-nitrobenzoyl)indolizine-1,2-dicarboxylate **(5j)**.

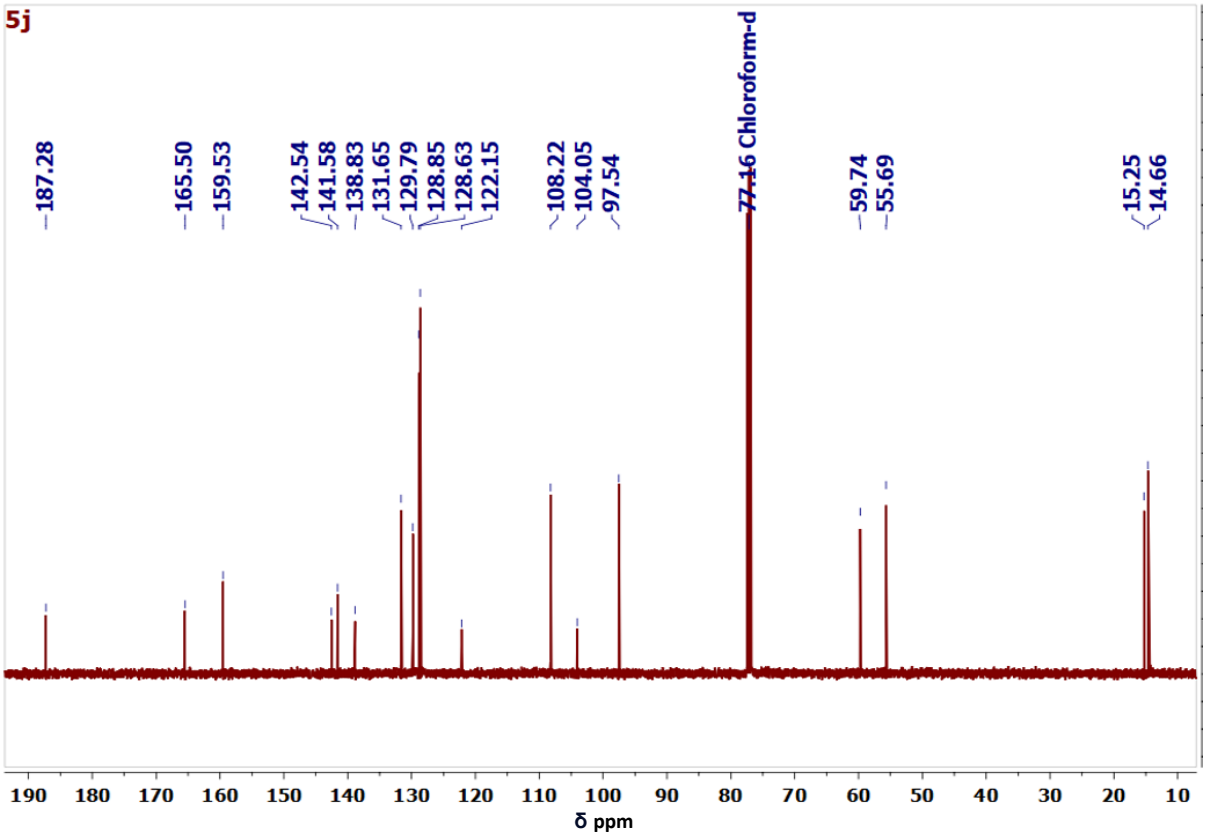


Figure S23- ^{13}C-NMR spectra of the diethyl 7-methoxy-3-(4-nitrobenzoyl)indolizine-1,2-dicarboxylate **(5j)**.

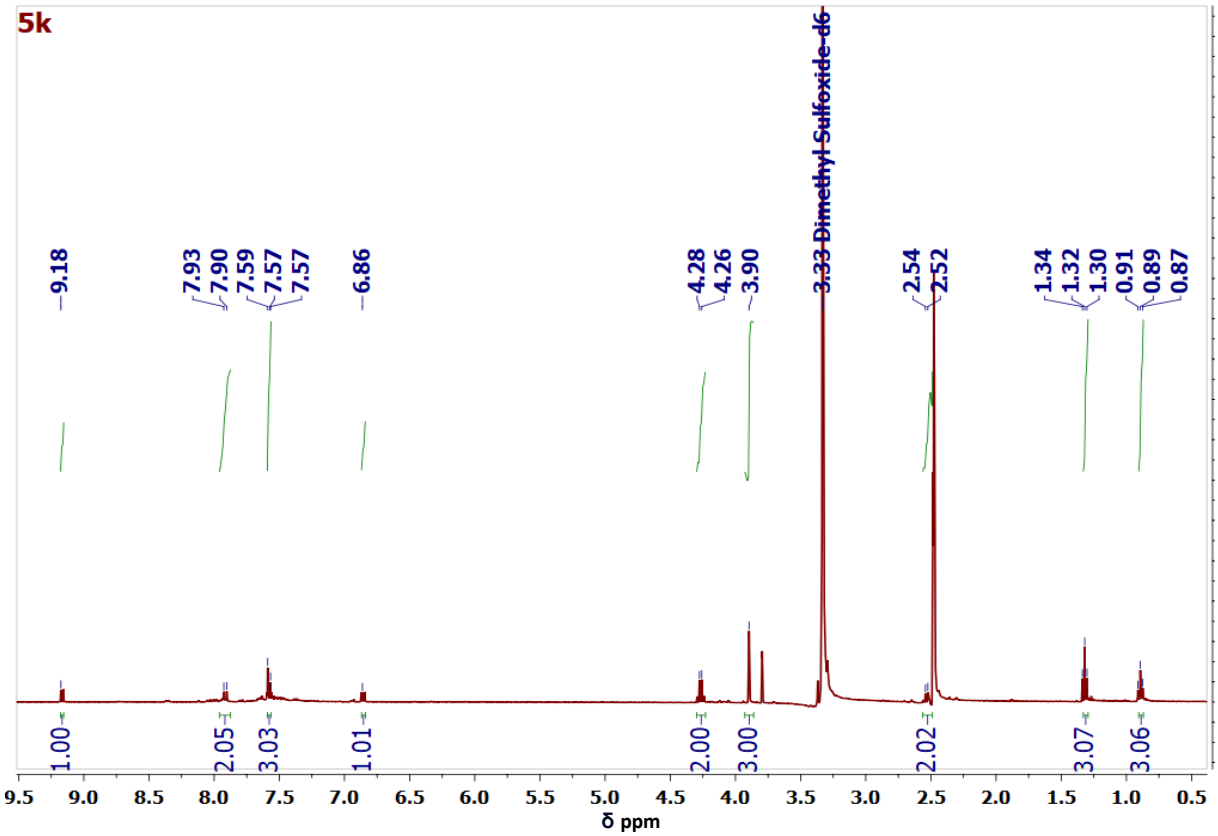


Figure S24- ^{1}H-NMR spectra of the ethyl 3-(4-chlorobenzoyl)-7-methoxy-2-methylindolizine-1-carboxylate **(5k)**.

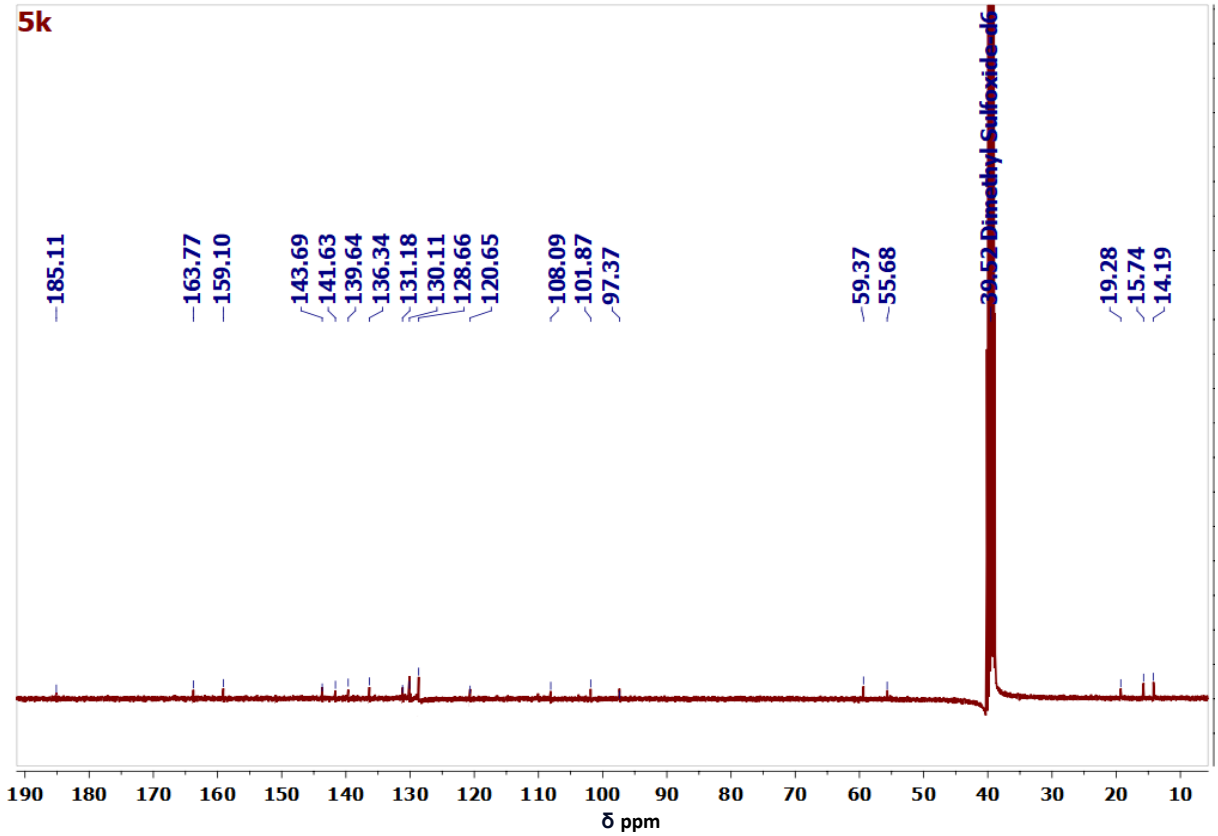


Figure S25- ^{13}C-NMR spectra of the ethyl 3-(4-chlorobenzoyl)-7-methoxy-2-methylindolizine-1-carboxylate **(5k)**.

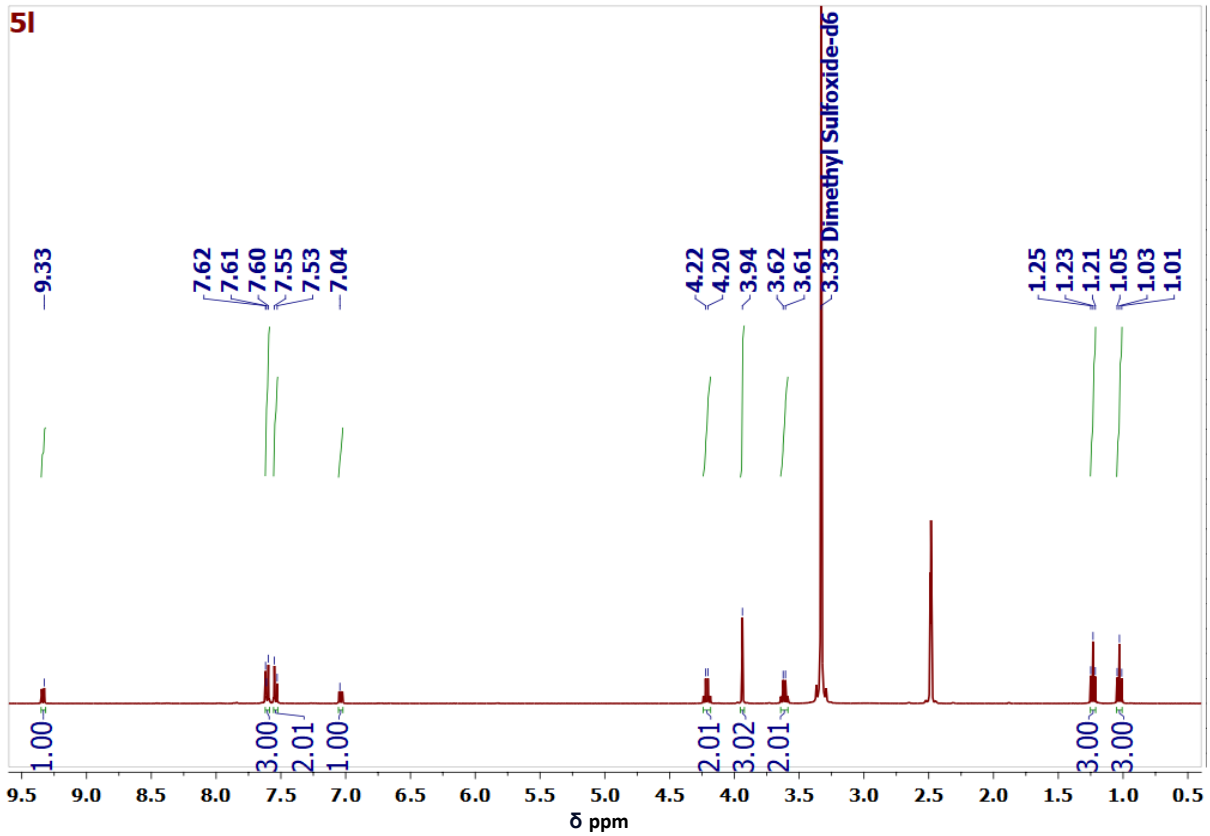


Figure S26- ^{1}H-NMR spectra of the diethyl 3-(4-chlorobenzoyl)-7-methoxyindolizine-1,2-dicarboxylate **(5l)**.

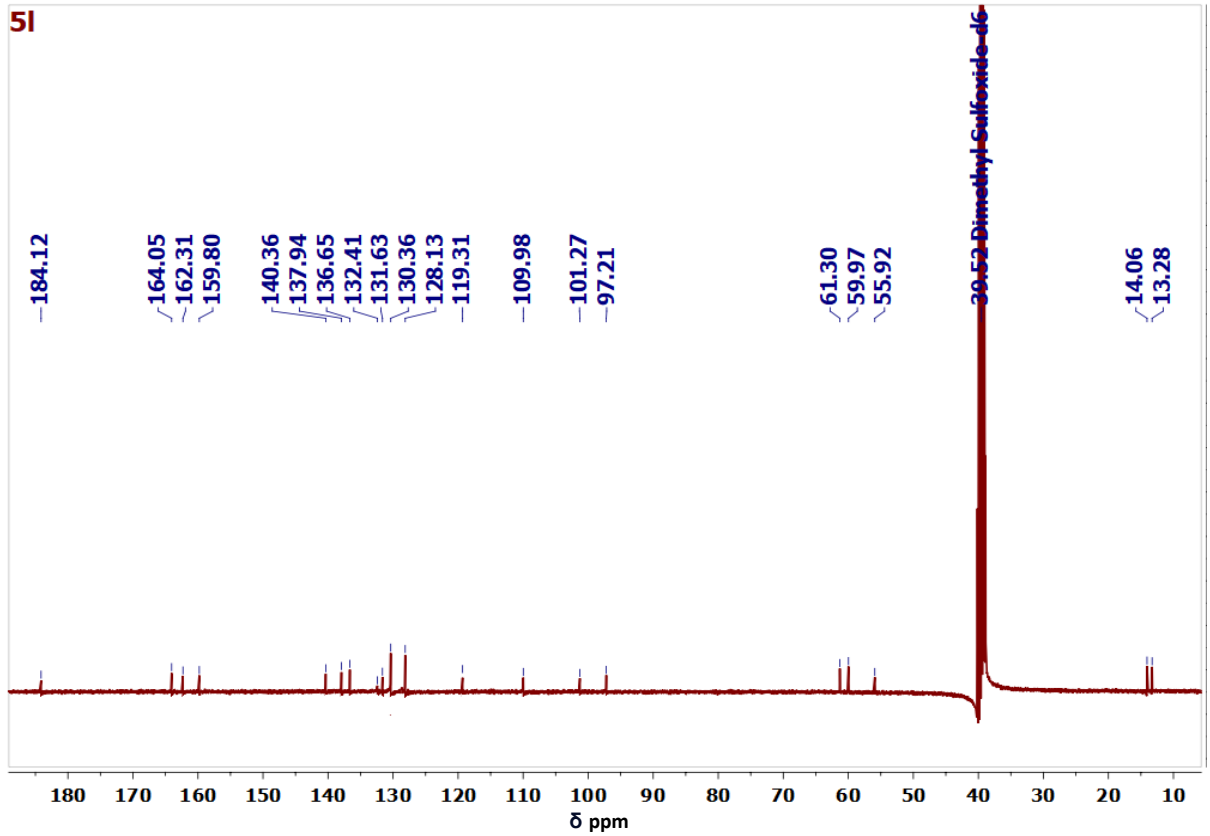


Figure S27- ^{13}C-NMR spectra of the diethyl 3-(4-chlorobenzoyl)-7-methoxyindolizine-1,2-dicarboxylate **(5l)**.

