

Electronic Supporting Information

Design, synthesis and biological evaluation of benzimidazole-rhodanine conjugates as potent topoisomerase II inhibitors

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¹H NMR and 2D NOESY (DMSO-*d*₆) Spectrum of Compound 3a

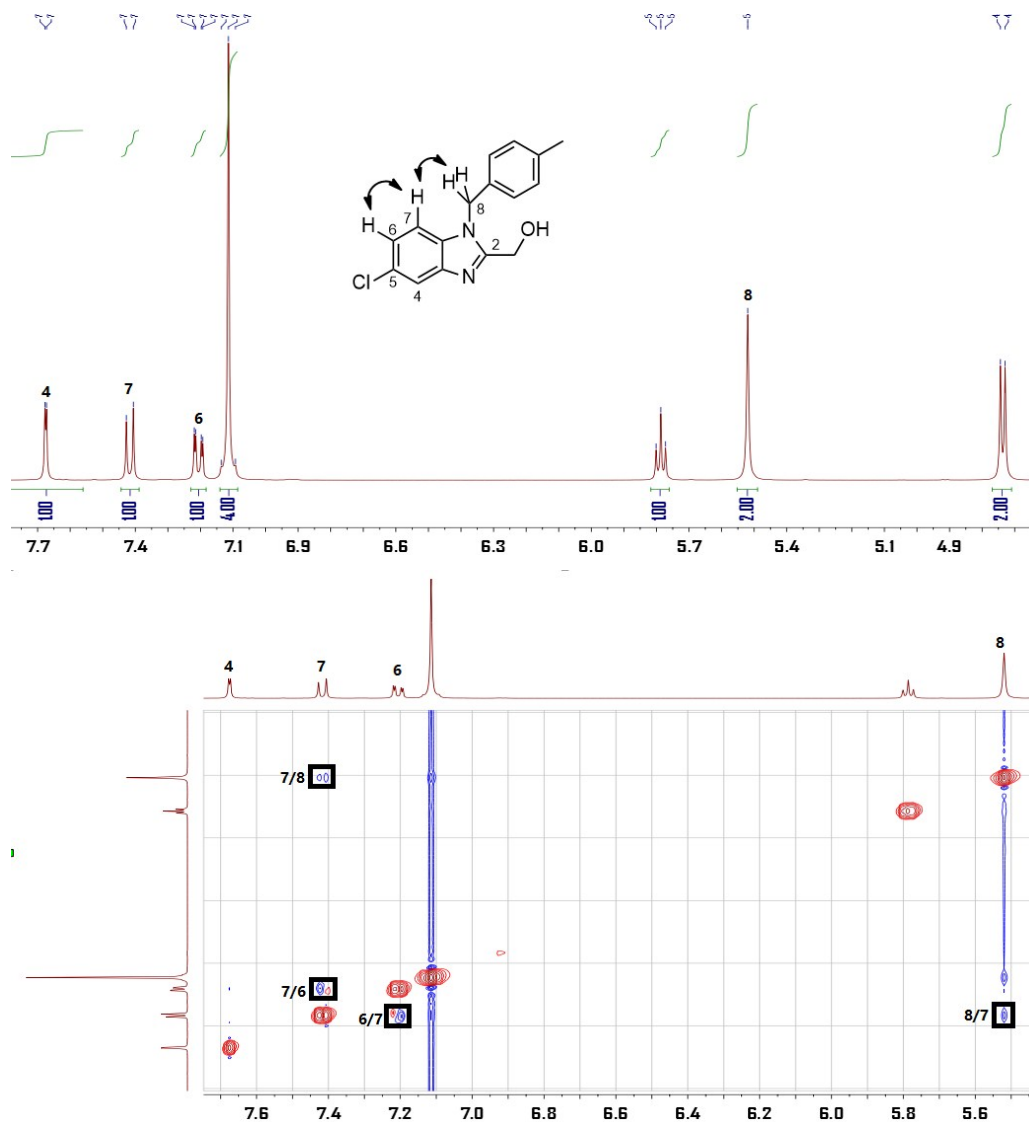


Fig. S1. ¹H NMR (upper) and 2D NOESY analysis of **3a**. The protons on the aromatic ring (6-H, 7-H, and 8-H) are easily assigned on the basis of 2D NOESY relations.

^1H NMR and 2D NOESY ($\text{DMSO}-d_6$) Spectrum of Compound **3b**

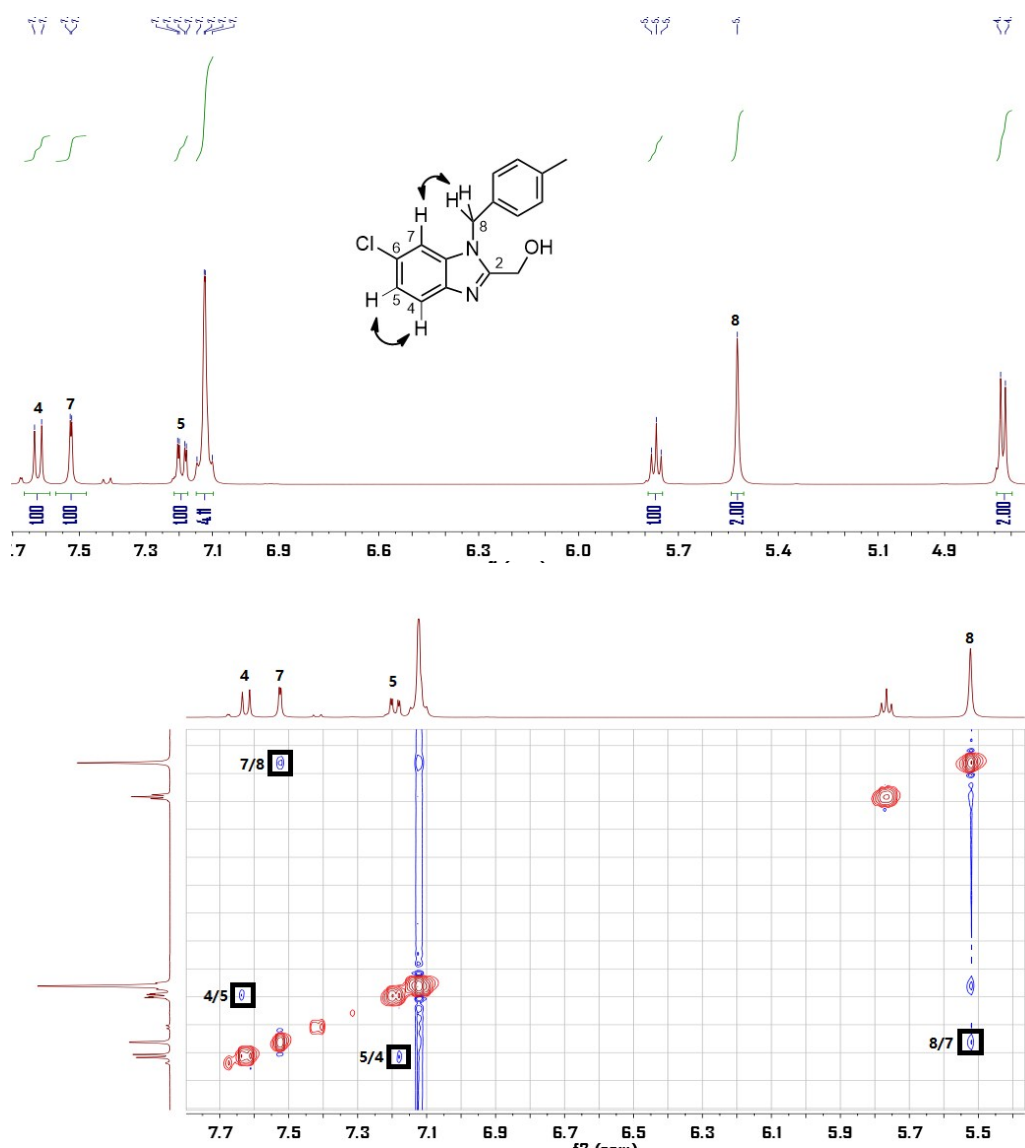
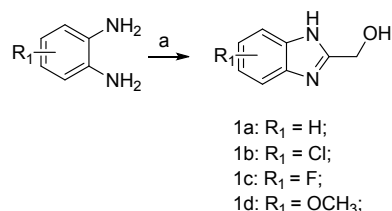