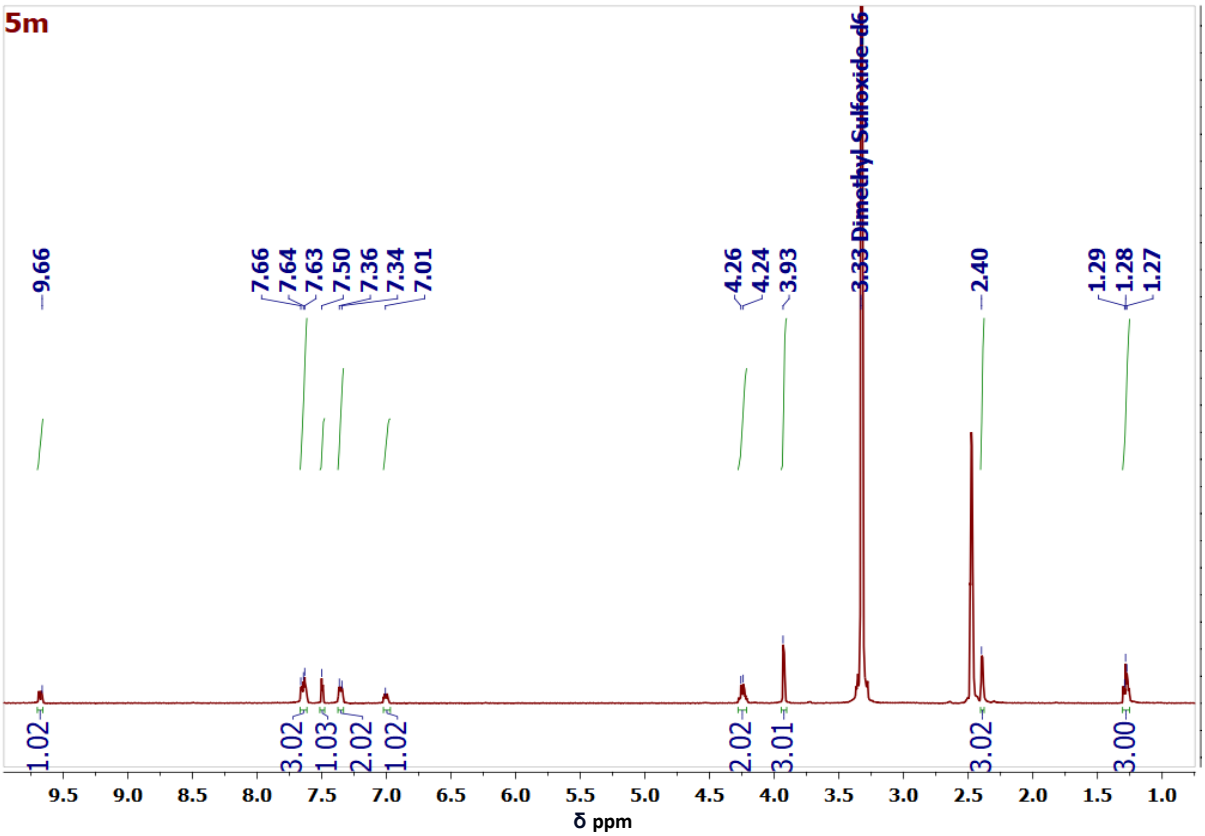


Figure S28- ^{1}H-NMR spectra of the ethyl 7-methoxy-3-(4-methylbenzoyl)indolizine-1-carboxylate **(5m)**.

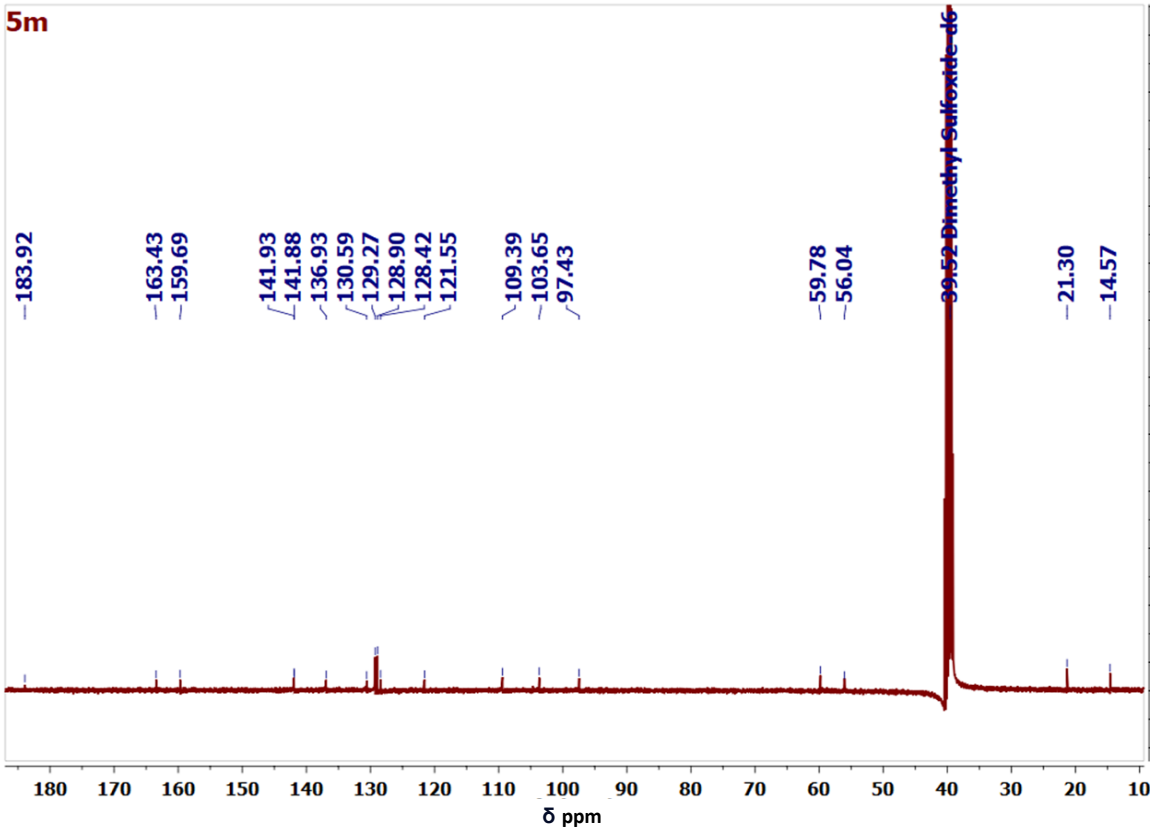


Figure S29- ^{13}C-NMR spectra of the ethyl 7-methoxy-3-(4-methylbenzoyl)indolizine-1-carboxylate **(5m)**.

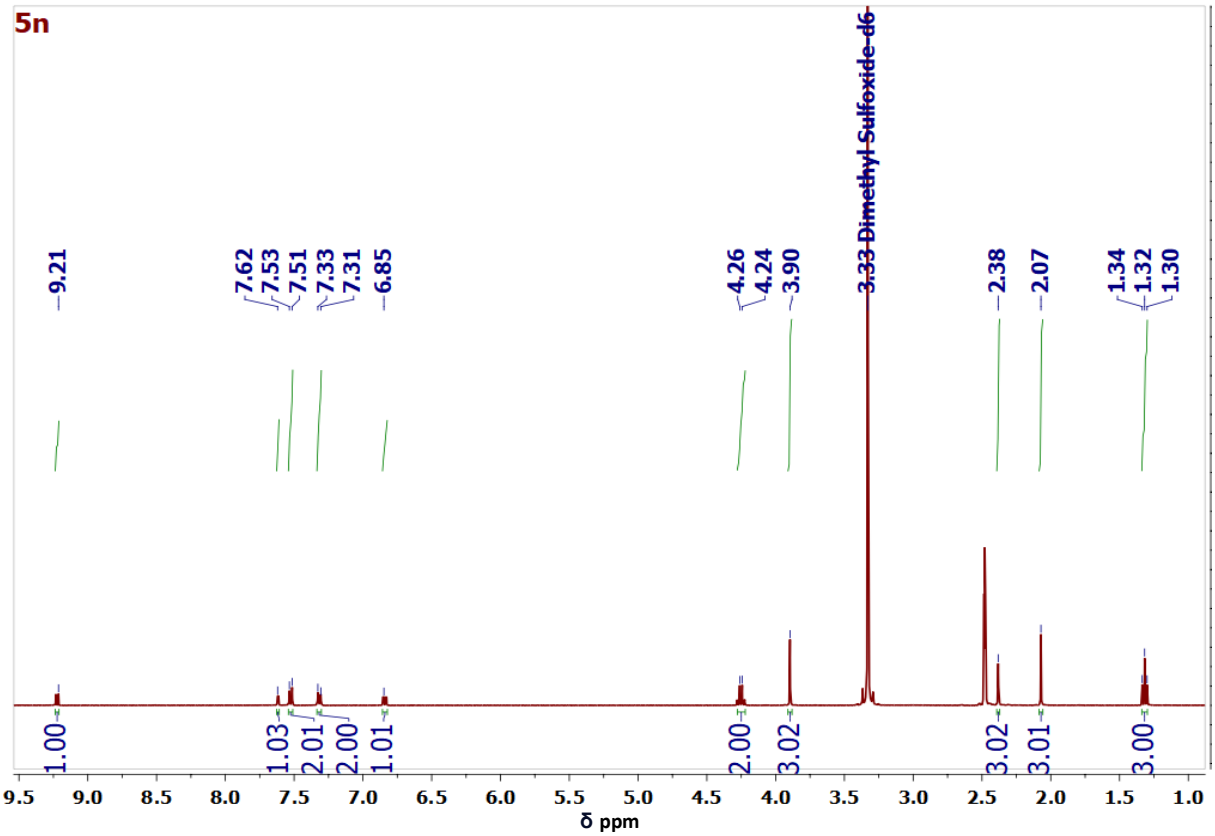


Figure S30- ^{1}H-NMR spectra of the ethyl 7-methoxy-2-methyl-3-(4-methylbenzoyl)indolizine-1-carboxylate **(5n)**.

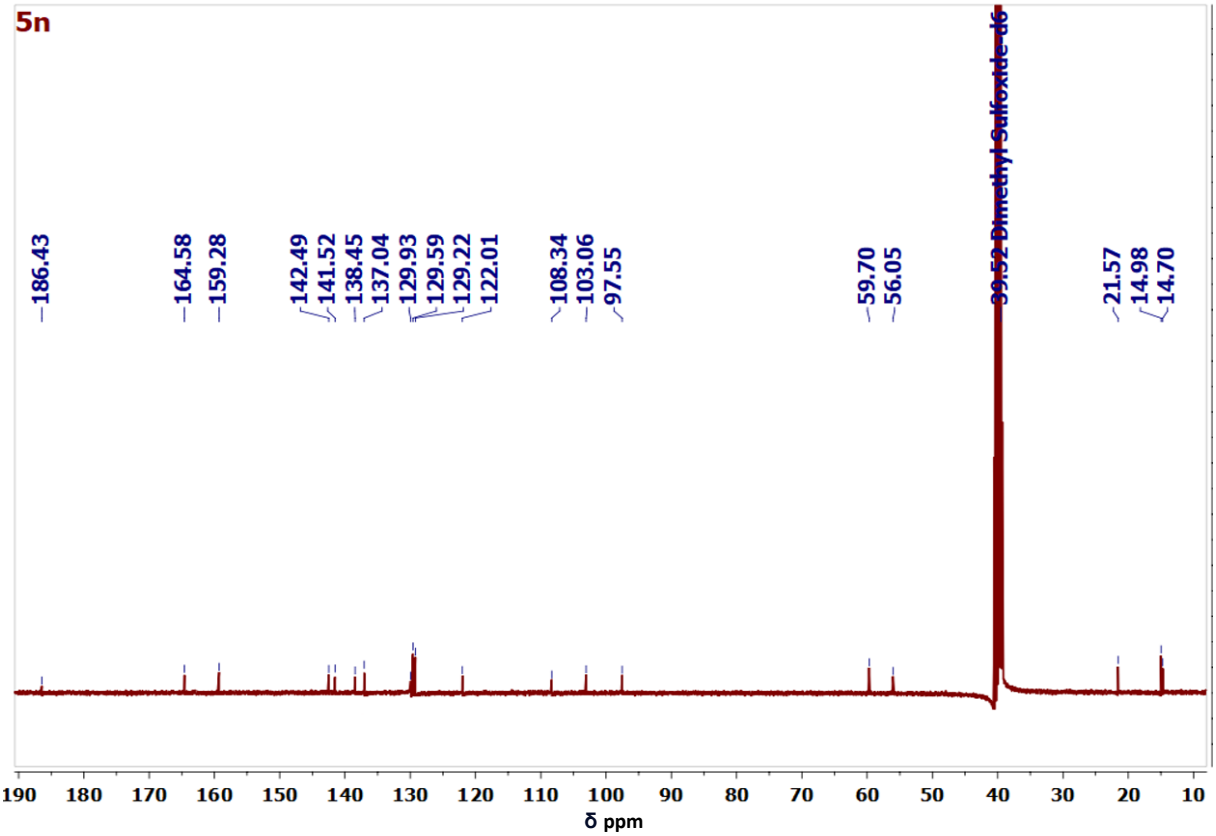


Figure S31- ^{13}C-NMR spectra of the ethyl 7-methoxy-2-methyl-3-(4-methylbenzoyl)indolizine-1-carboxylate **(5n)**.

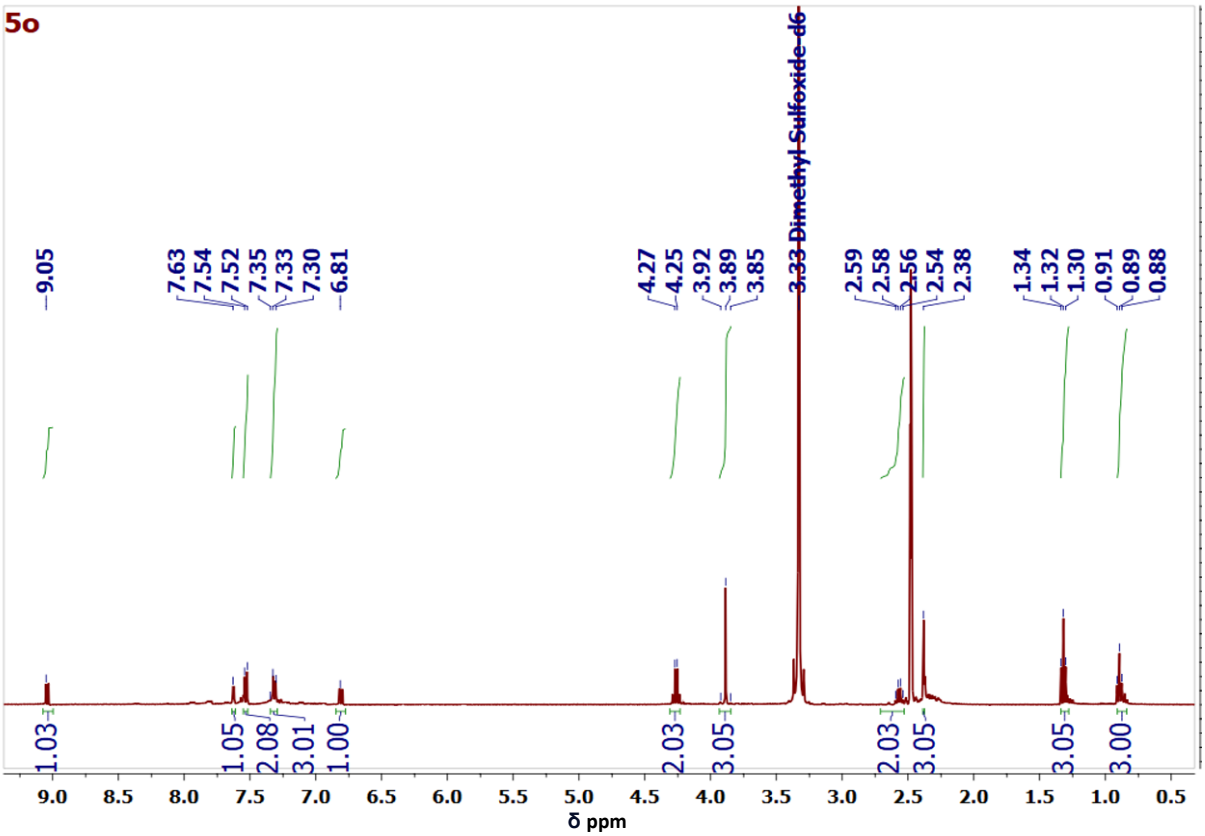


Figure S32- ^{1}H-NMR spectra of the ethyl 2-ethyl-7-methoxy-3-(4-methylbenzoyl)indolizine-1-carboxylate **(5o)**.

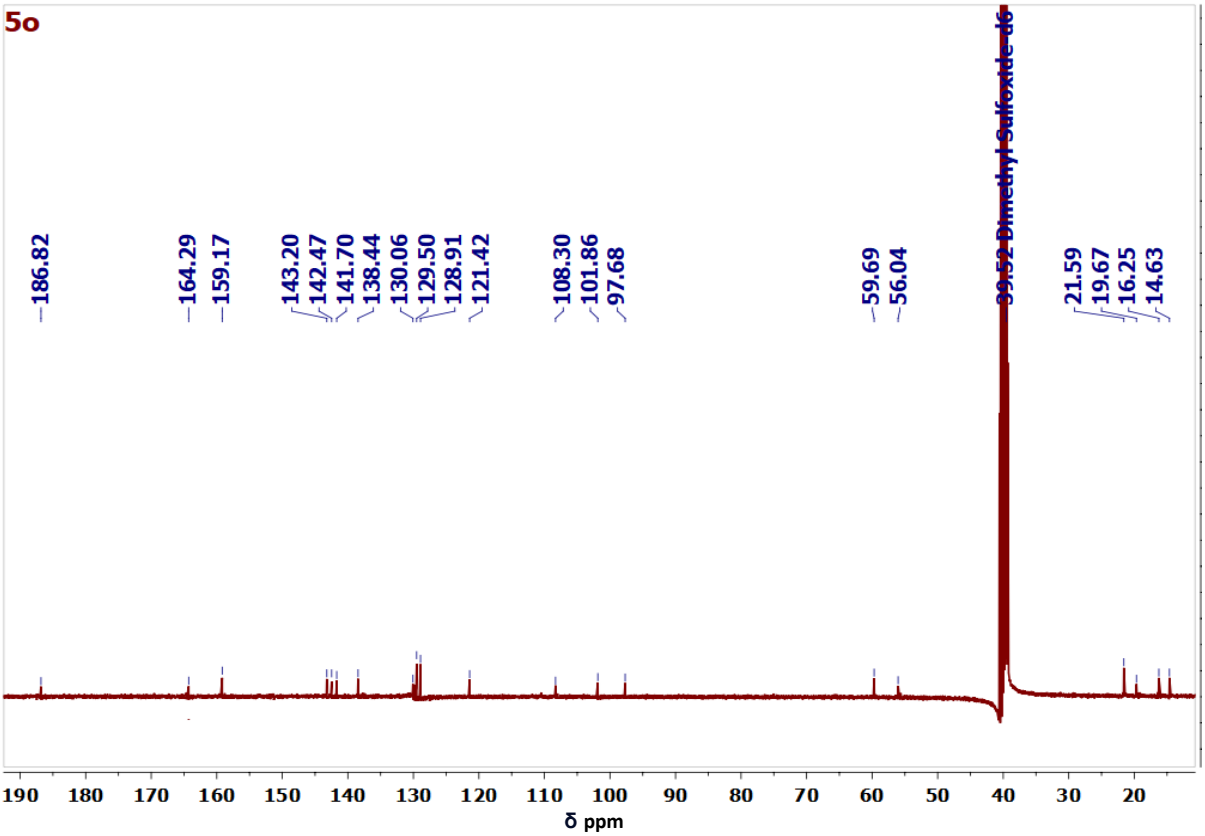


Figure S33- ^{13}C-NMR spectra of the ethyl 2-ethyl-7-methoxy-3-(4-methylbenzoyl)indolizine-1-carboxylate **(5o)**.