Fig. S2. ^1H NMR and 2D NOESY analysis of **3b**. The protons on the aromatic ring (4-H, 5-H, 7-H, and 8-H) are easily assigned on the basis of 2D NOESY relations.

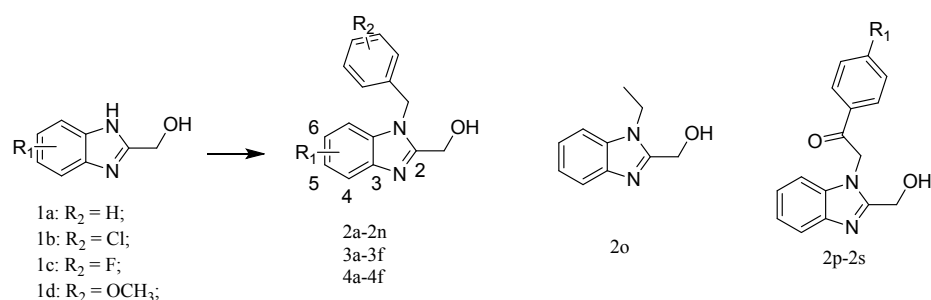
Chemistry

General method for the synthesis of 1a–1d



The mixture of a substituted benzene-1,2-diamine (10 mmol) and glycolic acid (30 mmol) in HCl (4 N, 30 mL) was heated to reflux at 100 °C for 6 h and the reaction was quenched with saturated aqueous sodium bicarbonate. The white solid were collected by filtration. They were used directly without further purification.

General method for the synthesis of 2a–2s, 3a–3f, and 4a–4g



- | | | |
|--|--|---|
| 2a: R ₁ = H, R ₂ = <i>p</i> -Br; | 3a: R ₁ = 5-Cl, R ₂ = <i>p</i> -CH ₃ ; | 2p: R ₁ = <i>p</i> -F; |
| 2b: R ₁ = H, R ₂ = <i>o</i> -F, <i>p</i> -Br; | 3b: R ₁ = 6-Cl, R ₂ = <i>p</i> -CH ₃ ; | 2q: R ₁ = <i>p</i> -OCH ₃ ; |
| 2c: R ₁ = H, R ₂ = <i>p</i> -CN; | 3c: R ₁ = 5-F, R ₂ = <i>p</i> -CH ₃ ; | 2r: R ₁ = <i>p</i> -Cl; |
| 2d: R ₁ = H, R ₂ = <i>p</i> -NO ₂ ; | 3d: R ₁ = 6-F, R ₂ = <i>p</i> -CH ₃ ; | 2s: R ₁ = <i>p</i> -CH ₃ ; |
| 2e: R ₁ = H, R ₂ = <i>p</i> -F; | 3e: R ₁ = 5-OCH ₃ , R ₂ = <i>p</i> -CH ₃ ; | |
| 2f: R ₁ = H, R ₂ = H; | 3f: R ₁ = 6-OCH ₃ , R ₂ = <i>p</i> -CH ₃ ; | |
| 2g: R ₁ = H, R ₂ = <i>p</i> -CH ₃ ; | 4a: R ₁ = 5-Cl, R ₂ = <i>o</i> -F; | |
| 2h: R ₁ = H, R ₂ = <i>p</i> -Cl; | 4b: R ₁ = 6-Cl, R ₂ = <i>o</i> -F; | |
| 2i: R ₁ = H, R ₂ = <i>p</i> -CF ₃ ; | 4c: R ₁ = 5-F, R ₂ = <i>o</i> -F; | |
| 2j: R ₁ = H, R ₂ = <i>o</i> -F; | 4d: R ₁ = 6-F, R ₂ = <i>o</i> -F; | |
| 2k: R ₁ = H, R ₂ = <i>o</i> -F; <i>p</i> -F; | 4e: R ₁ = 5-OCH ₃ , R ₂ = <i>o</i> -F; | |
| 2l: R ₁ = H, R ₂ = <i>m</i> -F; | 4f: R ₁ = 6-OCH ₃ , R ₂ = <i>o</i> -F; | |
| 2m: R ₁ = H, R ₂ = <i>m</i> -F; <i>p</i> -F; | | |
| 2n: R ₁ = H, R ₂ = <i>m</i> -OCH ₃ ; <i>m</i> -OCH ₃ ; | | |

The solution of a **1a–1d** (1 mmol) in DMF (2 mL) were added the appropriate benzyl bromide (2 mmol) and K₂CO₃ (5 mmol), and the reaction mixture was stirred at room temperature for 8 h. It was then diluted with DCM (8 mL) and H₂O (8 mL). The organic layer

was separated, and the aqueous layer was extracted with DCM (8 mL × 2). The combined organic layers were dried over Mg₂SO₄ and concentrated *in vacuo* to provide a crude product, which was purified by PTLC (DCM/ MeOH =100/5, v/v) to yield the title compound.

(1-(4-Bromobenzyl)-1H-benzo[d]imidazol-2-yl)methanol (2a)

1-Bromo-4-(bromomethyl) benzene and **1a** were used as reactants to give **2a**. While solid, Yield: 76%. ¹H NMR (400 MHz, CDCl₃) δ 7.69 (d, *J* = 7.9 Hz, 1H), 7.39 (d, *J* = 8.3 Hz, 2H), 7.26 – 7.19 (m, 2H), 7.16 (d, *J* = 7.7 Hz, 1H), 6.97 (d, *J* = 8.2 Hz, 2H), 5.41 (s, 2H), 4.86 (s, 2H).

(1-(4-Bromo-2-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)methanol (2b)

4-Bromo-1-(bromomethyl)-2-fluorobenzene and **1a** were used as reactants to give **2b**. While solid. Yield: 83%. ¹H NMR (400 MHz, CDCl₃) δ 7.71 (d, *J* = 7.7 Hz, 1H), 7.30 (d, *J* = 9.7 Hz, 1H), 7.26 – 7.15 (m, 3H), 7.10 (d, *J* = 8.2 Hz, 1H), 7.03 – 6.95 (m, 1H), 5.45 (s, 2H), 4.91 (s, 2H).

4-((2-(Hydroxymethyl)-1H-benzo[d]imidazol-1-yl)methyl)benzotrile (2c)

4-(Bromomethyl)benzotrile and **1a** were used as reactants to give **2c**. While solid. Yield: 71%. ¹H NMR (400 MHz, CDCl₃) δ 7.68 (d, *J* = 7.7 Hz, 1H), 7.54 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 7.3 Hz, 1H), 7.22 (d, *J* = 7.4 Hz, 1H), 7.18 (d, *J* = 8.0 Hz, 2H), 7.11 (d, *J* = 7.8 Hz, 1H), 5.55 (s, 2H), 4.89 (s, 2H).

(1-(4-Nitrobenzyl)-1H-benzo[d]imidazol-2-yl)methanol (2d)

1-(Bromomethyl)-4-nitrobenzene and **1a** were used as reactants to give **2d**. While solid. Yield: 66%. ¹H NMR (400 MHz, CDCl₃) δ 8.12 (d, *J* = 8.5 Hz, 2H), 7.70 (d, *J* = 7.7 Hz, 1H), 7.29 (d, *J* = 7.1 Hz, 1H), 7.27 – 7.21 (m, 3H), 7.12 (d, *J* = 7.8 Hz, 1H), 5.60 (s, 2H), 4.91 (s, 2H).

(1-(4-Fluorobenzyl)-1H-benzo[d]imidazol-2-yl)methanol (2e)

1-(Bromomethyl)-4-fluorobenzene and **1a** were used as reactants to give **2e**. While solid.

Yield: 87%. ¹H NMR (400 MHz, CDCl₃) δ 7.71 (d, *J* = 7.8 Hz, 1H), 7.25–7.19 (m, 3H), 7.12 – 7.06 (m, 2H), 7.00 – 6.92 (m, 2H), 5.42 (s, 2H), 4.87 (s, 2H).

(1-benzyl-1H-benzo[d]imidazol-2-yl)methanol (2f)

(Bromomethyl)benzene and **1a** were used as reactants to give **2f**. While solid. Yield: 69%. ¹H

NMR (400 MHz, CDCl₃) δ 7.72 (d, *J* = 7.6 Hz, 1H), 7.32 – 7.22 (m, 6H), 7.13 – 7.07 (m, 2H), 5.45 (s, 2H), 4.87 (s, 2H).

(1-(4-Methylbenzyl)-1H-benzo[d]imidazol-2-yl)methanol (2g)

1-(Bromomethyl)-4-methylbenzene and **1a** were used as reactants to give **2g**. While solid.

Yield: 73%. ¹H NMR (400 MHz, CDCl₃) δ 7.72 (d, *J* = 8.1 Hz, 1H), 7.25 – 7.19 (m, 3H), 7.09 (d, *J* = 7.7 Hz, 2H), 6.99 (d, *J* = 7.7 Hz, 2H), 5.40 (s, 2H), 4.87 (s, 2H), 2.30 (s, 3H).

(1-(4-Chlorobenzyl)-1H-benzo[d]imidazol-2-yl)methanol (2h)

1-(Bromomethyl)-4-chlorobenzene and **1a** were used as reactants to give **2h**. While solid.

Yield: 84%. ¹H NMR (400 MHz, CDCl₃) δ 7.70 (d, *J* = 7.6 Hz, 1H), 7.29 – 7.25 (d, *J* = 8.2 Hz, 3H), 7.21 (d, *J* = 7.4 Hz, 1H), 7.17 (d, *J* = 7.6 Hz, 1H), 7.03 (d, *J* = 8.1 Hz, 2H), 5.43 (s, 2H), 4.87 (s, 2H).

(1-(4-(Trifluoromethyl)benzyl)-1H-benzo[d]imidazol-2-yl)methanol (2i)

1-(Bromomethyl)-4-(trifluoromethyl)benzene and **1a** were used as reactants to give **2j**. While

solid. Yield: 86%. ¹H NMR (400 MHz, CDCl₃) δ 7.71 (d, *J* = 7.7 Hz, 1H), 7.53 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 7.2 Hz, 1H), 7.23 (d, 1H), 7.20 (d, *J* = 8.2 Hz, 2H), 7.16 (d, *J* = 7.7 Hz, 1H), 5.54 (s, 2H), 4.90 (s, 2H).

(1-(2-Fluorobenzyl)-1H-benzo[d]imidazol-2-yl)methanol (2j)

1-(Bromomethyl)-2-fluorobenzene and **1a** were used as reactants to give **2j**. While solid. Yield: 77%. ¹H NMR (400 MHz, CDCl₃) δ 7.71 (d, *J* = 7.3 Hz, 1H), 7.30 – 7.22 (m, 3H), 7.10 (d, *J* = 9.2 Hz, 1H), 6.98 (d, *J* = 7.4 Hz, 1H), 6.84 (d, *J* = 7.4 Hz, 1H), 5.50 (s, 2H), 4.92 (s, 2H).