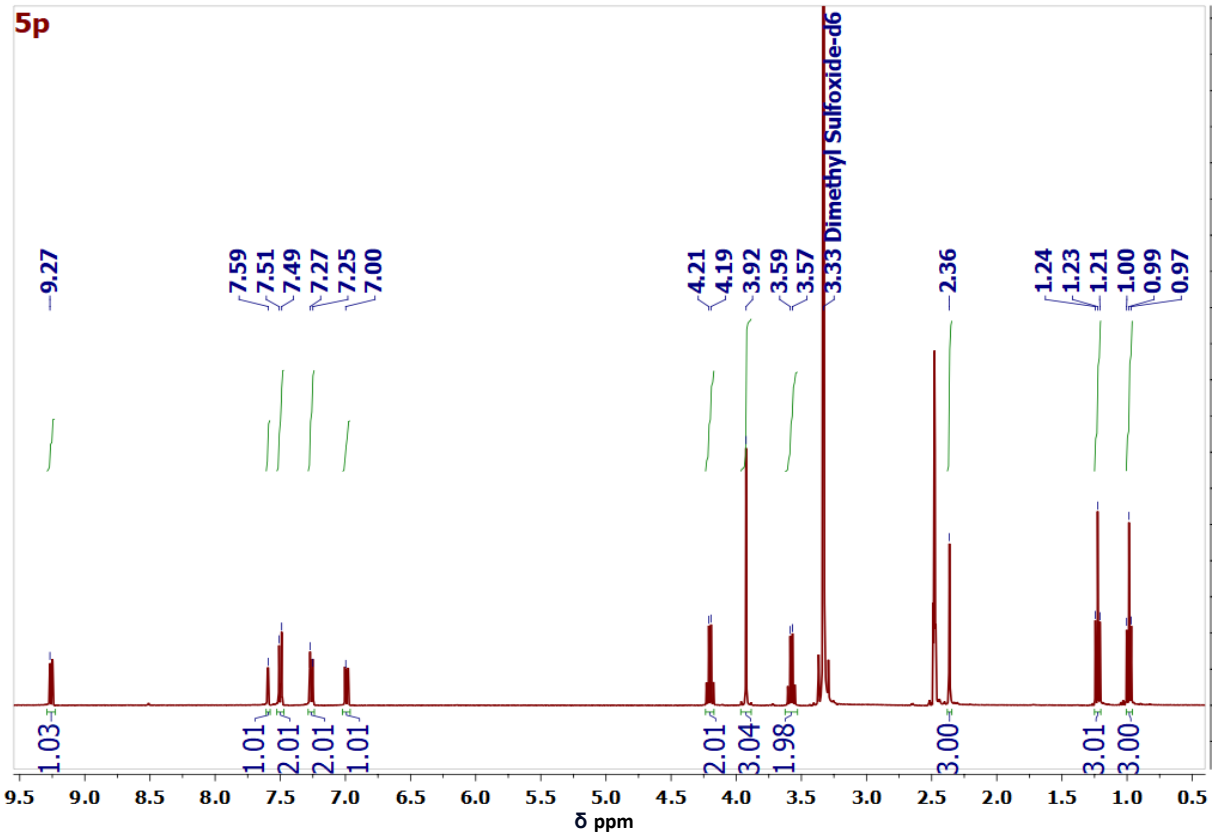


Figure S34- ^{1}H-NMR spectra of the diethyl 7-methoxy-3-(4-methylbenzoyl)indolizine-1,2-dicarboxylate **(5p)**.

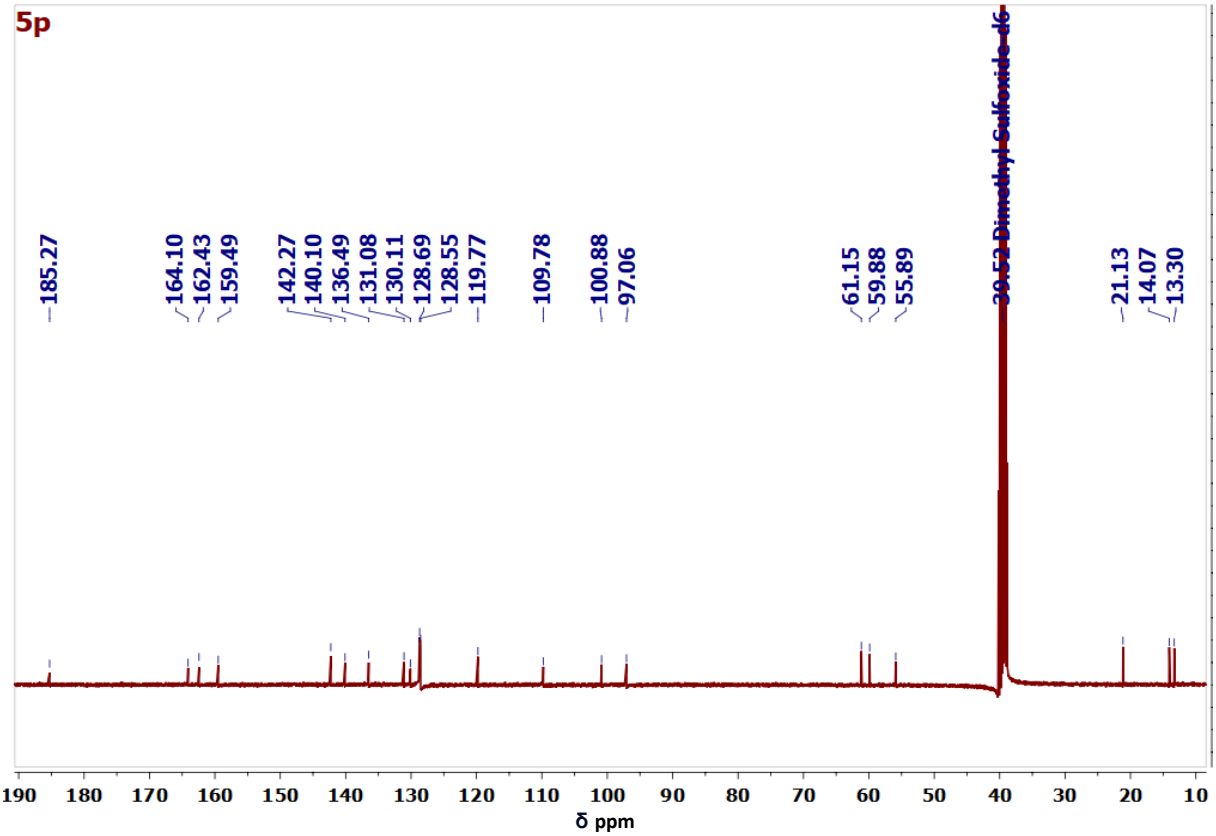


Figure S35- ^{13}C-NMR spectra of the diethyl 7-methoxy-3-(4-methylbenzoyl)indolizine-1,2-dicarboxylate **(5p)**.

3. Single-Crystal Morphology

3.1 Optical images of crystals of the synthesized compounds

The morphology of the obtained crystals was analyzed using a Nikon Polarized optical microscope (POM). The single crystals of the indolizine derivatives (**5a**, **5b**, **5d**, **5h**, **5l**, **5n**, and **5p**) are shown in **Figure S36**.

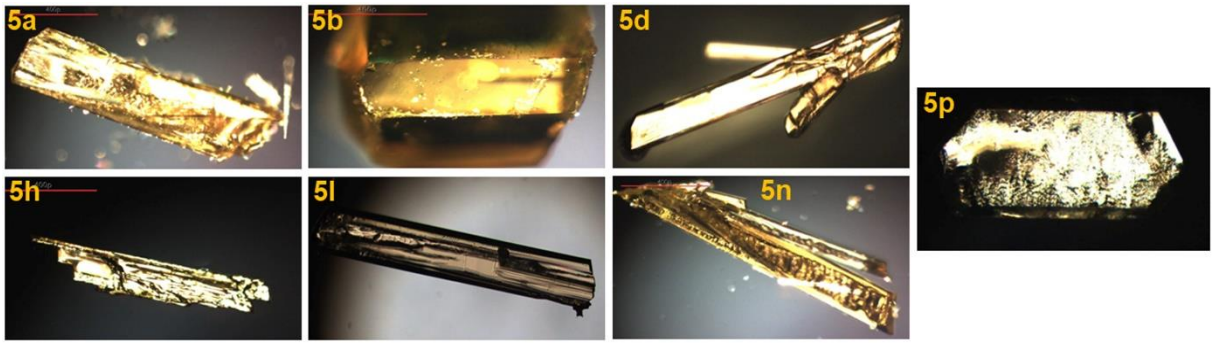


Figure S36- Optical images of single crystals view of pure indolizine derivatives.

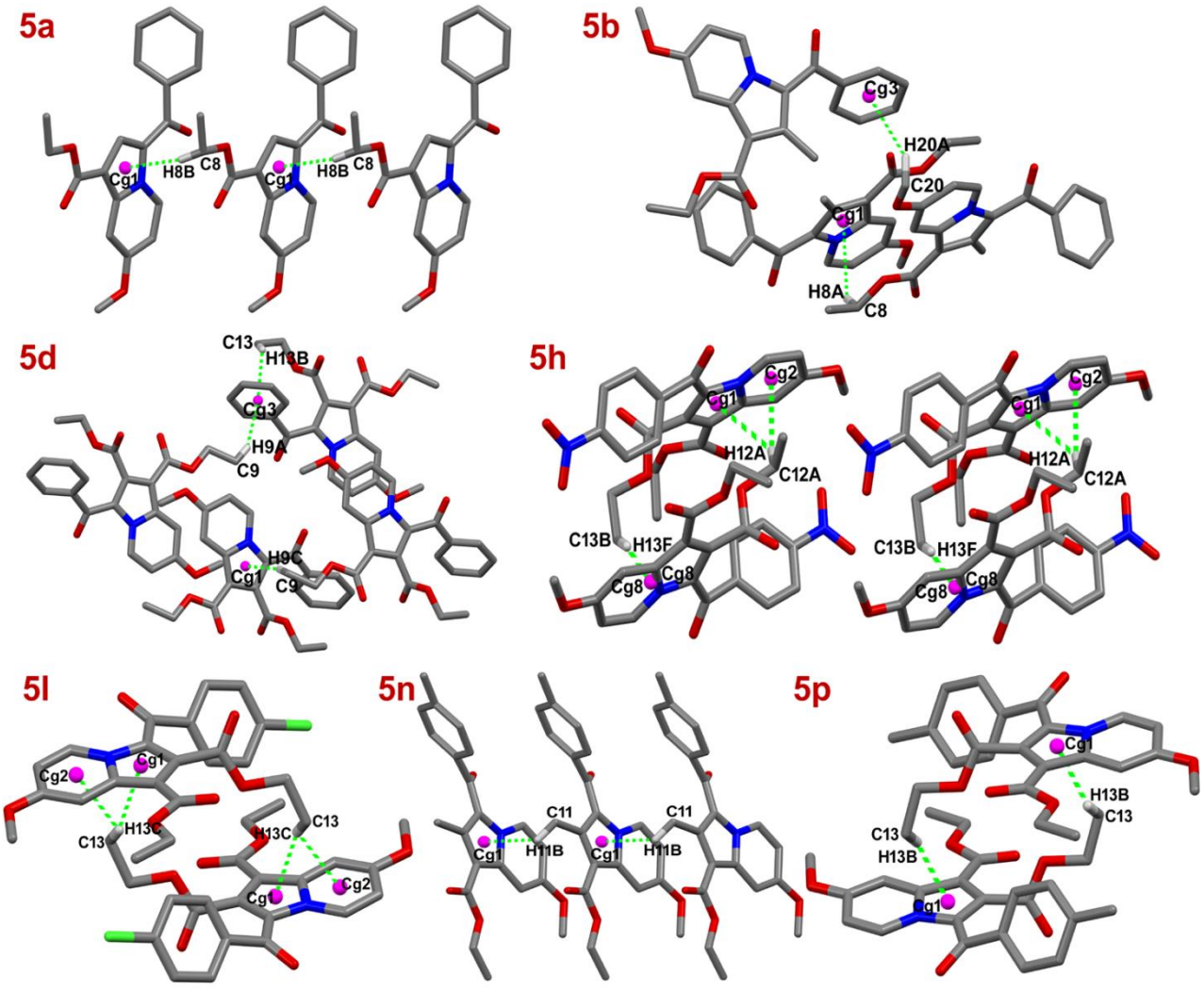


Figure S37- The C-H···π contacts exist in the crystal structures in its molecular assembly.

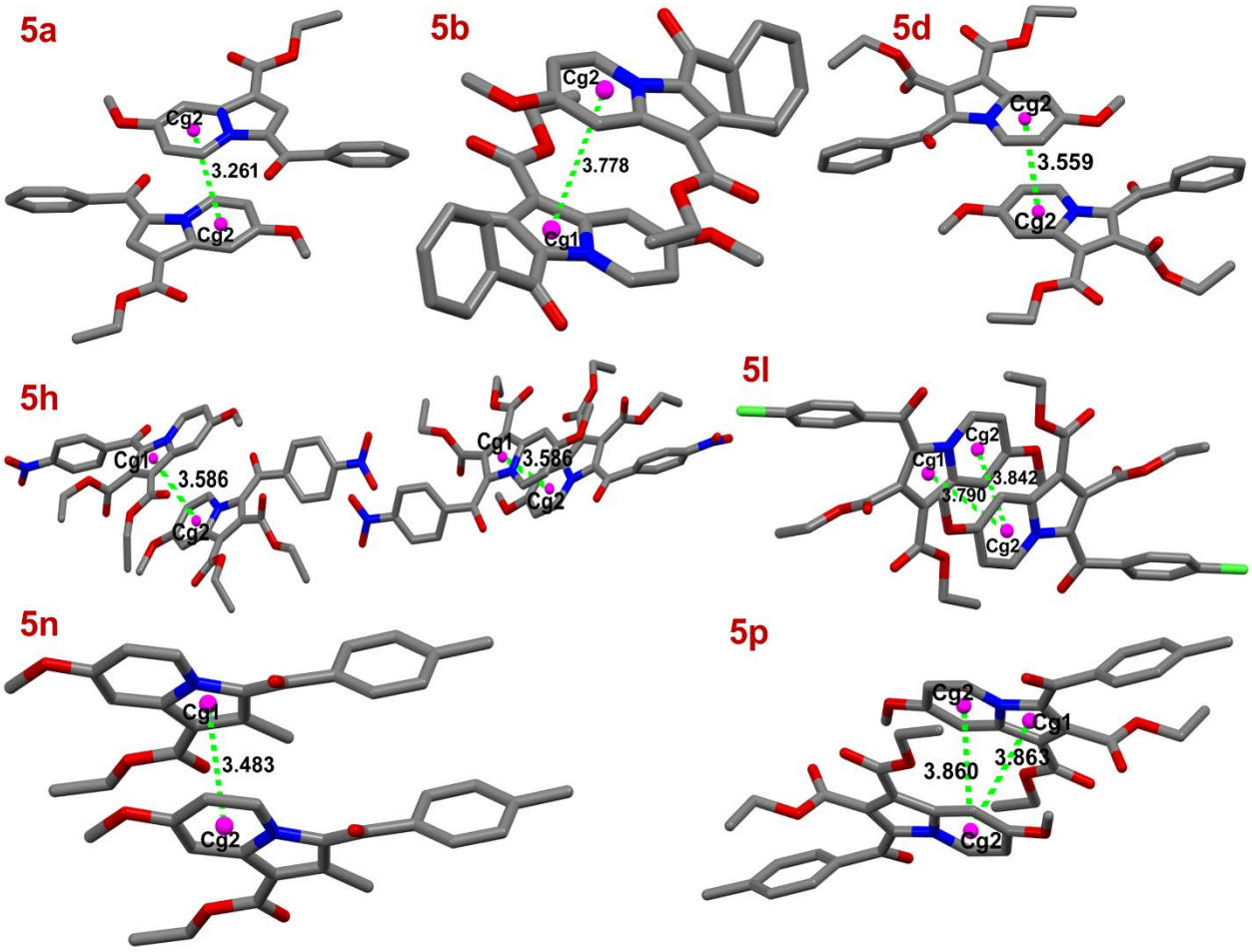


Figure S38- The π···π (Cg···Cg) interactions are present within the molecular assembly of crystal structures in **5a**, **5b**, **5d**, **5h**, **5l**, **5n**, and **5p**

Table S1- The crystal data and structure refinement details for the compounds **5a**, **5b**, **5d**, **5h**, **5l**, **5n**, and **5p**.