(1-(2,4-Difluorobenzyl)-1H-benzo[d]imidazol-2-yl)methanol (2k)

1-(Bromomethyl)-2,4-difluorobenzene and **1a** were used as reactants to give **2k**. While solid. Yield: 71%. ¹H NMR (400 MHz, CDCl₃) δ 7.70 (d, *J* = 7.6 Hz, 1H), 7.26 – 7.16 (m, 3H), 6.90 – 6.82 (m, 2H), 6.70 (d, *J* = 8.3 Hz, 1H), 5.46 (s, 2H), 4.92 (s, 2H).

(1-(3-Fluorobenzyl)-1H-benzo[d]imidazol-2-yl)methanol (2l)

1-(Bromomethyl)-3-fluorobenzene and **1a** were used as reactants to give **2l**. While solid. Yield: 84%. ¹H NMR (400 MHz, CDCl₃) δ 7.72 (d, *J* = 7.5 Hz, 1H), 7.26–7.18(m, 4H), 6.97 (d, *J* = 8.3 Hz, 1H), 6.89 (d, *J* = 7.6 Hz, 1H), 6.82 (d, *J* = 9.3 Hz, 1H), 5.46 (s, 2H), 4.88 (s, 2H), 4.37 (s, 1H).

(1-(3,4-Difluorobenzyl)-1H-benzo[d]imidazol-2-yl)methanol (2m)

4-(Bromomethyl)-1,2-difluorobenzene and **1a** were used as reactants to give **2m**. While solid. Yield: 74%. ¹H NMR (400 MHz, CDCl₃) δ 7.70 (d, *J* = 7.7 Hz, 1H), 7.26 – 7.20 (m, 2H), 7.16 (d, *J* = 7.5 Hz, 1H), 7.11–7.05 (m, 1H), 7.01 – 6.93 (m, 1H), 6.86 (d, *J* = 6.6 Hz, 1H), 5.42 (s, 2H), 4.88 (s, 2H).

(1-(3,5-Dimethoxybenzyl)-1H-benzo[d]imidazol-2-yl)methanol (2n)

1-(Bromomethyl)-3,5-dimethoxybenzene and **1a** were used as reactants to give **2n**. While solid. Yield: 85%. ¹H NMR (400 MHz, CDCl₃) δ 7.72 (d, *J* = 7.8 Hz, 1H), 7.22 (d, *J* = 14.1 Hz, 3H), 6.35 (s, 1H), 6.25 (s, 2H), 5.37 (s, 2H), 4.87 (s, 2H), 3.69 (s, 6H).

(1-Ethyl-1H-benzo[d]imidazol-2-yl)methanol (2o)

Bromoethane and **1a** were used as reactants to give **2o**. ¹H NMR (400 MHz, CDCl₃-d₆) δ 7.68 (d, *J* = 6.7, 2.2 Hz, 1H), 7.32 (d, *J* = 6.7, 2.1 Hz, 1H), 7.28 – 7.21 (m, 2H), 4.88 (s, 2H), 4.29 (q, *J* = 7.3 Hz, 2H), 1.46 (t, *J* = 7.3 Hz, 3H).

1-(4-Fluorophenyl)-2-(2-(hydroxymethyl)-1H-benzo[d]imidazol-1-yl)ethanone (2p)

2-Bromo-1-(4-fluorophenyl)ethanone and **1a** were used as reactants to give **2p**. While solid. Yield: 77%. ¹H NMR (400 MHz, CDCl₃) δ 8.12–8.02 (dd, *J* = 8.6, 5.3 Hz, 2H), 7.72 – 7.67 (m, 1H), 7.25 – 7.19 (m, 4H), 7.12 – 7.08 (m, 1H), 5.65 (s, 2H), 4.80 (s, 2H).

2-(2-(hydroxymethyl)-1H-benzo[d]imidazol-1-yl)-1-(4-methoxyphenyl)ethanone(2q)

2-Bromo-1-(4-methoxyphenyl)ethanone and **1a** were used as reactants to give **2q**. While solid. Yield: 88%. ¹H NMR (400 MHz, CDCl₃) δ 8.01 (d, *J* = 8.8 Hz, 2H), 7.72 (dd, *J* = 6.3, 2.2 Hz, 1H), 7.26 – 7.20 (m, 2H), 7.12 (dd, *J* = 6.4, 2.4 Hz, 1H), 7.01 (d, *J* = 8.9 Hz, 2H), 5.64 (s, 2H), 4.83 (s, 2H), 3.91 (s, 3H).

1-(4-chlorophenyl)-2-(2-(hydroxymethyl)-1H-benzo[d]imidazol-1-yl)ethanone (2r)

2-Bromo-1-(4-chlorophenyl)ethanone and **1a** were used as reactants to give **2r**. While solid. Yield: 81%. ¹H NMR (400 MHz, CDCl₃) δ 7.96 (d, *J* = 8.5 Hz, 2H), 7.70 (d, *J* = 8.6 Hz, 1H), 7.51 (s, 2H), 7.26 – 7.22 (m, 2H), 7.12 – 7.09 (m, 1H), 5.65 (s, 2H), 4.81 (s, 2H).

2-(2-(Hydroxymethyl)-1H-benzo[d]imidazol-1-yl)-1-(p-tolyl)ethanone (2s)

2-Bromo-1-(p-tolyl)ethanone and **1a** were used as reactants to give **2s**. While solid. Yield: 75%. ¹H NMR (400 MHz, CDCl₃) δ 7.93 (d, *J* = 8.1 Hz, 2H), 7.71 (d, *J* = 7.9 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.25 – 7.20 (m, 2H), 7.13 – 7.09 (m, 1H), 5.66 (s, 2H), 4.81 (s, 2H), 2.46 (s, 3H).

(5 or 6-Chloro-1-(4-methylbenzyl)-1H-benzo[d]imidazol-2-yl)methanol (3a and 3b)

1-(Bromomethyl)-4-methylbenzene and **1b** were used as reactants to give **3a** and **3b**. For **3a**: while solid. Yield: 36%. ¹H NMR (400 MHz, CDCl₃) δ 7.67 (d, *J* = 1.3 Hz, 1H), 7.21–7.09 (m, 4H), 6.98 (d, *J* = 8.0 Hz, 2H), 5.40 (s, 2H), 4.88 (s, 2H), 2.31 (s, 3H). For **3b**: while solid. Yield: 41%. ¹H NMR (400 MHz, CDCl₃) δ 7.61 (d, *J* = 9.3 Hz, 1H), 7.23 – 7.19 (m, 2H), 7.10 (d, *J* = 7.9 Hz, 2H), 6.97 (d, *J* = 8.0 Hz, 2H), 5.35 (s, 2H), 4.85 (s, 2H), 2.32 (s, 3H).

(5 or 6-Fluoro-1-(4-methylbenzyl)-1H-benzo[d]imidazol-2-yl)methanol (3c and 3d)

1-(Bromomethyl)-4-methylbenzene and **1c** were used as reactants to give **3c** and **3d**. For **3c**: while solid. Yield: 33%. ¹H NMR (400 MHz, CDCl₃) δ 7.42 – 7.30 (m, 1H), 7.12 – 7.08 (m, 3H), 7.02 – 6.94 (dd, *J* = 8.0, 3.7 Hz, 3H), 5.39 (s, 2H), 4.86 (s, 2H), 2.31 (s, 3H). For **3d**: while solid. Yield: 27%. ¹H NMR (400 MHz, CDCl₃) δ 7.68 – 7.60 (m, 1H), 7.10 (d, *J* = 8.0 Hz, 2H), 6.99 (d, *J* = 8.2 Hz, 3H), 6.92 – 6.84 (m, 1H), 5.36 (s, 2H), 4.86 (s, 2H), 2.31 (s, 3H).

(5 or 6-Methoxy-1-(4-methylbenzyl)-1H-benzo[d]imidazol-2-yl)methanol (3e and 3f)

1-(Bromomethyl)-4-methylbenzene and **1d** were used as reactants to give **3e** and **3f**. For **3e**: while solid. Yield: 42%. ¹H NMR (400 MHz, CDCl₃) δ 7.17 (d, *J* = 2.1 Hz, 1H), 7.12 – 7.04 (m, 3H), 6.98 (d, *J* = 8.0 Hz, 2H), 6.91 – 6.83 (m, 1H), 5.38 (s, 2H), 4.85 (s, 2H), 3.82 (s, 3H), 2.30 (s, 3H). For **3f**: while solid. Yield: 38%. ¹H NMR (400 MHz, CDCl₃) δ 7.58 (d, *J* = 8.8 Hz, 1H), 7.09 (d, *J* = 7.9 Hz, 2H), 6.99 (d, *J* = 8.0 Hz, 2H), 6.87 (dd, *J* = 8.7, 2.2 Hz, 1H), 6.65 (d, *J* = 2.1 Hz, 1H), 5.36 (s, 2H), 4.82 (s, 2H), 3.77 (s, 3H), 2.30 (s, 3H).

(5 or 6-Chloro-1-(2-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)methanol (4a and 4b)

1-(Bromomethyl)-2-fluorobenzene and **1b** were used as reactants to give **4a** and **4b**. For **4a**: while solid. Yield: 37%. ¹H NMR (400 MHz, CDCl₃) δ 7.66 (s, 1H), 7.32 – 7.27 (m, 1H), 7.21 – 7.15 (m, 1H), 7.18 – 7.06 (m, 2H), 7.02 (t, *J* = 7.5 Hz, 1H), 6.87 (t, *J* = 7.1 Hz, 1H), 5.49 (s,

2H), 4.92 (s, 2H). For **4b**: while solid. Yield: 29%. ¹H NMR (400 MHz, CDCl₃) δ 7.61 (d, *J* = 8.3 Hz, 1H), 7.33 – 7.27 (m, 1H), 7.25 – 7.20 (m, 2H), 7.14 – 7.09 (m, 1H), 7.03 (t, *J* = 7.5 Hz, 1H), 6.85 (t, *J* = 7.2 Hz, 1H), 5.46 (s, 2H), 4.90 (s, 2H).

(5 or 6-fluoro-1-(2-fluorobenzyl)-1H-benzo[d]imidazol-2-yl)methanol(4c and 4d)

1-(Bromomethyl)-2-fluorobenzene and **1c** were used as reactants to give **4c** and **4d**. For **4c**: while solid. Yield: 42%. ¹H NMR (400 MHz, CDCl₃) δ 7.41 – 7.33 (m, 1H), 7.32 – 7.27 (m, 1H), 7.17 – 7.08 (m, 2H), 7.04 – 6.94 (m, 2H), 6.87 (t, *J* = 7.6 Hz, 1H), 5.49 (s, 2H), 4.92 (s, 2H). For **4d**: while solid. Yield: 38%. ¹H NMR (400 MHz, CDCl₃) δ 7.63 (d, *J* = 8.7, 4.7 Hz, 1H), 7.35 – 7.29 (m, 1H), 7.14 – 7.08 (m, 1H), 7.03 (t, *J* = 5.1 Hz, 1H), 7.01 – 6.95 (m, 1H), 6.94 – 6.86 (m, 2H), 5.46 (s, 2H), 4.91 (s, 2H).

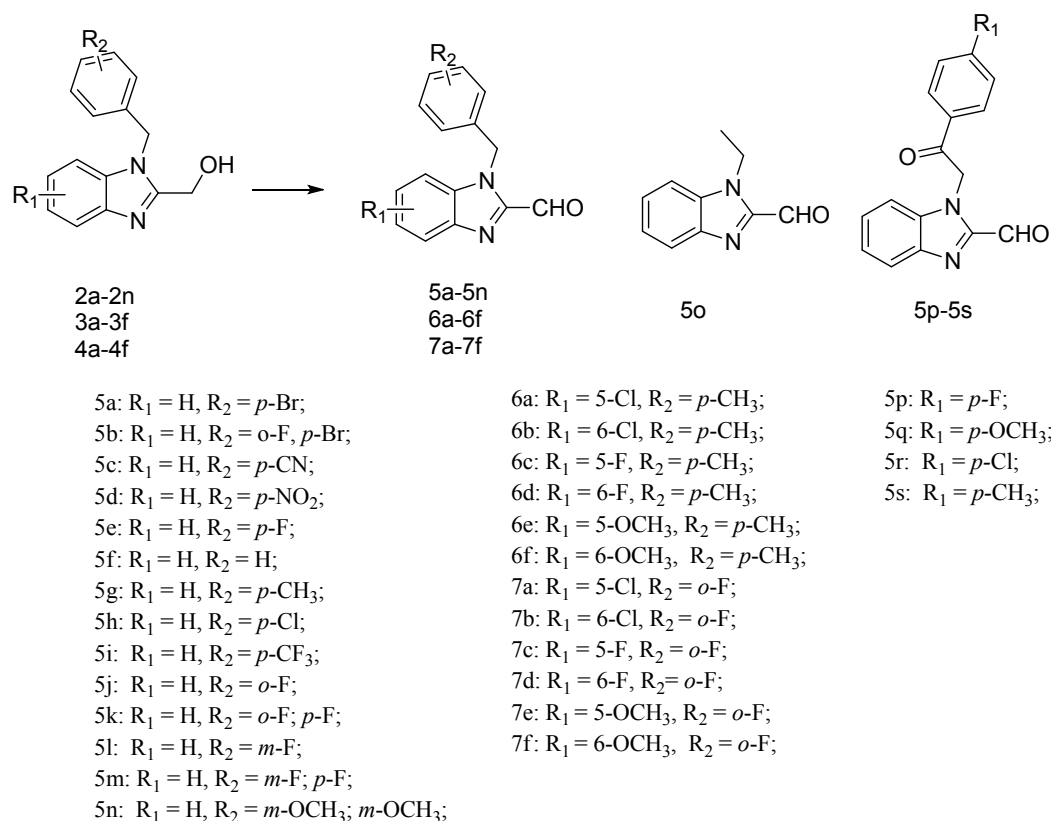
(1-(2-Fluorobenzyl)-5 or 6-methoxy-1H-benzo[d]imidazol-2-yl)methanol (4e and 4f)