DATA	**5a**	**5b**	**5d**	**5h**	**5l**	**5n**	**5p**
Chemical formula	$C_{19}H_{17}NO_4$	$C_{20}H_{19}NO_4$	$C_{22}H_{21}NO_6$	$C_{22}H_{20}N_2O_8$	$C_{22}H_{20}ClNO_6$	$C_{21}H_{21}NO_4$	$C_{23}H_{23}NO_6$
Formula weight	323.34	337.36	395.4	439.4	429.9	351.39	409.42
CCDC	2380090	2380091	2380092	2380093	2380094	2380095	2380096
Temperature (K)	100 (2)	100 (2)	100 (2)	100 (2)	100 (2)	100 (2)	100 (2)
Wavelength (Å)	0.700	0.700	0.700	0.700	0.700	0.700	0.700
Crystal system	Triclinic	Monoclinic	Triclinic	Monoclinic	Triclinic	Monoclinic	Triclinic
Space group	*P*-1	$P2_1/c$	*P*-1	$P2_1/c$	*P*-1	$P2_1/c$	*P*-1
a (Å)	6.240 (1)	9.930 (2)	7.310 (2)	11.833 (2)	9.550 (2)	24.539 (5)	9.580 (2)
b (Å)	10.620 (2)	7.670 (2)	8.960 (2)	17.576 (4)	11.380 (2)	4.481 (9)	11.380 (2)
c (Å)	12.070 (2)	21.320 (4)	15.570 (3)	19.870 (4)	11.470 (2)	16.013 (3)	11.390 (2)
α (˚)	86.286 (3)	90.000	95.173 (3)	90.000	95.068 (3)	90.000	95.148 (3)
β (˚)	82.155 (3)	95.524 (3)	101.921 (3)	100.91 (3)	112.646 (3)	97.338 (3)	113.083 (3)
γ (˚)	83.833 (3)	90.000	104.047 (3)	90.000	113.025 (3)	90.000	112.083(3)
Volume($Å^3$)	786.77 (4)	1622.22 (2)	957.33 (2)	4057.8 (2)	1016.03 (3)	1746.36 (7)	1014.46 (3)
Z', *Z*	1, 2	1, 4	1, 2	2, 8	1, 2	1, 4	1, 2
Density (g cm^{-3})	1.36	1.38	1.37	1.44	1.40	1.34	1.34
Absorption coeff. (μ) (mm^{-1})	0.056	0.056	0.060	0.067	0.176	0.054	0.058
F (000)	340	712	416	1836	448	744	432
Crystal size (mm^3)	0.10 X 0.05 X 0.02	0.10 X 0.05 X 0.02	0.10 X 0.05 X 0.02	0.10 X 0.05 X 0.02	0.10 X 0.05 X 0.02	0.10 X 0.05 X 0.02	0.10 X 0.05 X 0.02
θ range for data collection (˚)	1.7-29.8	2.8-29.7	1.3-29.8	1.5-29.8	2.0-29.7	0.8-29.8	2.0-30.0
$h_{min,\ max}$, $k_{min,\ max}$, $l_{min,\ max}$.	-8, 8; -13, 15; -17, 17	-14, 14; -10, 10; -30, 30	-10, 10; -12, 12; -22, 22	-16, 14; -24, 24; -28, 28	-13, 13; -16, 16; -15, 16	-34, 34; -6, 4; -22, 22	-13, 13; -16, 16; -16, 16

Reflections collected	27764	41143	34967	69339	34016	28249	36113
No.of unique ref./Obs. ref.	4649/4548	4762/4687	5550/5358	12085/9387	5915/5852	5220/4476	6108/5947
Number of. Parameters	286	303	248	738	352	319	364
R_{all}, R_{obs}	0.043, 0.042	0.038, 0.038	0.042, 0.041	0.060, 0.044	0.034, 0.034	0.050, 0.043	0.039, 0.038
wR_{all}, wR_{obs}	0.115, 0.114	0.103, 0.103	0.110, 0.109	0.123, 0.113	0.094, 0.094	0.126, 0.119	0.103, 0.103
$\Delta\rho_{min,\ max}$ ($eÅ^{-3}$)	-0.313, 0.793	-0.275, 0.523	-0.331, 0.510	-0.427, 0.401	-0.295, 0.475	-0.216, 0.436	-0.332, 0.510
Goodness-of-fit on F^2(S)	1.030	1.046	1.051	1.027	1.031	1.002	1.040

Table S2- C-H···π H-bonding interactions are observed with the compounds **5a**, **5b**, **5d**, **5h**, **5l**, **5n**, and **5p**.

Code	C-H···Cg H-bonding interactions					Symmetry
5a	**D-X···A**	**D-X(Å)**	**X···A(Å)**	**D···A(Å)**	**<D-X···A(º)**	**(i)** -1+x, y, z
	C8-H8B···Cg1[i]	0.968(1)	2.862(1)	3.788(1)	160.7(1)	
*Cg1[i] is the centroid of the five-membered ring N1-C5-C6-C10-C11						
5b	**D-X···A**	**D-X(Å)**	**X···A(Å)**	**D···A(Å)**	**<D-X···A(º)**	
	C8-H8A···Cg1[i]	0.992(1)	2.954(1)	3.651(1)	128.3(8)	**(i)** 1-x, 1-y, 1-z;
	C20-H20A···Cg3[ii]	1.000(1)	2.973(1)	3.825(1)	143.7(9)	**(ii)** x, 3/2-y, 1/2 +z
*Cg1[i] is the centroid of the five-membered ring N1-C5-C6-C10-C12 *Cg3[ii] is the centroid of the six-membered ring C14-C15-C16-C17-C18-C19						
5d	**D-X···A**	**D-X(Å)**	**X···A(Å)**	**D···A(Å)**	**<D-X···A(º)**	
	C9-H9A···Cg3[i]	1.007(1)	2.927(1)	3.867(1)	155.2(1)	**(i)** 1+x, -1+y, z;
	C9-H9C···Cg1[ii]	0.973(1)	2.884(1)	3.837(1)	166.9(1)	**(ii)** 1+x, y, z;
	C13-H13B···Cg3[iii]	0.987(1)	2.788(1)	3.523(1)	132.0(1)	**(iii)** x, y, z
*Cg1[ii] is the centroid of the five-membered ring N1-C5-C6-C10-C14 *Cg3[i, iii] is the centroid of the six-membered ring C16-C17-C18-C19-C20-C21						
5h	**D-X···A**	**D-X(Å)**	**X···A(Å)**	**D···A(Å)**	**<D-X···A(º)**	**(i)** -1+x, y, z;
	C12A-H12A···Cg1[i]	1.015(2)	2.876(2)	3.764(2)	146.6(1)	**(ii)** -1+x, y, z;
	C12A-H12A···Cg2[ii]	1.012(2)	2.901(2)	3.828(2)	151.7(1)	**(iii)** 1+x, y, z;
	C13B-H13F···Cg8[iii]	0.990(2)	2.961(3)	3.868(2)	170.0(2)	
*Cg1[i] is the centroid of the five-membered ring N1B-C5B-C6B-C10B-C14B *Cg2[ii] is the centroid of the six-membered ring N1B-C1B-C2B-C3B-C4B-C5B *Cg8[iii] is the centroid of the nine-membered indolizine ring N1A-C1A-C2A-C3A-C4A-C5A-C6A-C10A-C14A						
5l	**D-X···A**	**D-X(Å)**	**X···A(Å)**	**D···A(Å)**	**<D-X···A(º)**	**(i)** 1-x, 1-y, 1-z;
	C13-H13C···Cg1[i]	0.978(1)	2.787(2)	3.689(1)	154.0(1)	**(ii)** 1-x, 1-y, 1-z
	C13-H13C···Cg2[ii]	0.978(1)	2.970(2)	3.674(1)	130.0(2)	
*Cg1[i] is the centroid of the five-membered ring N1-C5-C6-C10-C14 *Cg1[ii] is the centroid of the six-membered ring N1-C1-C2-C3-C4-C5						
5n	**D-X···A**	**D-X(Å)**	**X···A(Å)**	**D···A(Å)**	**<D-X···A(º)**	
	C11-H11B···Cg1[i]	0.987(2)	2.915(1)	3.4281(1)	113.4.(1)	**(i)** x,1+y, z
*Cg1[i] is the centroid of the five-membered ring N1-C5-C6-C10-C12						
5p	**D-X···A**	**D-X(Å)**	**X···A(Å)**	**D···A(Å)**	**<D-X···A(º)**	
	C13-H13B···Cg1[i]	0.962(1)	2.771(2)	3.660(1)	153.5(1)	**(i)** 1-x, 1-y, 1-z
*Cg1[i] is the centroid of the five-membered ring N1-C5-C6-C10-C14						

Table S3- Geometric parameters describing the π···π (Cg···Cg) interactions for the compounds **5a**, **5b**, **5d**, **5h**, **5l**, **5n**, and **5p**.

Code	Ring (I)-Ring(J)[a]	*Rc*[b] (Å)	*R1v*[c] (Å)	*R2v*[d] (Å)	*α*[e] (°)	β[f] (°)	γ[g] (°)	Symmetry code
5a	Cg(2)···Cg(2)^{i}	3.621(9)	3.305(3)	3.305(3)	0.00(4)	24.1	24.1	**i)** 1-x, 1-y, -z
5b	Cg(1)···Cg(2)^{i}	3.778(9)	3.329(3)	3.358(3)	0.94(4)	27.3	28.2	**i)** 1-x, 2-y, -z
5d	Cg(2)···Cg(2)^{i}	3.559(7)	3.203(3)	3.203(3)	0.00(4)	25.8	25.8	**i)** 2-x, 1-y, 1-z
5h	Cg(1)···Cg(2)^{i}	3.586(1)	3.484(5)	3.470(6)	7.73(7)	14.6	13.7	**i)** 1/2+x, 1/2-y, -1/2+z
5l	Cg(1)···Cg(2)^{i}	3.790(9)	3.480(3)	3.385(3)	3.66(4)	26.7	23.4	**i)** -x, -y, 1-z;
	Cg(2)···Cg(2)^{ii}	3.842(9)	3.422(3)	3.422(3)	0.00(4)	27.0	27.0	**ii)** -x, -y, 1-z
5n	Cg(1)···Cg(2)^{i}	3.483(9)	3.380(4)	3.418(4)	3.01(5)	11.0	13.9	**i)** x, 1+y, z
5p	Cg(1)···Cg(2)^{i}	3.863(9)	3.475(3)	3.390(3)	2.95(4)	28.6	25.9	**i)** -x, -y, 1-z;
	Cg(2)···Cg(2)^{ii}	3.860(9)	3.429(3)	3.429(3)	0.00(4)	27.3	27.3	**ii)** -x, -y, 1-z

[a]Cg(1) are the centroids of the rings N1-C5-C6-C10-C11 (**5a**), N1-C5-C6-C10-C12 (**5b**, **5n**), N1-C5-C6-C10-C14 (**5d**, **5l**, and **5p**), and, N1-C5A-C6A-C10A-C14A (**5h**). Similarly [a]Cg(2) N1-C1-C2-C3-C4-C5 (**5a**, **5b**, **5d**, **5l**, **5n**, and **5p**) N1B-C1B-C2B-C3B-C4B-C5B (**5h**). [b]Centroid distance between ring I and ring J. [c]Vertical distance from ring centroid I to ring J. [d]Vertical distance from ring centroid J to ring I. [e]Dihedral angle between mean planes I and J. [f]Angle between the centroid vector Cg(I)···Cg(J) and the normal to the plane (I). [g]Angle between the centroid vector Cg(I)···Cg(J) and the normal to the plane (J).

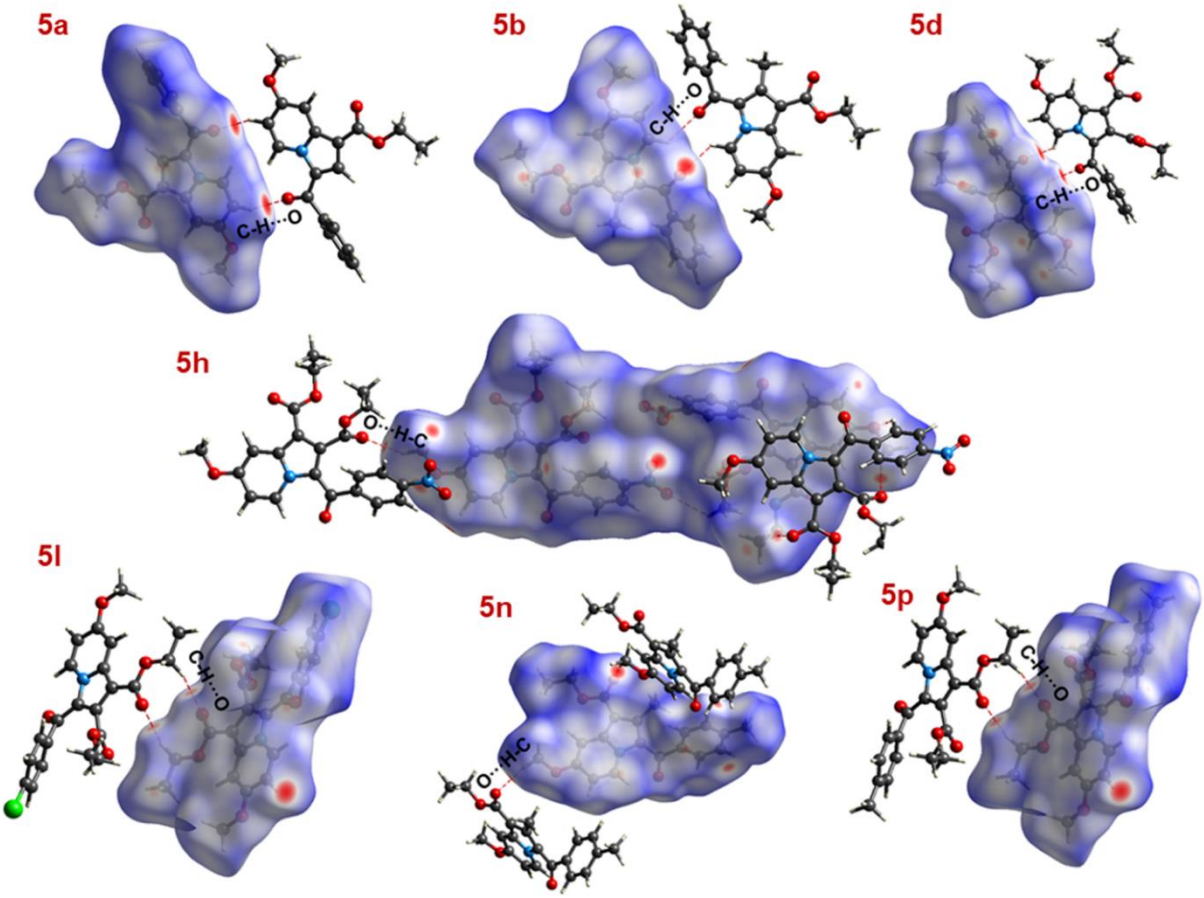


Figure S39- The C-H···O interactions in the (**5a**, **5b**, **5d**, **5h**, **5l**, **5n**, and **5p**) compounds contribute to dimer formation in the Hirshfeld-mapped surfaces.

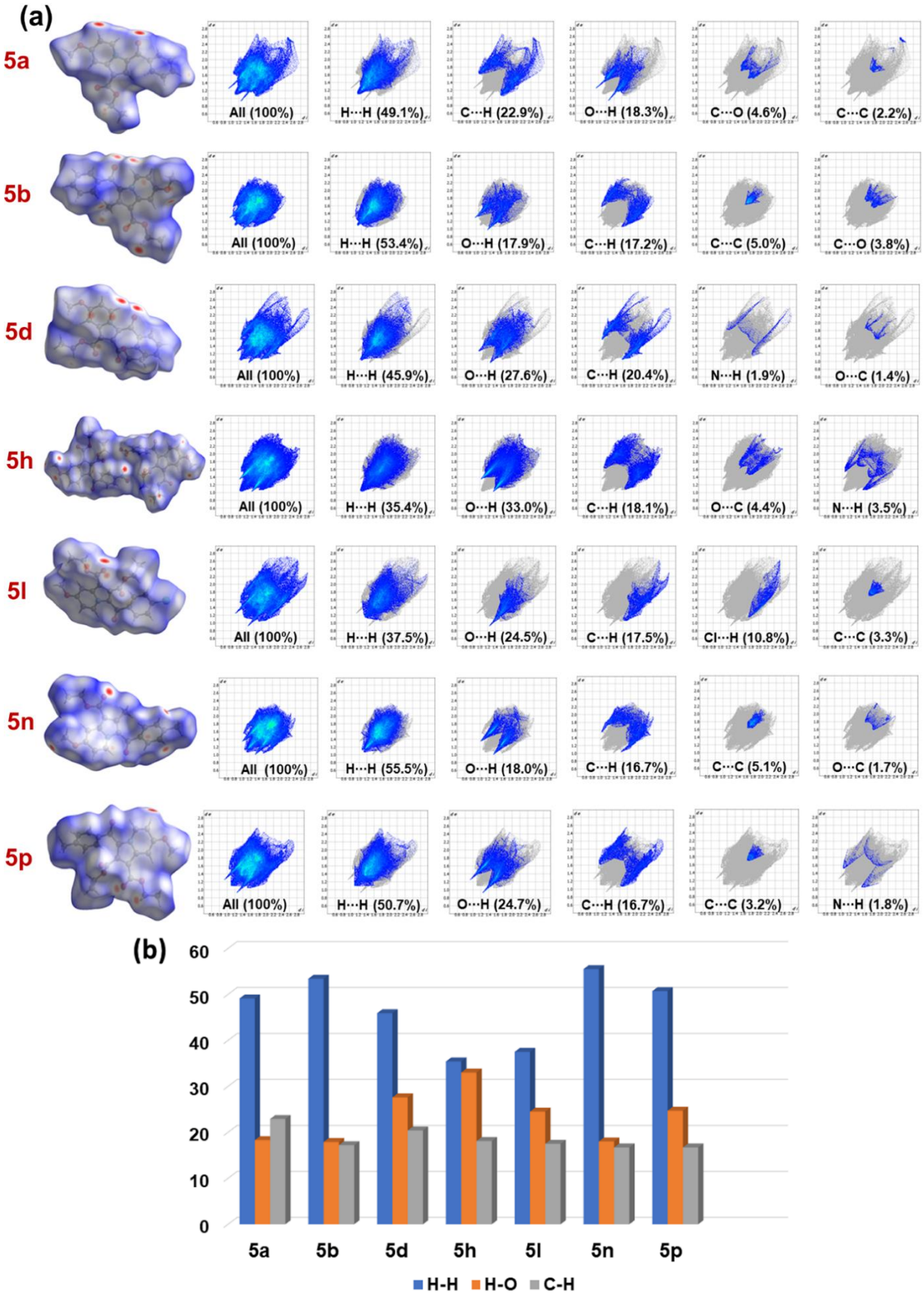


Figure S40- (a) 2D plots: shows the various percentage interactions present in the **5a**, **5b**, **5d**, **5h**, **5l**, **5n**, and **5p** molecules, including short contact interactions, **(b)** The major short contact contributions derived from H···H, O···H/H···O, C···H/H···C contacts.

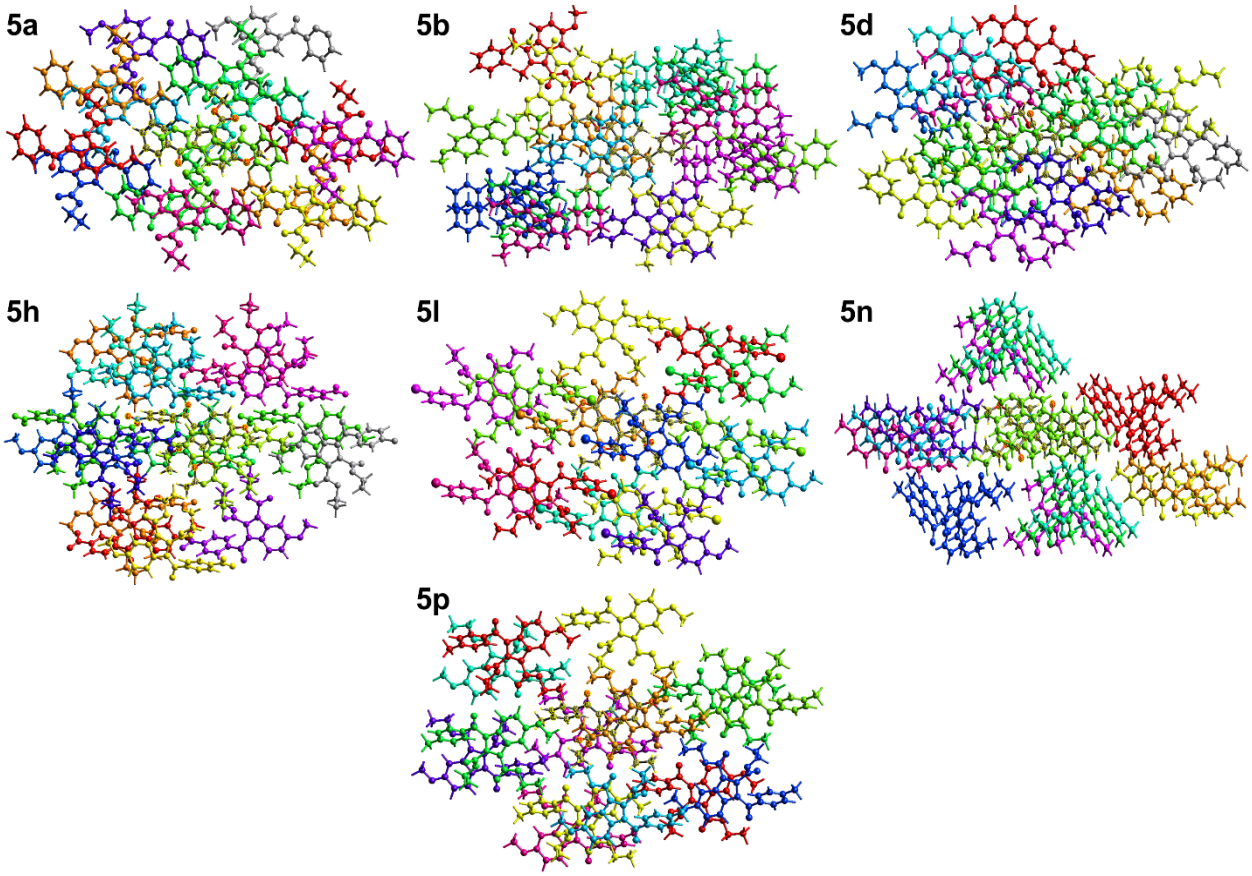


Figure S41- Depiction of molecular interactions between the central analyzed molecule (black color) and surrounding molecules in a cluster with a radius of 3.8 Å for the compounds **5a**, **5b**, **5d**, **5h**, **5l**, **5n**, and **5p**.

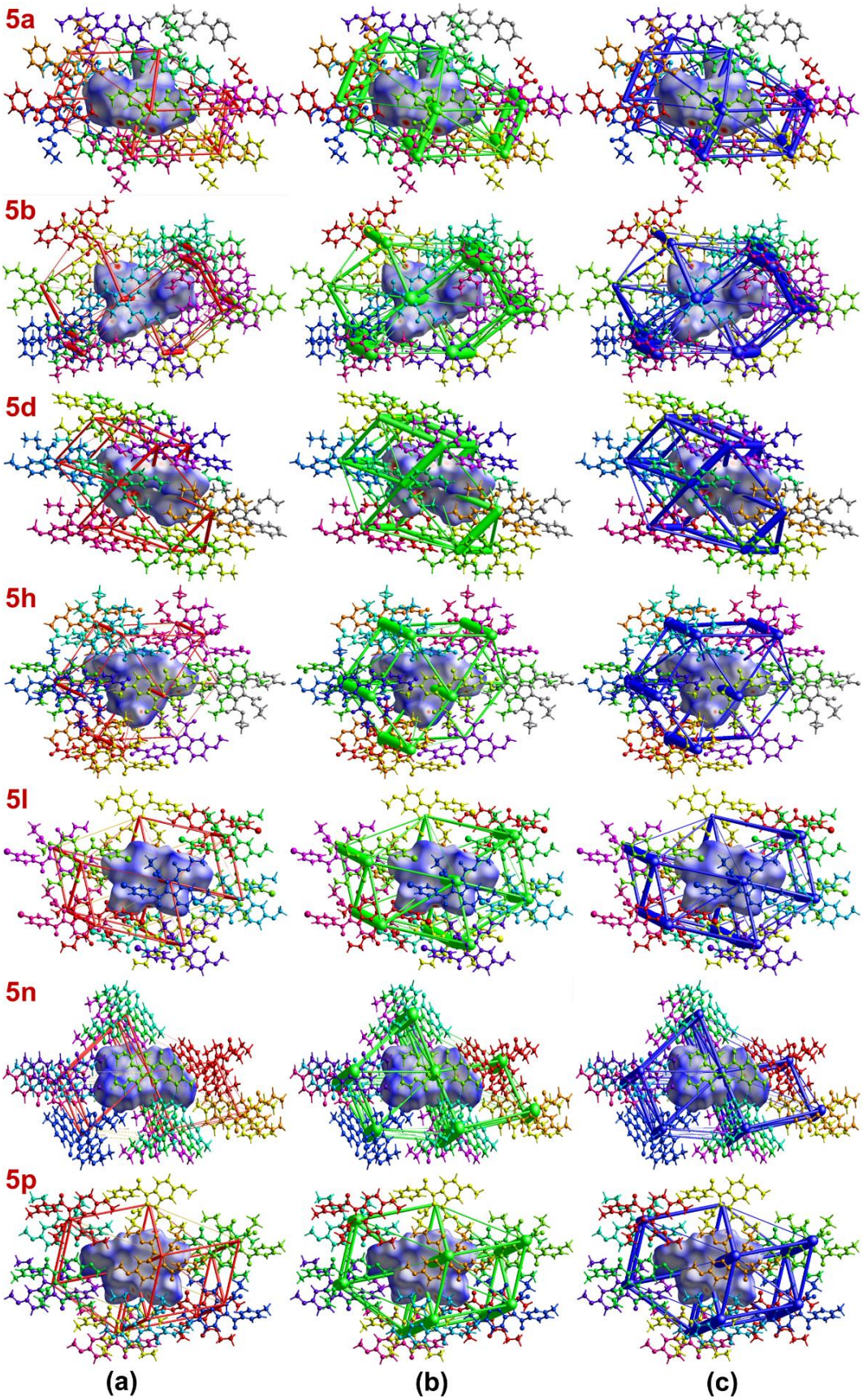
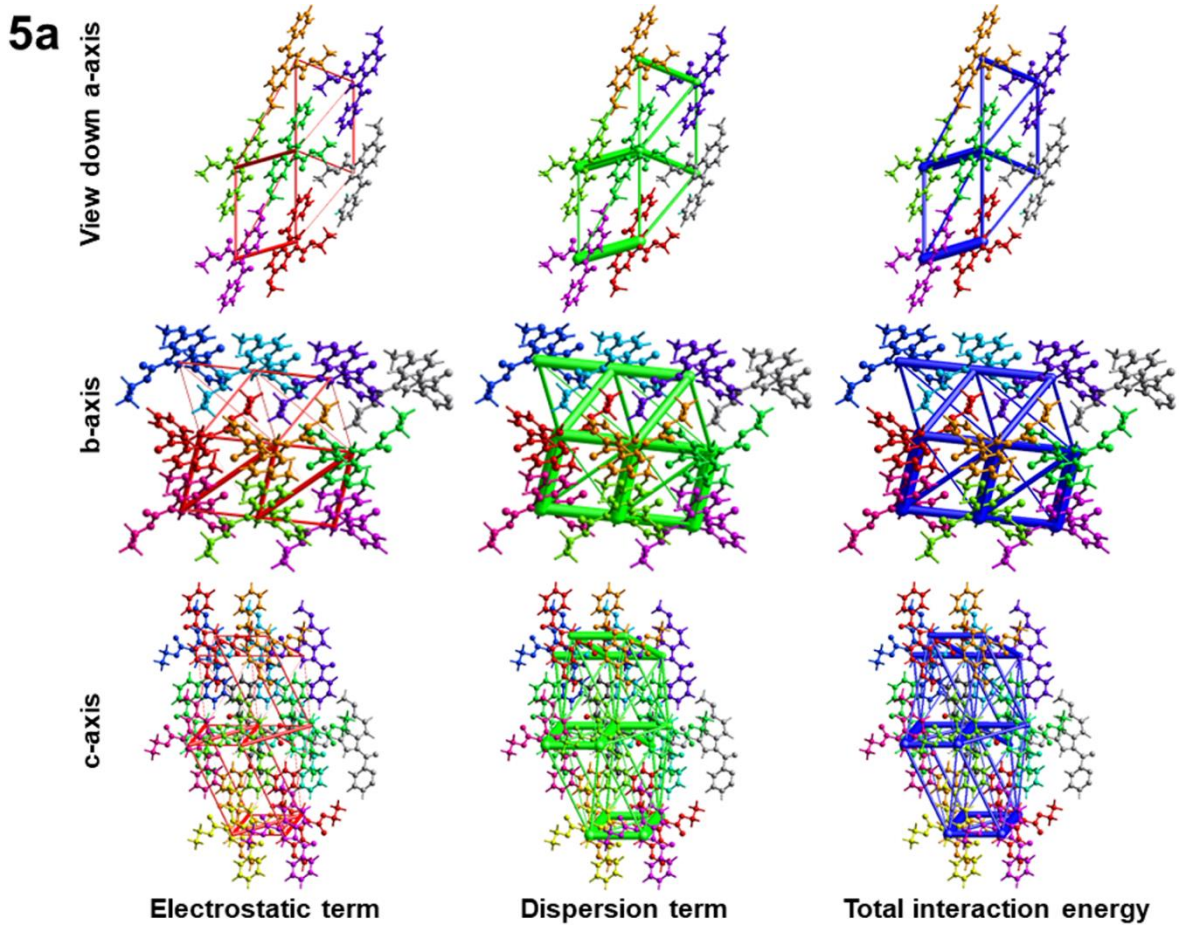
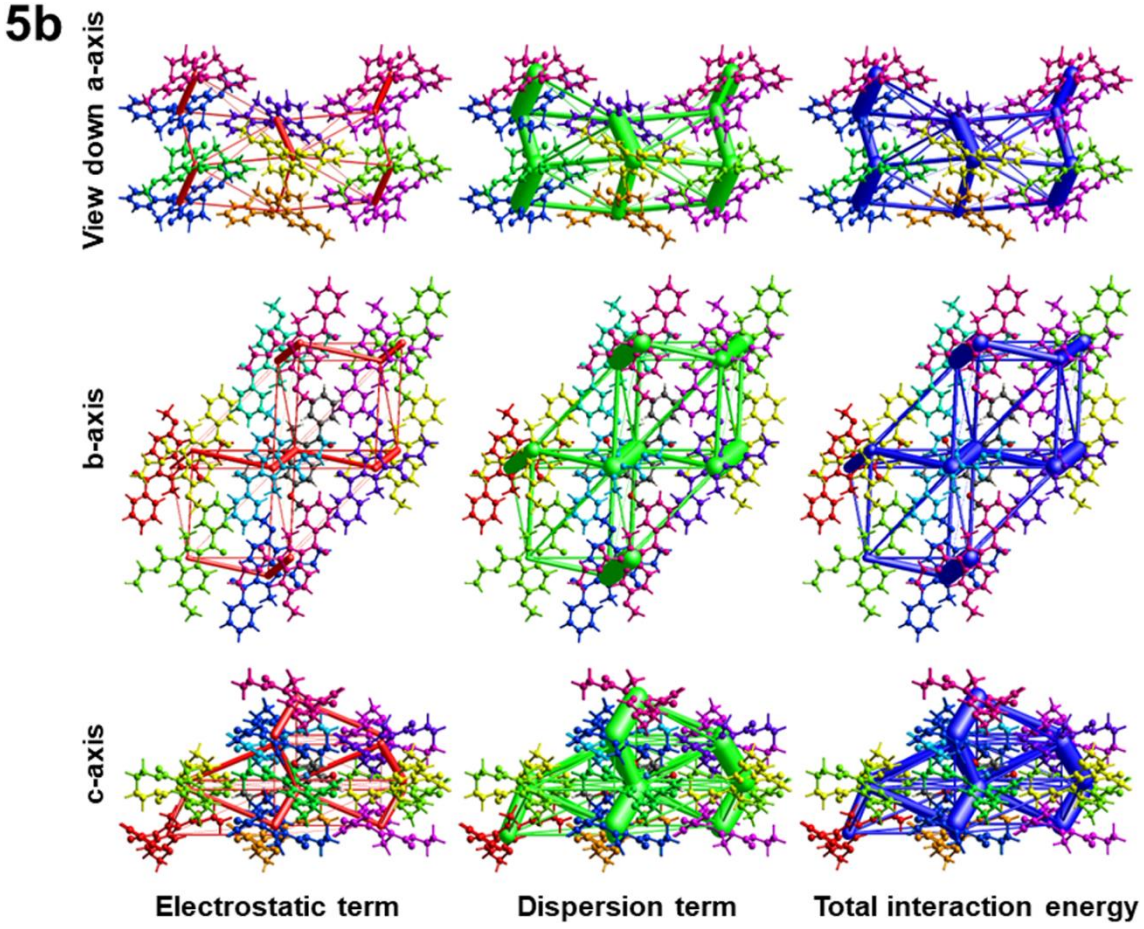
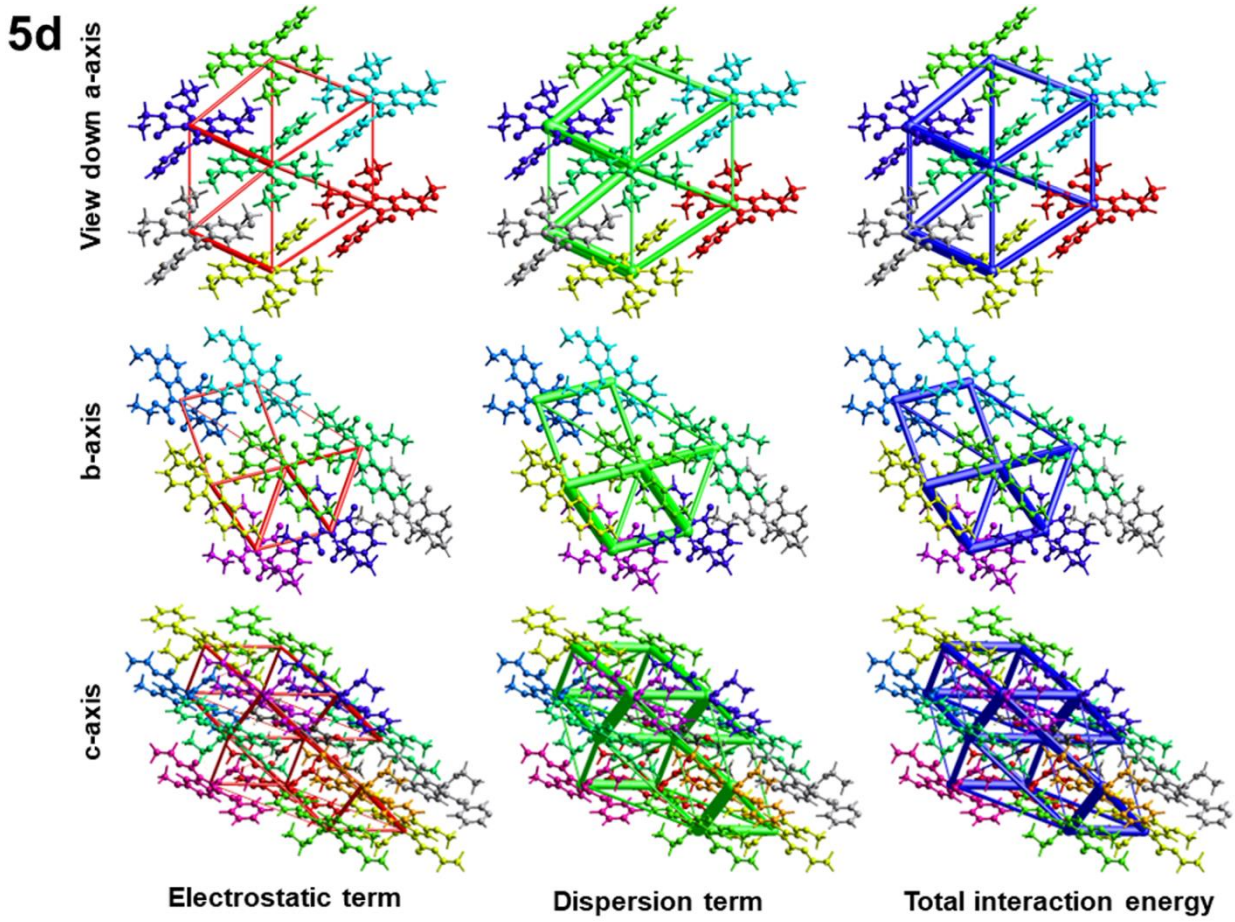
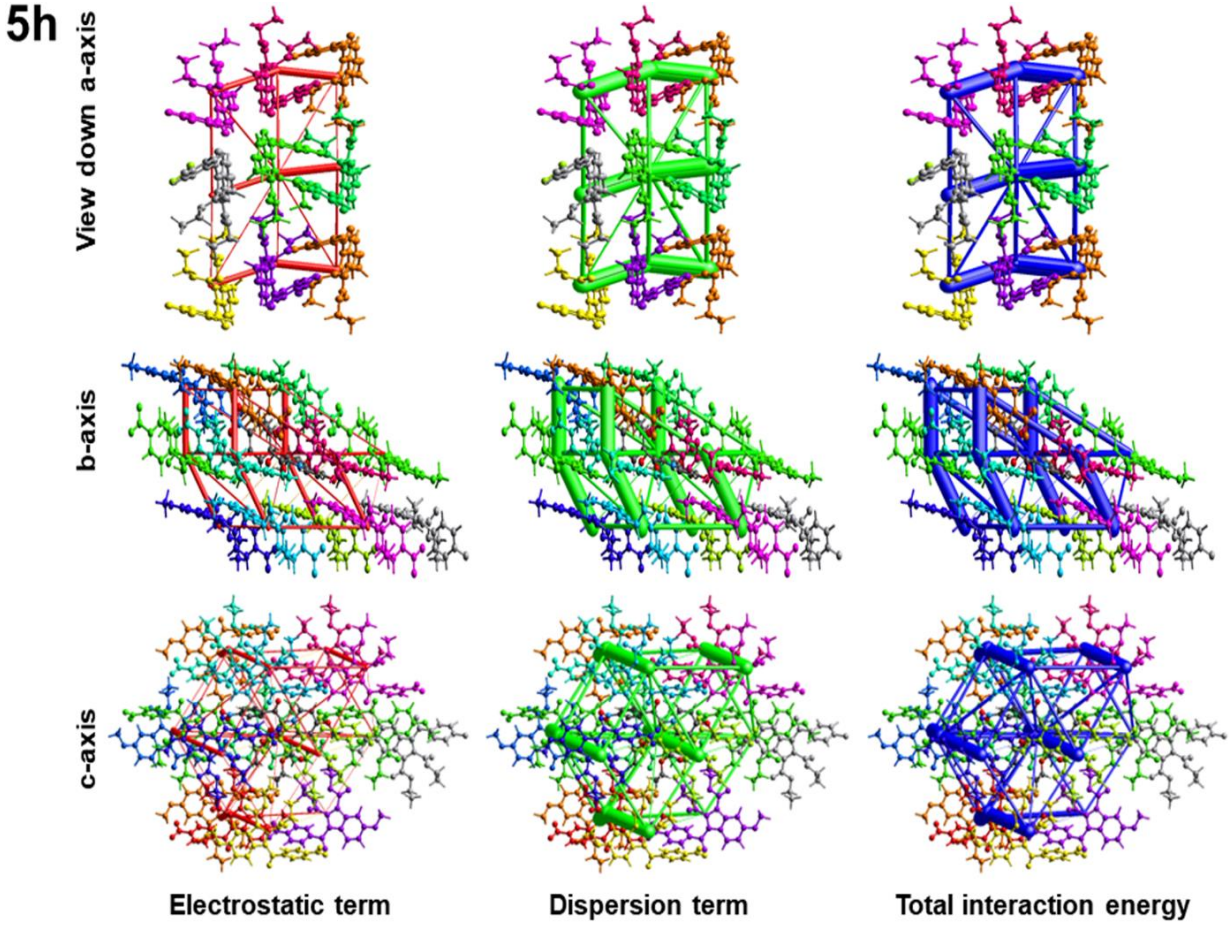