1-(Bromomethyl)-2-fluorobenzene and **1d** were used as reactants to give **4e** and **4f**. For **4e**: while solid. Yield: 34%. ¹H NMR (400 MHz, CDCl₃) δ 7.26 – 7.22 (m, 1H), 7.18 (d, *J* = 2.3 Hz, 1H), 7.12 – 7.07 (m, 2H), 6.97 (t, *J* = 7.5 Hz, 1H), 6.87 – 6.80 (m, 2H), 5.47 (s, 2H), 4.89 (s, 2H), 3.83 (s, 3H). For **4f**: while solid. Yield: 40%. ¹H NMR (400 MHz, CDCl₃) δ 7.58 (d, *J* = 8.8 Hz, 1H), 7.30 – 7.26 (m, 1H), 7.13 – 7.08 (m, 1H), 7.00 (t, *J* = 7.5 Hz, 1H), 6.89 – 6.83 (m, 2H), 6.65 (d, *J* = 2.2 Hz, 1H), 5.46 (s, 2H), 4.88 (s, 2H), 3.78 (s, 3H).

General method for the synthesis of 5a–5s, 6a–6f, and 7a–7g

To a solution of **2a–2s**, **3a–3f**, or **4a–4f** (1 mmol) in DCM (10 mL) was added Dess-Martin reagent (1.1 mmol), and the reaction was stirred at 4 °C for 1 h. The reaction was quenched with a saturated aqueous sodium thiosulfate solution (3 mL) and subsequent mixture was extracted with DCM (10 mL × 3). The combined organic extracts were dried over Mg₂SO₄

and concentrated. The crude product obtained was purified by PTLC (DCM/MeOH = 100/5, v/v) to yield the title products.



1-(4-Bromobenzyl)-1H-benzo[d]imidazole-2-carbaldehyde (5a)

Compound **2a** was used as reactant to give **5a**. While solid. Yield: 48%. ¹H NMR (400 MHz, CDCl₃) δ 10.14 (s, 1H), 7.97 (d, *J* = 7.7 Hz, 1H), 7.49 – 7.39 (m, 5H), 7.04 (d, *J* = 8.1 Hz, 2H), 5.80 (s, 2H).

1-(4-Bromo-2-fluorobenzyl)-1H-benzo[d]imidazole-2-carbaldehyde (5b)

Compound **2b** was used as reactant to give **5b**. While solid. Yield: 53%. ¹H NMR (400 MHz, CDCl₃) δ 10.15 (s, 1H), 7.96 (d, *J* = 7.9 Hz, 1H), 7.50 – 7.39 (m, 3H), 7.31 – 7.27 (m, 1H), 7.22 – 7.16 (m, 1H), 6.80 (t, *J* = 8.1 Hz, 1H), 5.87 (s, 2H).

4-((2-Formyl-1H-benzo[d]imidazol-1-yl)methyl)benzotrile(5c)

Compound **2c** was used as reactant to give **5c**. While solid. Yield: 52%. ¹H NMR (400 MHz,

CDCl₃) δ 10.12 (s, 1H), 7.99 (d, J = 8.0 Hz, 1H), 7.60 (d, J = 8.1 Hz, 2H), 7.51 – 7.42 (m, 2H), 7.40 (d, J = 7.9 Hz, 1H), 7.24 (d, J = 8.0 Hz, 2H), 5.90 (s, 2H).

1-(4-Nitrobenzyl)-1H-benzod[imidazole]-2-carbaldehyde (5d)

Compound **2d** was used as reactant to give **5d**. While solid. Yield: 47%. ¹H NMR (400 MHz, CDCl₃) δ 10.13 (s, 1H), 8.16 (d, J = 8.4 Hz, 2H), 8.00 (d, J = 7.9 Hz, 1H), 7.52 – 7.39 (m, 3H), 7.30 (d, J = 8.3 Hz, 2H), 5.95 (s, 2H).

1-(4-Fluorobenzyl)-1H-benzod[imidazole]-2-carbaldehyde (5e)

Compound **2e** was used as reactant to give **5e**. While solid. While solid. Yield: 57%. ¹H NMR (400 MHz, CDCl₃) δ 10.14 (s, 1H), 7.96 (d, J = 8.0 Hz, 1H), 7.50 – 7.38 (m, 3H), 7.21 – 7.13 (m, 2H), 6.98 (t, J = 8.5 Hz, 2H), 5.82 (s, 2H).

1-Benzyl-1H-benzod[imidazole]-2-carbaldehyde (5f)

Compound **2f** was used as reactant to give **5f**. While solid. Yield: 64%. ¹H NMR (400 MHz, CDCl₃) δ 10.15 (s, 1H), 7.96 (d, J = 7.9 Hz, 1H), 7.48 – 7.38 (m, 3H), 7.30 – 7.25 (m, 3H), 7.17 (d, J = 7.1 Hz, 2H), 5.87 (s, 2H).

1-(4-Methylbenzyl)-1H-benzod[imidazole]-2-carbaldehyde (5g)

Compound **2g** was used as reactant to give **5g**. While solid. Yield: 58%. ¹H NMR (400 MHz, CDCl₃) δ 10.15 (s, 1H), 7.95 (d, J = 7.9 Hz, 1H), 7.49 – 7.37 (m, 3H), 7.12 – 7.05 (m, 4H), 5.82 (s, 2H), 2.29 (s, 3H).