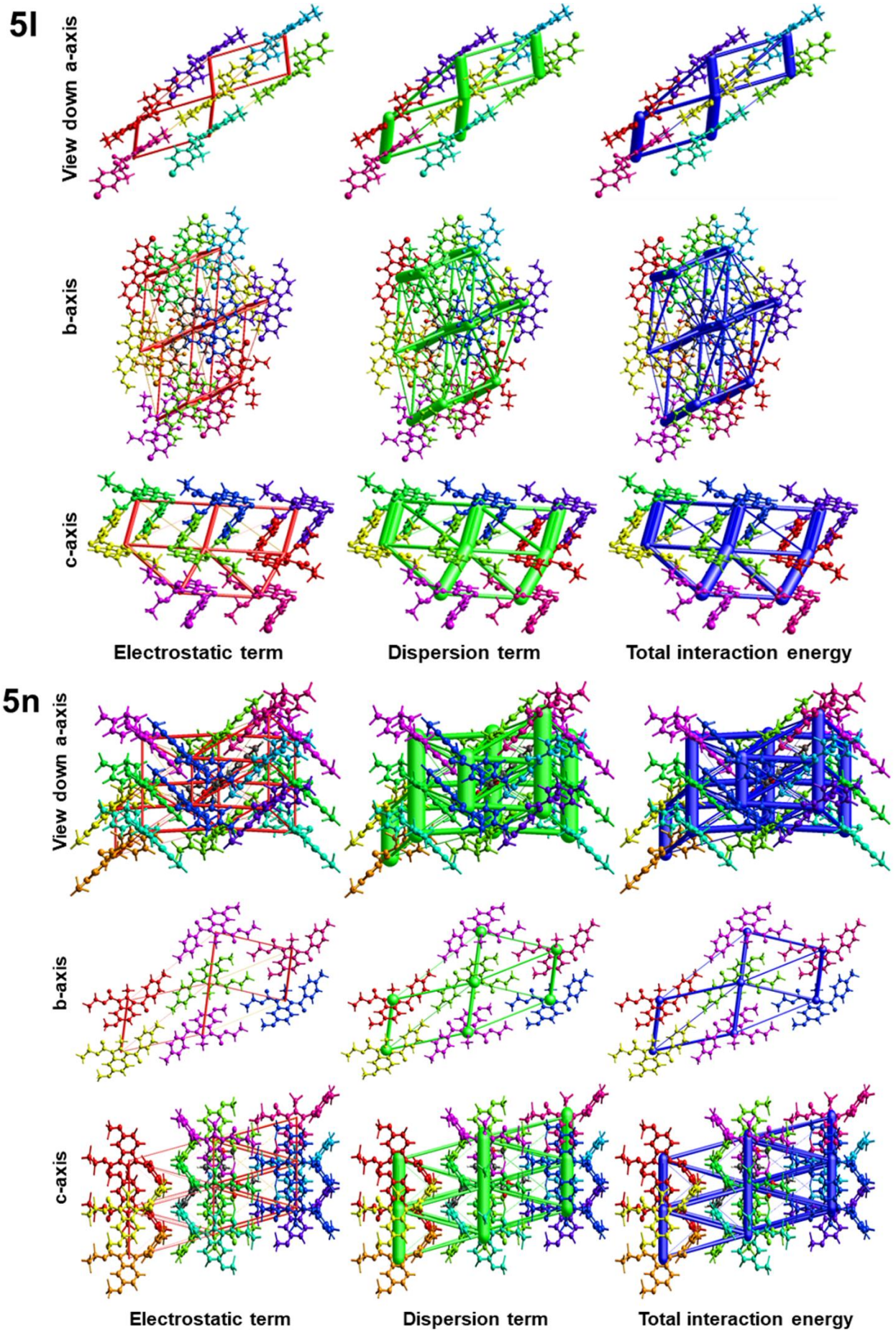
Figure S42- d_{norm} mapped on the Hirshfeld surface of molecules **5a**, **5b**, **5d**, **5h**, **5l**, **5n**, and **5p** with energy framework in the form of **(a)** Coulombic energy, **(b)** dispersion energy, and **(c)** total energy.


5a
View down a-axis
b-axis
c-axis
Electrostatic term
Dispersion term
Total interaction energy


5b
View down a-axis
b-axis
c-axis
Electrostatic term
Dispersion term
Total interaction energy


5d
View down a-axis
b-axis
c-axis
Electrostatic term
Dispersion term
Total interaction energy


5h
View down a-axis
b-axis
c-axis
Electrostatic term
Dispersion term
Total interaction energy


5l
View down a-axis
b-axis
c-axis
Electrostatic term
Dispersion term
Total interaction energy
5n
View down a-axis
b-axis
c-axis
Electrostatic term
Dispersion term
Total interaction energy

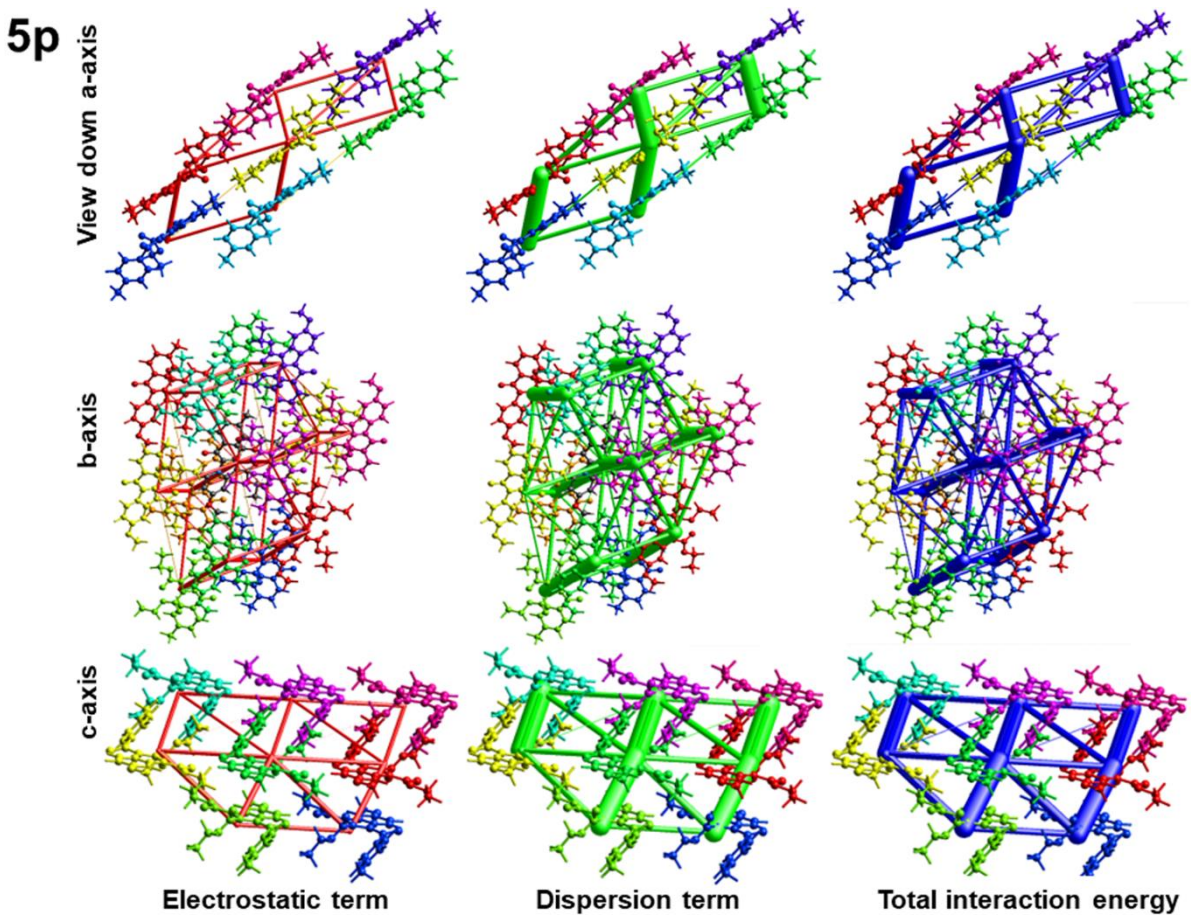


Figure S43- The energy components of compounds **5a**, **5b**, **5d**, **5h**, **5l**, **5n**, and **5p** viewed the crystallographic *a, b,* and *c* axes. The thickness of solid cylinders in each framework indicates the magnitude of interaction energies between the molecular pairs.

Table S4- Scale factors for benchmarked energy models for 5a, **5b**, **5d**, **5h**, **5l**, **5n**, and **5p**.

Energy Model	k_ele	k_pol	k_disp	k_rep
CE-HF ... HF/3-21G electron densities	1.019	0.651	0.901	0.811
CE-B3LYP ... B3LYP/6-31G(d,p) electron densities	1.057	0.740	0.871	0.618

Table S5- Overall energy profile for 5a (in kJ/mol)

Colour	N	Symop	R	Electron Density	E_ele	E_pol	E_dis	E_rep	E_tot
	2	x, y, z	11.73	B3LYP/6-31G(d,p)	-10.7	-2.8	-16.5	12.6	-19.9
	2	x, y, z	10.62	B3LYP/6-31G(d,p)	-0.2	-0.4	-15.0	6.2	-9.8
	1	-x, -y, -z	13.76	B3LYP/6-31G(d,p)	-4.5	-0.6	-8.1	0.0	-12.3
	1	-x, -y, -z	5.97	B3LYP/6-31G(d,p)	-21.2	-2.5	-78.7	48.0	-63.2
	2	x, y, z	6.24	B3LYP/6-31G(d,p)	-7.8	-2.7	-57.0	34.8	-38.3
	1	-x, -y, -z	7.90	B3LYP/6-31G(d,p)	-8.2	-1.0	-45.9	29.2	-31.3
	1	-x, -y, -z	10.28	B3LYP/6-31G(d,p)	-2.8	-0.4	-19.6	10.3	-13.9
	1	-x, -y, -z	12.55	B3LYP/6-31G(d,p)	-2.3	-0.1	-6.9	0.0	-8.5
	1	-x, -y, -z	11.49	B3LYP/6-31G(d,p)	-1.6	-0.2	-15.8	10.9	-8.9
	1	-x, -y, -z	14.41	B3LYP/6-31G(d,p)	-0.5	-0.7	-7.4	0.0	-7.5
	1	-x, -y, -z	9.00	B3LYP/6-31G(d,p)	-21.4	-6.1	-17.3	32.9	-21.9

Table S6- Overall energy profile for 5b (in kJ/mol)

Colour	N	Symop	R	Electron Density	E_ele	E_pol	E_dis	E_rep	E_tot
	1	-x, -y, -z	13.42	B3LYP/6-31G(d,p)	-2.3	-0.8	-11.7	0.0	-13.3
	1	-x, -y, -z	5.58	B3LYP/6-31G(d,p)	-13.9	-2.4	-89.4	56.1	-59.6
	2	x, y, z	9.93	B3LYP/6-31G(d,p)	-6.9	-2.7	-13.7	12.8	-13.3
	2	x, -y+1/2, z+1/2	14.90	B3LYP/6-31G(d,p)	-1.5	-0.1	-7.4	0.0	-8.1
	2	x, -y+1/2, z+1/2	10.69	B3LYP/6-31G(d,p)	-7.2	-1.4	-27.4	19.8	-20.3
	2	-x, y+1/2, -z+1/2	9.80	B3LYP/6-31G(d,p)	-5.4	-2.4	-12.9	9.2	-13.1
	1	-x, -y, -z	4.39	B3LYP/6-31G(d,p)	-37.4	-6.0	-122.9	91.8	-94.3
	2	-x, y+1/2, -z+1/2	13.43	B3LYP/6-31G(d,p)	1.0	-0.2	-2.9	0.0	-1.6
	1	-x, -y, -z	8.22	B3LYP/6-31G(d,p)	-23.2	-9.3	-33.4	28.0	-43.2
	2	-x, y+1/2, -z+1/2	12.40	B3LYP/6-31G(d,p)	0.3	-0.6	-14.7	0.0	-13.0
	2	x, -y+1/2, z+1/2	12.69	B3LYP/6-31G(d,p)	-2.9	-0.5	-5.6	0.0	-8.3

Table S7- Overall energy profile for 5d (in kJ/mol)

Colour	N	Symop	R	Electron Density	E_ele	E_pol	E_dis	E_rep	E_tot
	1	-x, -y, -z	9.23	B3LYP/6-31G(d,p)	-13.8	-8.0	-30.4	25.7	-31.1
	1	-x, -y, -z	9.72	B3LYP/6-31G(d,p)	-15.1	-2.7	-52.7	36.6	-41.2
	2	x, y, z	12.87	B3LYP/6-31G(d,p)	-9.3	-0.8	-13.4	0.0	-22.1
	2	x, y, z	8.96	B3LYP/6-31G(d,p)	0.4	-0.9	-12.3	2.2	-9.5
	2	x, y, z	7.31	B3LYP/6-31G(d,p)	-14.3	-6.9	-54.8	32.1	-48.1

	1	-x, -y, -z	10.17	B3LYP/6-31G(d,p)	-12.4	-5.4	-31.3	23.4	-29.9
	1	-x, -y, -z	13.61	B3LYP/6-31G(d,p)	-4.1	-0.3	-16.4	0.0	-18.7
	1	-x, -y, -z	7.48	B3LYP/6-31G(d,p)	-20.4	-1.9	-74.6	51.7	-55.9
	1	-x, -y, -z	8.82	B3LYP/6-31G(d,p)	-24.6	-7.2	-27.4	32.2	-35.4
	1	-x, -y, -z	11.62	B3LYP/6-31G(d,p)	-2.2	-0.1	-12.9	8.6	-8.4

Table S8- Overall energy profile for 5h (in kJ/mol)

Colour	N	Symop	R	Electron Density	E_ele	E_pol	E_dis	E_rep	E_tot
	1	-	11.03	B3LYP/6-31G(d,p)	-3.1	-2.3	-18.9	11.9	-14.0
	2	-x+1/2, y+1/2, -z+1/2	11.32	B3LYP/6-31G(d,p)	-5.8	-1.4	-20.1	11.9	-17.3
	1	-x, -y, -z	12.46	B3LYP/6-31G(d,p)	-4.2	-0.2	-10.2	0.0	-13.4
	1	-	7.16	B3LYP/6-31G(d,p)	-25.4	-6.2	-92.8	58.3	-76.2
	2	x, y, z	11.83	B3LYP/6-31G(d,p)	-10.4	-2.2	-24.0	17.3	-22.8
	1	-	4.64	B3LYP/6-31G(d,p)	-35.3	-6.5	-101.6	67.5	-89.0
	1	-	10.34	B3LYP/6-31G(d,p)	-9.1	-3.4	-21.6	18.6	-19.5
	1	-x, -y, -z	8.44	B3LYP/6-31G(d,p)	-2.1	-1.3	-17.5	4.4	-15.7
	1	-	12.23	B3LYP/6-31G(d,p)	-7.5	-5.7	-22.5	0.0	-31.7
	1	-	9.15	B3LYP/6-31G(d,p)	2.1	-0.3	-4.7	0.0	-2.0
	1	-	10.86	B3LYP/6-31G(d,p)	-4.4	-2.5	-21.7	12.2	-17.8
	1	-x, -y, -z	13.23	B3LYP/6-31G(d,p)	-7.3	-0.8	-12.5	0.0	-19.2
	1	-	10.16	B3LYP/6-31G(d,p)	-7.0	-2.9	-21.6	17.2	-17.7

Table S9- Overall energy profile for 5l (in kJ/mol)