1-(4-Chlorobenzyl)-1H-benzod[imidazole]-2-carbaldehyde (5h)

Compound **2h** was used as reactant to give **5h**. While solid. Yield: 64%. ¹H NMR (400 MHz, CDCl₃) δ 10.14 (s, 1H), 7.96 (d, J = 7.8 Hz, 1H), 7.49 – 7.39 (m, 3H), 7.27 (d, J = 5.9 Hz, 2H), 7.11 (d, J = 8.0 Hz, 2H), 5.82 (s, 2H).

1-(4-(Trifluoromethyl)benzyl)-1H-benzod[imidazole]-2-carbaldehyde (5i)

Compound **2i** was used as reactant to give **5i**. While solid. Yield: 55%. ¹H NMR (400 MHz, CDCl₃) δ 10.14 (s, 1H), 7.98 (d, *J* = 8.0 Hz, 1H), 7.56 (d, *J* = 8.0 Hz, 2H), 7.48 – 7.44 (m, 3H), 7.26 (s, 2H), 5.92 (s, 2H).

1-(2-Fluorobenzyl)-1H-benzod[imidazole]-2-carbaldehyde (5j)

Compound **2j** was used as reactant to give **5j**. While solid. Yield: 49%. ¹H NMR (400 MHz, CDCl₃) δ 10.17 (s, 1H), 7.95 (d, *J* = 7.9 Hz, 1H), 7.50 – 7.38 (m, 3H), 7.25 (d, *J* = 10.5 Hz, 1H), 7.09 (t, *J* = 9.2 Hz, 1H), 7.01 (t, *J* = 7.5 Hz, 1H), 6.91 (t, *J* = 7.5 Hz, 1H), 5.94 (s, 2H).

1-(2,4-Difluorobenzyl)-1H-benzod[imidazole]-2-carbaldehyde (5k)

Compound **2k** was used as reactant to give **5k**. While solid. Yield: 67%. ¹H NMR (400 MHz, CDCl₃) δ 10.16 (s, 1H), 7.96 (d, *J* = 7.5 Hz, 1H), 7.51 – 7.39 (m, 3H), 6.99 – 6.95 (m, 1H), 6.85 (t, *J* = 8.0 Hz, 1H), 6.76 (t, *J* = 7.1 Hz, 1H), 5.88 (s, 2H).

1-(3-Fluorobenzyl)-1H-benzod[imidazole]-2-carbaldehyde (5l)

Compound **2l** was used as reactant to give **5l**. While solid. Yield: 55%. ¹H NMR (400 MHz, CDCl₃) δ 10.16 (s, 1H), 7.98 (d, *J* = 7.5 Hz, 1H), 7.50 – 7.39 (m, 3H), 7.29 – 7.26 (m, 1H), 6.96 (t, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 9.4 Hz, 1H), 5.85 (s, 2H).

1-(3,4-Difluorobenzyl)-1H-benzod[imidazole]-2-carbaldehyde (5m)

Compound **2m** was used as reactant to give **5m**. While solid. Yield: 46%. ¹H NMR (400 MHz, CDCl₃) δ 10.14 (s, 1H), 7.98 (d, *J* = 8.4 Hz, 1H), 7.51 – 7.41 (m, 3H), 7.13 – 7.05 (m, 1H), 7.03 – 6.97 (m, 1H), 6.93 (m, 1H), 5.80 (s, 2H).

1-(3,5-Dimethoxybenzyl)-1H-benzod[imidazole]-2-carbaldehyde (5n)

Compound **2n** was used as reactant to give **5n**. While solid. Yield: 49%. ¹H NMR (400 MHz, CDCl₃) δ 10.07 (s, 1H), 7.91 (d, *J* = 8.1 Hz, 1H), 7.75 (d, *J* = 8.3 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 1H), 7.40 (t, *J* = 7.6 Hz, 1H), 6.40 (s, 1H), 6.32 (s, 2H), 5.81 (s, 2H), 3.67 (s, 6H).

1-Ethyl-1H-benzo[d]imidazole-2-carbaldehyde (5o)

Compound **2o** was used as reactant to give **5o**. While solid. Yield: 42%. ¹H NMR (400 MHz, CDCl₃) δ 10.13 (s, 1H), 7.94 (d, *J* = 8.3 Hz, 1H), 7.55 – 7.45 (m, 2H), 7.46 – 7.34 (m, 1H), 4.67 (q, *J* = 7.2 Hz, 2H), 1.46 (t, *J* = 7.2 Hz, 3H).

1-(2-(4-Fluorophenyl)-2-oxoethyl)-1H-benzo[d]imidazole-2-carbaldehyde (5p)

Compound **2p** was used as reactant to give **5p**. While solid. Yield: 55%. ¹H NMR (400 MHz, CDCl₃) δ 10.09 (s, 1H), 8.14 – 8.06 (m, *J* = 7.0, 5.0, 2.4 Hz, 2H), 8.00 (d, *J* = 7.6 Hz, 1H), 7.50 – 7.40 (m, 2H), 7.32 (d, *J* = 7.9 Hz, 1H), 7.26 – 7.21 (m, 2H), 6.03 (s, 2H).

1-(2-(4-methoxyphenyl)-2-oxoethyl)-1H-benzo[d]imidazole-2-carbaldehyde (5q)

Compound **2q** was used as reactant to give **5q**. While solid. Yield: 59%. ¹H NMR (400 MHz, CDCl₃) δ 10.09 (s, 1H), 8.03 (d, *J* = 8.8 Hz, 2H), 7.98 (d, *J* = 7.8 Hz, 1H), 7.48 – 7.39 (m, 2H), 7.32 (d, *J* = 8.1 Hz, 1H), 7.03 (d, *J* = 8.8 Hz, 2H), 6.03 (s, 2H), 3.92 (s, 3H).

1-(2-(4-Chlorophenyl)-2-oxoethyl)-1H-benzo[d]imidazole-2-carbaldehyde (5r)

Compound **2r** was used as reactant to give **5r**. While solid. Yield: 63%. ¹H NMR (400 MHz, CDCl₃) δ 10.08 (s, 1H), 7.99 (d, *J* = 8.6 Hz, 3H), 7.54 (d, *J* = 8.5 Hz, 2H), 7.49 – 7.41 (m, 2H), 7.32 (d, *J* = 7.9 Hz, 1H), 6.02 (s, 2H).