Colour	N	Symop	R	Electron Density	E_ele	E_pol	E_dis	E_rep	E_tot
	2	x, y, z	11.76	B3LYP/6-31G(d,p)	-4.2	-1.0	-13.5	8.3	-11.8
	1	-x, -y, -z	7.22	B3LYP/6-31G(d,p)	-22.4	-8.1	-93.9	51.4	-79.7
	2	x, y, z	9.55	B3LYP/6-31G(d,p)	-15.9	-5.1	-26.0	26.9	-26.7
	2	x, y, z	11.47	B3LYP/6-31G(d,p)	-12.7	-3.1	-21.9	13.8	-26.3
	1	-x, -y, -z	11.49	B3LYP/6-31G(d,p)	2.7	-1.0	-24.5	13.5	-10.9
	1	-x, -y, -z	9.05	B3LYP/6-31G(d,p)	-20.9	-6.6	-34.0	28.9	-38.7
	1	-x, -y, -z	12.69	B3LYP/6-31G(d,p)	-4.3	-0.6	-18.4	0.0	-21.1
	1	-x, -y, -z	5.04	B3LYP/6-31G(d,p)	-25.4	-3.0	-97.5	62.6	-75.3
	1	-x, -y, -z	12.35	B3LYP/6-31G(d,p)	-1.1	-0.0	-4.4	0.0	-5.0
	1	-x, -y, -z	16.95	B3LYP/6-31G(d,p)	0.7	-0.7	-4.7	0.0	-3.9
	1	-x, -y, -z	15.25	B3LYP/6-31G(d,p)	4.0	-0.9	-10.7	0.0	-5.8

Table S10- Overall energy profile for 5n (in kJ/mol)

Colour	N	Symop	R	Electron Density	E_ele	E_pol	E_dis	E_rep	E_tot
	2	-x, y+1/2, -z+1/2	13.03	B3LYP/6-31G(d,p)	-4.0	-1.1	-17.4	0.0	-20.2
	1	-x, -y, -z	18.88	B3LYP/6-31G(d,p)	-0.3	-0.0	-1.6	0.0	-1.7
	1	-x, -y, -z	17.66	B3LYP/6-31G(d,p)	-1.2	-0.1	-4.8	0.0	-5.4
	2	x, y, z	4.48	B3LYP/6-31G(d,p)	-12.0	-3.2	-108.8	66.7	-68.6
	2	x, -y+1/2, z+1/2	8.02	B3LYP/6-31G(d,p)	-16.2	-4.5	-34.6	25.5	-34.9
	2	x, -y+1/2, z+1/2	9.44	B3LYP/6-31G(d,p)	-2.4	-1.1	-6.7	1.6	-8.2
	1	-x, -y, -z	14.08	B3LYP/6-31G(d,p)	1.9	-0.7	-12.9	0.0	-9.7
	2	-x, y+1/2, -z+1/2	12.70	B3LYP/6-31G(d,p)	-7.8	-1.4	-11.4	0.0	-19.2
	1	-x, -y, -z	14.24	B3LYP/6-31G(d,p)	-0.3	-0.1	-2.6	0.0	-2.7
	2	x, -y+1/2, z+1/2	8.94	B3LYP/6-31G(d,p)	-9.4	-2.3	-21.8	18.2	-19.5
	1	-x, -y, -z	15.29	B3LYP/631G(d,p)	1.4	-0.3	-3.1	0.0	-1.4

Table S11- Overall energy profile for 5p (in kJ/mol)

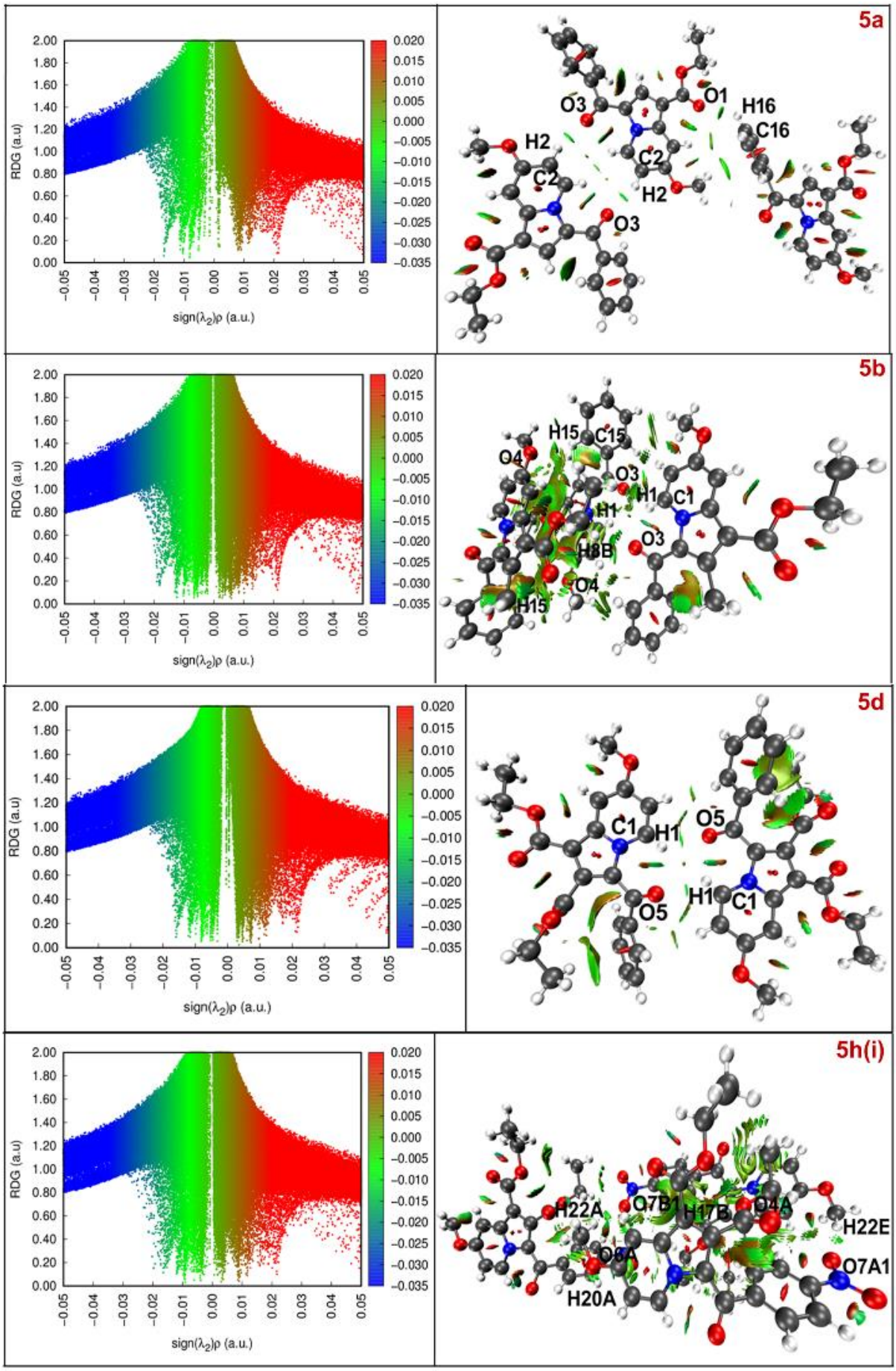
Colour	N	Symop	R	Electron Density	E_ele	E_pol	E_dis	E_rep	E_tot
	2	x, y, z	11.66	B3LYP/6-31G(d,p)	-5.4	-1.1	-13.6	8.4	-13.1
	1	-x, -y, -z	6.74	B3LYP/6-31G(d,p)	-22.7	-8.5	-93.4	49.9	-80.8
	2	x, y, z	9.58	B3LYP/6-31G(d,p)	-15.9	-5.3	-26.3	26.7	-27.0
	1	-x, -y, -z	16.35	B3LYP/6-31G(d,p)	0.6	-0.7	-5.1	0.0	-4.4
	2	x, y, z	11.39	B3LYP/6-31G(d,p)	-12.9	-3.5	-22.9	14.0	-27.6
	1	-x, -y, -z	11.89	B3LYP/6-31G(d,p)	-10.6	-3.9	-29.5	21.5	-26.6
	1	-x, -y, -z	8.77	B3LYP/6-31G(d,p)	-20.8	-7.3	-33.8	30.0	-38.4
	1	-x, -y, -z	14.60	B3LYP/6-31G(d,p)	3.3	-0.7	-11.0	0.0	-6.6
	1	-x, -y, -z	13.26	B3LYP/6-31G(d,p)	-1.6	-0.3	-24.4	0.0	-23.2
	1	-x, -y, -z	5.42	B3LYP/6-31G(d,p)	-16.0	-2.7	-98.1	59.1	-67.8
	1	-x, -y, -z	12.72	B3LYP/6-31G(d,p)	-0.4	-0.0	-4.2	0.0	-4.2

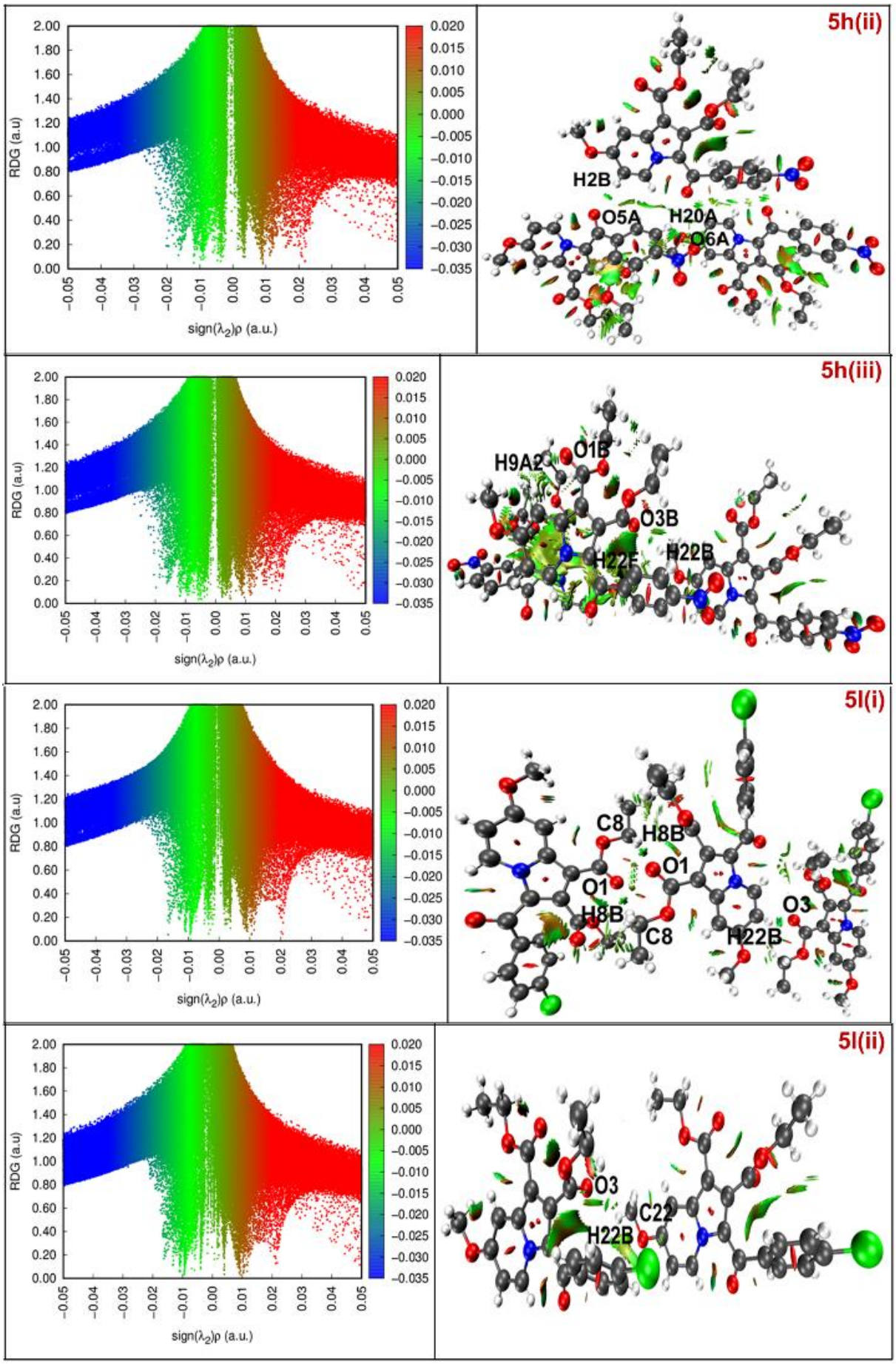
Table S12- The interaction energies for the compounds **5a**, **5b**, **5d**, **5h**, **5l**, **5n**, and **5p**.

Compd Code	Calculated Interaction Energies in kJ/mol				
	E_ele	**E_pol**	**E_dis**	**E_rep**	**E_tot**
5a	-81.2	-17.5	-288.2	184.9	-235.5
5b	-99.4	-26.4	-342.0	217.7	-288.1
5d	-115.8	-34.2	-326.2	212.5	-300.3
5h	-119.5	-35.7	-389.7	219.3	-356.3
5l	-99.5	-30.1	-349.5	205.4	-305.2
5n	-50.3	-14.8	-225.7	112.0	-191.5
5p	-102.4	-34.0	-362.3	109.8	-319.7

Table S13- The computational details and its reactivity parameters for the compounds **5a**, **5b**, **5d**, **5h**, **5l**, **5n**, and **5p**.

Parameters (eV)	Symbol and formula	5a	5b	5d	5h	5l	5n	5p
HOMO	E_{HOMO} (eV)	-5.7222	-5.5076	-5.7326	-6.0924	-5.8646	-5.5503	-5.7144
LUMO	E_{LUMO} (eV)	-1.5951	-1.6112	-1.7353	-2.8305	-1.8882	-1.5772	-1.6332
Energy gap	$\Delta E = E_{LUMO} - E_{HOMO}$ (eV)	4.1271	3.8960	3.9973	3.2618	3.9764	3.9731	4.0812
Ionization energies	$I = - E_{HOMO}$ (eV)	5.7223	5.5076	5.7326	6.0924	5.8646	5.5503	5.7144
Electron affinity	$A = - E_{LUMO}$ (eV)	1.5951	1.6112	1.7353	2.8305	1.8882	1.5772	1.6332
Electronegativity	$\chi = (I + A)/2$ (eV)	3.6587	3.5594	3.7339	4.4614	3.8764	3.5637	3.6738
Chemical hardness	$\eta = \Delta E/2$ (eV)	2.0636	1.9482	1.9987	1.6309	1.9882	1.9866	2.0406
Chemical softness	$S = 1/2\eta$ (eV^{-1})	0.2423	0.2566	0.2502	0.3066	0.2515	0.2517	0.2450
Chemical potential	$\mu = - \chi$ (eV)	-3.6587	-3.5594	-3.7339	-4.4614	-3.8764	-3.5637	-3.6738
Global electrophilicity index	$\omega = \mu^2/2\eta$ (eV)	3.2434	3.2515	3.4879	6.1022	3.7789	3.1965	3.3071
Maximum charge transfer index	$\Delta N_{max} = - \mu/\eta$	1.7730	1.827	1.8682	2.7355	1.9497	1.7939	1.8004
Dipole moment	D = δd (Debye)	2.6082	3.6754	3.7182	7.7687	7.2677	2.7700	5.4836


5a
RDG (a.u)
sign(λ2)ρ (a.u.)
O3
O1
H16
C16
H2
C2
C2
H2
O3
5b
RDG (a.u)
sign(λ2)ρ (a.u.)
H15
C15
O4
O3
H1
C1
H1
O3
H8B
O4
H15
5d
RDG (a.u)
sign(λ2)ρ (a.u.)
C1
H1
O5
O5
H1
C1
5h(i)
RDG (a.u)
sign(λ2)ρ (a.u.)
H22A
O7B1
H17B
O4A
H22E
O8A
O7A1
H20A


RDG (a.u)
sign(λ2)ρ (a.u.)
5h(ii)
H2B
O5A
H20A
O6A
5h(iii)
H9A2
O1B
O3B
H22F
H22B
5l(i)
C8
H8B
O1
O1
H8B
C8
O3
H22B
5l(ii)
O3
C22
H22B

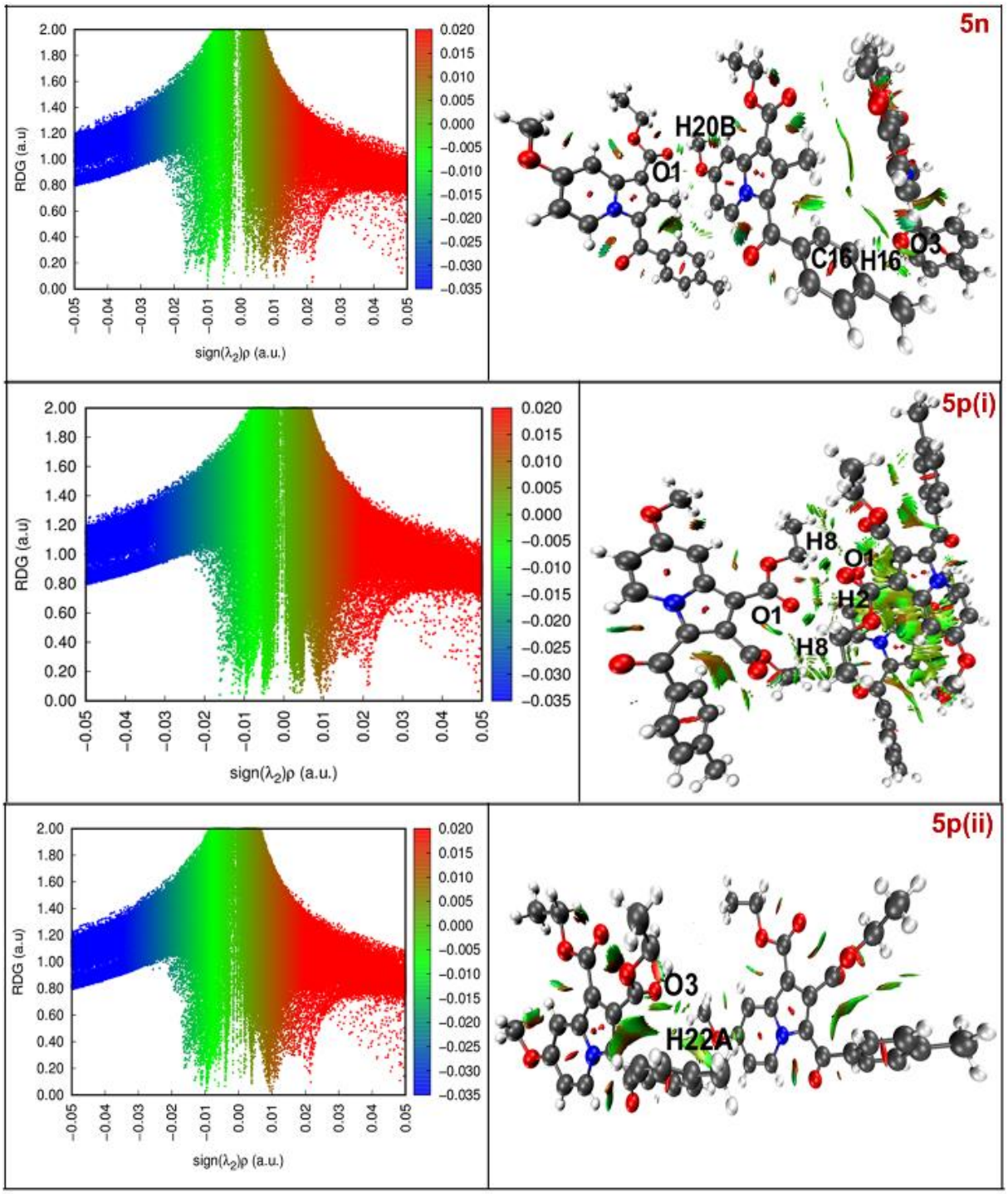


Figure S44- 2D NCI plots (on the left) and 3D gradient isosurfaces (on the right) illustrate the inter-molecular HB interactions within compounds **5a**, **5b**, **5d**, **5h**, **5l**, **5n**, and **5p**.

Table S14- Topological parameters concerning the intra and intermolecular interactions within compounds **5a**, **5b**, **5d**, **5h**, **5l**, **5n**, and **5p** with their respective (3, −1) BCPs, including various properties such as ρ(r): electron density; $\nabla^2\rho(r)$: Laplacian of electron density; G(r): kinetic energy density; V(r): potential energy density; H(r): total electronic density; (all units are in a.u.); D: HB bond distance (in Å); E_{int} (in kcal/mol).

Code	Interaction	D	E_{int}= 216.2 ρ(r)	ρ(r)	$\nabla^2\rho(r)$	G(r)	V(r)	H(r)	|V(r)|/G(r)
5a	H1⋯O3	2.246	3.6754	0.017	0.065	0.014	-0.011	0.003	0.7857
	H4⋯O1	2.501	1.7296	0.008	0.030	0.006	-0.005	0.001	0.8333
	H2⋯O3	2.281	3.0268	0.014	0.056	0.014	-0.012	0.002	0.8571
	H16⋯O1	2.586	1.5134	0.007	0.025	0.005	-0.004	0.001	0.8000
5b	H1⋯O3	2.179	4.1078	0.019	0.076	0.016	-0.013	0.003	0.8125
	H4⋯O2	2.359	2.8106	0.013	0.052	0.011	-0.009	0.002	0.8181
	H11B⋯O1	2.467	1.9458	0.009	0.046	0.007	-0.005	0.002	0.7142
	H1⋯O3	2.478	1.7296	0.008	0.034	0.007	-0.005	0.002	0.7142
	H8B⋯O3	2.398	2.1620	0.010	0.048	0.008	-0.006	0.002	0.7500
	H15⋯O4	2.495	1.9458	0.009	0.029	0.006	-0.005	0.001	0.8333
5d	H1⋯O5	2.267	3.243	0.015	0.059	0.012	-0.010	0.002	0.8333
	H4⋯O2	2.399	2.3782	0.011	0.050	0.010	-0.008	0.002	0.8000
	H1⋯O5	2.390	2.1620	0.010	0.049	0.008	-0.007	0.001	0.8750
5h	H1B⋯O5B	2.269	3.243	0.015	0.058	0.013	-0.011	0.002	0.8461
	H4B⋯O1B	2.497	1.9458	0.009	0.028	0.006	-0.005	0.002	0.8333
	H22B⋯O7B1	2.489	1.7296	0.008	0.026	0.006	-0.004	0.002	0.6667
	H17B⋯O4A	2.600	1.5134	0.007	0.025	0.005	-0.004	0.001	0.8000
	H18A⋯O6A	2.533	1.5134	0.007	0.026	0.006	-0.005	0.001	0.8333
	H22E⋯O7A1	2.524	1.5134	0.007	0.024	0.005	-0.004	0.001	0.8000
	H2B⋯O5A	2.519	1.7296	0.008	0.026	0.005	-0.004	0.001	0.8000

	H9A2⋯O1B	2.573	1.5134	0.007	0.024	0.005	-0.004	0.001	0.8000
	H22F⋯O3B	2.521	1.7296	0.008	0.025	0.006	-0.005	0.001	0.8333
	H22B⋯O3B	2.540	1.5134	0.007	0.027	0.005	-0.004	0.001	0.8000
5l	H1⋯O5	2.244	3.4592	0.016	0.063	0.013	-0.011	0.002	0.8161
	H4⋯O2	2.355	2.8106	0.013	0.054	0.011	-0.009	0.002	0.8181
	H2⋯O1	2.282	3.0268	0.014	0.056	0.013	-0.011	0.002	0.8461
	H8B⋯O1	2.537	1.5134	0.007	0.027	0.006	-0.005	0.001	0.8333
	H22B⋯O3	2.574	1.5134	0.007	0.027	0.006	-0.004	0.002	0.6667
5n	H1⋯O3	2.262	3.6754	0.017	0.067	0.014	-0.012	0.003	0.8571
	H4⋯O2	2.337	3.0268	0.014	0.055	0.013	-0.011	0.002	0.8461
	H11B⋯O1	2.457	1.9458	0.009	0.046	0.006	-0.005	0.001	0.8333
	H16⋯O3	2.524	1.7296	0.008	0.026	0.006	-0.005	0.001	0.8333
	H20B⋯O1	2.473	1.9458	0.009	0.027	0.006	-0.005	0.001	0.8333
5p	H1⋯O5	2.262	3.4592	0.016	0.062	0.013	-0.011	0.002	0.8461
	H4⋯O2	2.361	2.5944	0.012	0.053	0.011	-0.009	0.002	0.8181
	H2⋯O1	2.284	3.0268	0.014	0.055	0.009	-0.007	0.002	0.7778
	H8B⋯O1	2.495	1.7296	0.008	0.027	0.006	-0.005	0.001	0.8333
	H22A⋯O3	2.583	1.5134	0.007	0.028	0.006	-0.005	0.001	0.8333

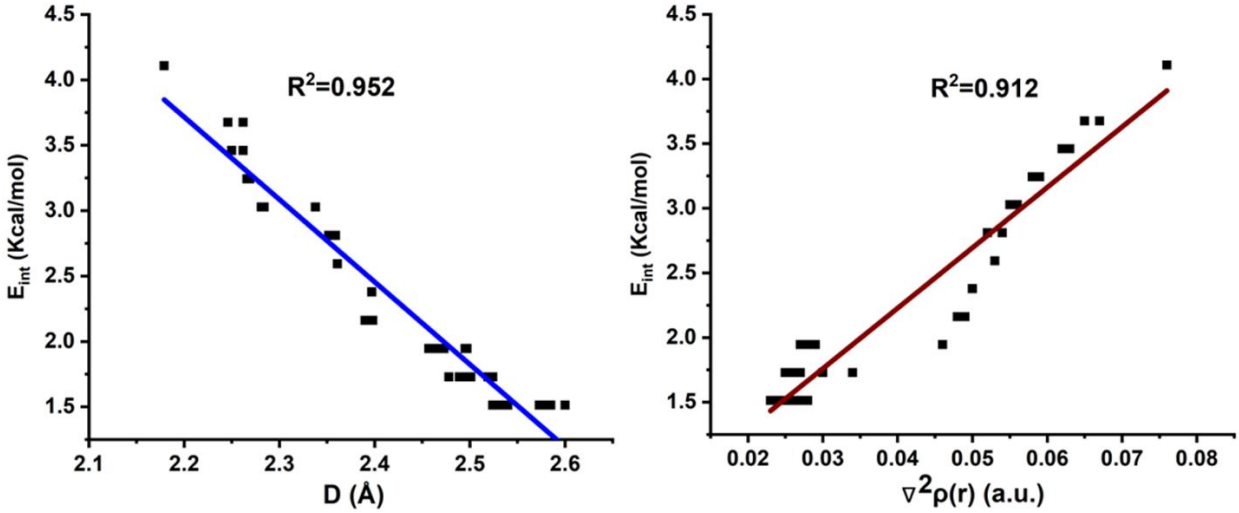


Figure S45- Plot of interaction energies (E_{int}) against contact distances (D) on the left and Laplacian of electron density ($\nabla^2\rho(r)$) on the right for the systems under investigation.

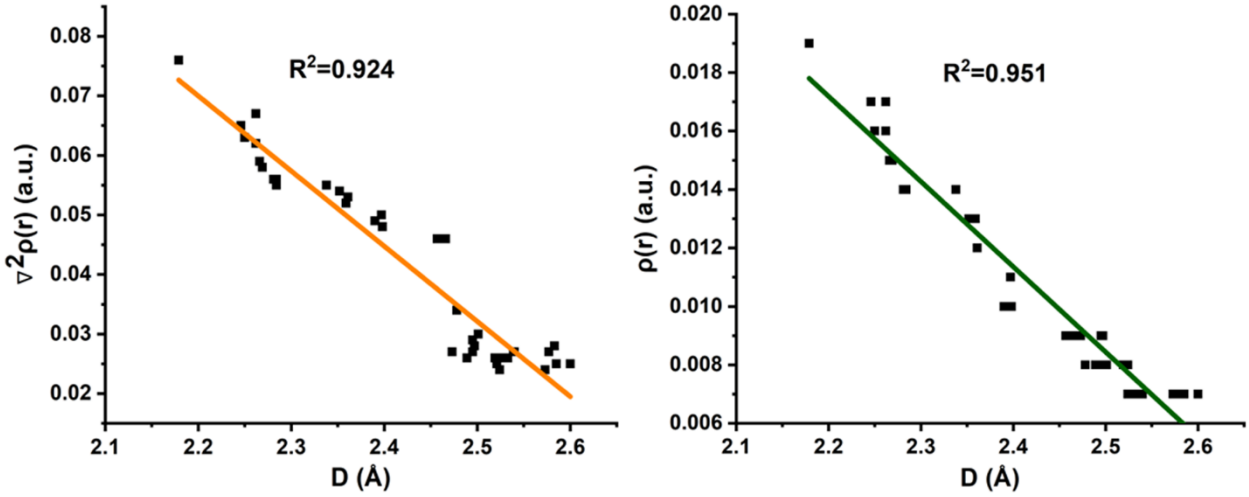


Figure S46- $\nabla^2\rho(r)$ (on the left) and $\rho(r)$ (on the right) versus contact distances (D) are the topological parameters for the studied systems.

Table S15- Analysis of in-silico ADME profiles for the potent compounds (**5a-p**) using the Swiss ADME online server.

	Compounds Code		Units	5a	5b	5c	5d	5e	5f	5g	5h	5i	5j	5k	5l	5m	5n	5o	5p
ADMET PROFILE	Physiochemical parameters	Formula		$C_{19}H_{17}NO_4$	$C_{20}H_{19}NO_4$	$C_{21}H_{21}NO_4$	$C_{22}H_{21}NO_6$	$C_{19}H_{16}N_2O_6$	$C_{20}H_{18}N_2O_6$	$C_{21}H_{20}N_2O_6$	$C_{22}H_{20}N_2O_8$	$C_{19}H_{16}ClNO_4$	$C_{20}H_{18}ClNO_4$	$C_{21}H_{20}ClNO_4$	$C_{22}H_{20}ClNO_6$	$C_{20}H_{19}NO_4$	$C_{21}H_{21}NO_4$	$C_{22}H_{23}NO_4$	$C_{23}H_{23}NO_6$
		Molecular weight	g/mol	323.34	337.37	351.40	395.41	368.34	382.37	396.39	440.40	357.79	371.81	385.84	429.85	337.37	351.40	365.42	409.43
		Mol. refractivity	-	89.85	94.82	99.62	105.94	98.67	103.64	108.44	114.76	94.86	99.83	104.63	110.95	94.82	99.78	104.59	110.90
		TPSA	Å²	57.01	57.01	57.01	83.31	102.8.	102.83	102.83	129.13	57.01	57.01	57.01	83.31	57.01	57.01	57.01	83.31
	Lipophilicity	ILOGP	-	3.47	3.43	3.70	3.85	3.17	3.10	3.36	3.54	3.79	3.78	3.69	4.12	3.78	3.78	3.65	4.20
		SILICOS-IT	-	3.24	3.77	4.16	3.66	1.10	1.63	2.03	1.54	3.88	4.41	4.81	4.32	3.77	4.29	4.69	4.20
	Water Solubility	Log S (ESOL), Class	-	-4.66 Moderately soluble	-4.96 Moderately soluble	-5.23 Moderately soluble	-4.97 Moderately soluble	-4.71 Moderately soluble	-5.02 Moderately soluble	-5.30 Moderately soluble	-5.04 Moderately soluble	-5.25 Moderately soluble	-5.55 Moderately soluble	-5.83 Moderately soluble	-5.56 Moderately soluble	-4.96 Moderately soluble	-5.26 Moderately soluble	-5.54 Moderately soluble	-5.27 Moderately soluble
	Pharmacokinetics	GI absorption	High/Low	High	High	High	High	High	High	High	High	High	High	High	High	High	High	High	High
		Intestinal absorption (human)	% Absorbed	99.37	99.055	98.596	99.634	100	92.696	92.774	93.508	98.136	98.137	98.022	98.208	99.594	99.087	99.48	99.667
		BBB permeant	-	Yes	Yes	Yes	No	No	No	No	No	Yes	Yes	Yes	No	Yes	Yes	Yes	No
		Log K_p (skin perm.)	cm/s	-5.18	-5.00	-4.78	-5.46	-5.57	-5.46	-5.18	-5.86	-4.94	-4.76	-4.54	-5.22	-5.00	-4.83	-4.60	-5.28
		Caco2 permeability	log Papp in 10^{-6} cm/s	1.342	1.345	1.105	1.036	0.939	0.838	0.854	0.357	1.069	1.192	1.169	0.715	1.265	1.112	1.171	1.155
		CYP1A2	Yes/No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
		CYP2D6	Yes/No	Yes	No	Yes	No	Yes	No	No	No	Yes	No	No	No	No	No	No	No
	Drug-likeness Rules	Lipinski (Pfizer)	Yes/No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
		Ghose (Amgen)	Yes/No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
		Veber (GSK)	Yes/No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
		Egan (Pharmacia)	Yes/No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
		Muege (Bayer)	Yes/No	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes	No	No	Yes
		Bioavailability Score	-	0.55	0.55	0.55	0.55	0.55	0.55	0.55	0.55	0.55	0.55	0.55	0.55	0.55	0.55	0.55	0.55
		Alerts: PAINS	-	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		Alerts: Brenk	-	0	0	0	1	2	2	2	2	0	0	0	1	0	0	0	1
		Synthetic Accessibility	-	2.61	2.80	2.99	3.16	2.80	2.97	3.15	3.32	2.63	2.81	3.00	3.17	2.73	2.91	3.10	3.28
	Excretion	Total Clearance	log ml/min/kg	0.739	0.757	0.794	0.817	0.797	0.777	0.756	0.984	0.797	0.332	0.348	0.363	0.757	0.758	0.802	0.82
		Renal OCT2 substrate	Yes/No	Yes	Yes	No	Yes	No	No	No	No	No	No	No	No	No	No	No	No

Table S16- Predicted toxicity data of identified potent compounds (**5a-p**).

Model Name	Units	Compounds Code															
		5a	**5b**	**5c**	**5d**	**5e**	**5f**	**5g**	**5h**	**5i**	**5j**	**5k**	**5l**	**5m**	**5n**	**5o**	**5p**
AMES toxicity	**Yes/No**	No	No	No	Yes	Yes	Yes	Yes	Yes	No	No	No	No	Yes	No	No	No
Max. tolerated dose (human)	**Log mg/kg/day**	-0.722	-0.639	-0.42	-0.334	-0.408	-0.664	-0.471	-0.335	-0.308	-0.251	-0.081	-0.269	-0.314	-0.6	-0.085	-0.279
hERG I inhibitor	**Yes/No**	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
hERG II inhibitor	**Yes/No**	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
Oral Rat Chronic Toxicity (LD50)	**Mol/kg**	2.39	2.386	2.387	2.593	2.954	3.094	3.106	3.111	2.366	2.383	2.427	2.629	2.301	2.375	2.329	2.567
Oral Rat Chronic Toxicity (LOAEL)	**Log mg/kg_bw/day**	1.027	1.079	1.129	1.235	1.859	1.302	1.335	1.734	1.058	0.94	0.83	0.982	1.155	1.009	0.908	1.289
Hepatotoxicity	**Yes/No**	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Skin Sensitisation	**Yes/No**	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
T. Pyriformis toxicity	**Log ug/L**	0.601	0.743	0.838	0.39	0.417	0.601	0.612	0.343	0.466	0.532	0.615	0.386	0.461	0.761	0.62	0.389
Minnow toxicity	**Log mM**	1.719	1.596	1.373	1.944	-1.639	1.17	0.948	1.536	-0.793	-0.929	-0.874	1.646	-0.575	1.498	-0.656	1.864

References

1. S. J. Keam, *Drugs*, 2019, **79**, 1797-1803.
2. S. R. Tetali, E. Kunapaeddi, R. P. Mailavaram, V. Singh, P. Borah, P. K. Deb, K. N. Venugopala, W. Hourani and R. K. Tekade, *Tuberculosis,* 2020, **125**, 101989.
3. K. N. Venugopala, S. Chandrashekharappa, C. Tratrat, P. K. Deb, R. D. Nagdeve, S. K. Nayak, M. A. Morsy, P. Borah, F. M. Mahomoodally and R. P. Mailavaram, *Molecules*, 2021, **26**, 3550.
4. R. D. Nagdeve, J. S. Thakur, S. Chandrashekharappa, K. M. Bairagi, P. K. Deb, K. N. Venugopala, P. K. Mondal, M. Polentarutti, O. I. Alwassil and V. Mohanlall, *J. Mol. Struct.*, 2024, **1308**, 138080.