1-(2-Oxo-2-(p-tolyl)ethyl)-1H-benzo[d]imidazole-2-carbaldehyde (5s)

Compound **2s** was used as reactant to give **5s**. While solid. Yield: 49%. ¹H NMR (400 MHz, CDCl₃) δ 10.10 (s, 1H), 7.99 – 7.95 (m, 3H), 7.50 – 7.38 (m, 3H), 7.38 – 7.30 (m, 3H), 6.05 (s, 2H), 2.47 (s, 3H).

5-Chloro-1-(4-methylbenzyl)-1H-benzo[d]imidazole-2-carbaldehyde (6a)

Compound **3a** was used as reactant to give **6a**. While solid. Yield: 57%. ¹H NMR (400 MHz, CDCl₃) δ 10.13 (s, 1H), 7.92 (s, 1H), 7.38 (s, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 7.04 (d, *J* = 8.1 Hz, 2H), 5.80 (s, 2H), 2.30 (s, 3H).

6-Chloro-1-(4-methylbenzyl)-1H-benzo[d]imidazole-2-carbaldehyde (6b)

Compound **3b** was used as reactant to give **6b**. While solid. Yield: 39%. ¹H NMR (400 MHz, CDCl₃) δ 10.12 (s, 1H), 7.86 (d, *J* = 8.8 Hz, 1H), 7.45 (d, *J* = 1.6 Hz, 1H), 7.39 – 7.31 (m, 1H), 7.11 (d, *J* = 8.0 Hz, 2H), 7.05 (d, *J* = 8.0 Hz, 2H), 5.77 (s, 2H), 2.31 (s, 3H).

5-Fluoro-1-(4-methylbenzyl)-1H-benzo[d]imidazole-2-carbaldehyde (6c)

Compound **3c** was used as reactant to give **6c**. While solid. Yield: 45%. ¹H NMR (400 MHz, CDCl₃) δ 10.13 (s, 1H), 7.61 – 7.67 (m, 1H), 7.41 – 7.35 (m, 1H), 7.26 – 7.18 (m, 1H), 7.10 (d, *J* = 8.0 Hz, 2H), 7.05 (d, *J* = 8.1 Hz, 2H), 5.81 (s, 2H), 2.30 (s, 3H).

6-Fluoro-1-(4-methylbenzyl)-1H-benzo[d]imidazole-2-carbaldehyde (6d)

Compound **3d** was used as reactant to give **6d**. While solid. Yield: 36%. ¹H NMR (400 MHz, CDCl₃) δ 10.09 (s, 1H), 7.91 – 7.87 (m, 1H), 7.17 – 7.09 (m, 4H), 7.06 (d, *J* = 8.1 Hz, 2H), 5.77 (s, 2H), 2.30 (s, 3H).

5-Methoxy-1-(4-methylbenzyl)-1H-benzo[d]imidazole-2-carbaldehyde (6e)

Compound **3e** was used as reactant to give **6e**. While solid. Yield: 61%. ¹H NMR (400 MHz, CDCl₃) δ 10.10 (s, 1H), 7.36 – 7.28 (m, 2H), 7.10 (d, *J* = 2.2 Hz, 1H), 7.09 – 7.04 (m, 4H),

5.79 (s, 2H), 3.88 (s, 3H), 2.29 (s, 3H).

6-Methoxy-1-(4-methylbenzyl)-1H-benzod[*h*]imidazole-2-carbaldehyde (6f)

Compound **3f** was used as reactant to give **6f**. While solid. Yield: 63%. ¹H NMR (400 MHz, CDCl₃) δ 10.05 (s, 1H), 7.81 (d, *J* = 9.0 Hz, 1H), 7.10 (d, *J* = 8.2 Hz, 2H), 7.08 – 7.01 (m, 3H), 6.77 (d, *J* = 2.3 Hz, 1H), 5.78 (s, 2H), 3.84 (s, 3H), 2.30 (s, 3H).

5-Chloro-1-(2-fluorobenzyl)-1H-benzod[*h*]imidazole-2-carbaldehyde (7a)

Compound **4a** was used as reactant to give **7a**. While solid. Yield: 53%. ¹H NMR (400 MHz, CDCl₃) δ 10.14 (s, 1H), 7.93 (d, *J* = 0.8 Hz, 1H), 7.44 – 7.37 (m, 2H), 7.36 – 7.28 (m, 1H), 7.12 – 7.06 (m, 1H), 7.06 – 7.00 (m, 1H), 6.98 – 6.90 (m, *J* = 7.6, 1.4 Hz, 1H), 5.92 (s, 2H).

6-Chloro-1-(2-fluorobenzyl)-1H-benzod[*h*]imidazole-2-carbaldehyde(7b)

Compound **4b** was used as reactant to give **7b**. While solid. Yield: 56%. ¹H NMR (400 MHz, CDCl₃) δ 10.13 (s, 1H), 7.86 (d, *J* = 8.8 Hz, 1H), 7.47 (d, *J* = 1.6 Hz, 1H), 7.40 – 7.32 (m, 1H), 7.32 – 7.27 (m, 1H), 7.14 – 7.08 (m, 1H), 7.04 (t, *J* = 7.5 Hz, 1H), 6.94 (t, *J* = 7.5 Hz, 1H), 5.89 (s, 2H).

5-Fluoro-1-(2-fluorobenzyl)-1H-benzod[*h*]imidazole-2-carbaldehyde (7c)

Compound **4c** was used as reactant to give **7c**. While solid. Yield: 62%. ¹H NMR (400 MHz, CDCl₃) δ 10.14 (s, 1H), 7.63 – 7.55 (m, 1H), 7.47 – 7.39 (m, 1H), 7.31 – 7.26 (m, 1H), 7.23 – 7.19 (m, 1H), 7.12 – 7.07 (m, 1H), 7.13 – 7.05 (m, 1H), 6.97 – 6.93 (m, 1H), 5.92 (s, 2H).

6-Fluoro-1-(2-fluorobenzyl)-1H-benzod[*h*]imidazole-2-carbaldehyde (7d)

Compound **4d** was used as reactant to give **7d**. While solid. Yield: 57%. ¹H NMR (400 MHz, CDCl₃) δ 10.11 (s, 1H), 7.92 – 7.88 (m, 1H), 7.32 – 7.26 (m, 1H), 7.17 – 7.09 (m, 3H), 7.06 – 7.02 (m, 1H), 7.02 – 6.94 (m, 1H), 5.89 (s, 2H).

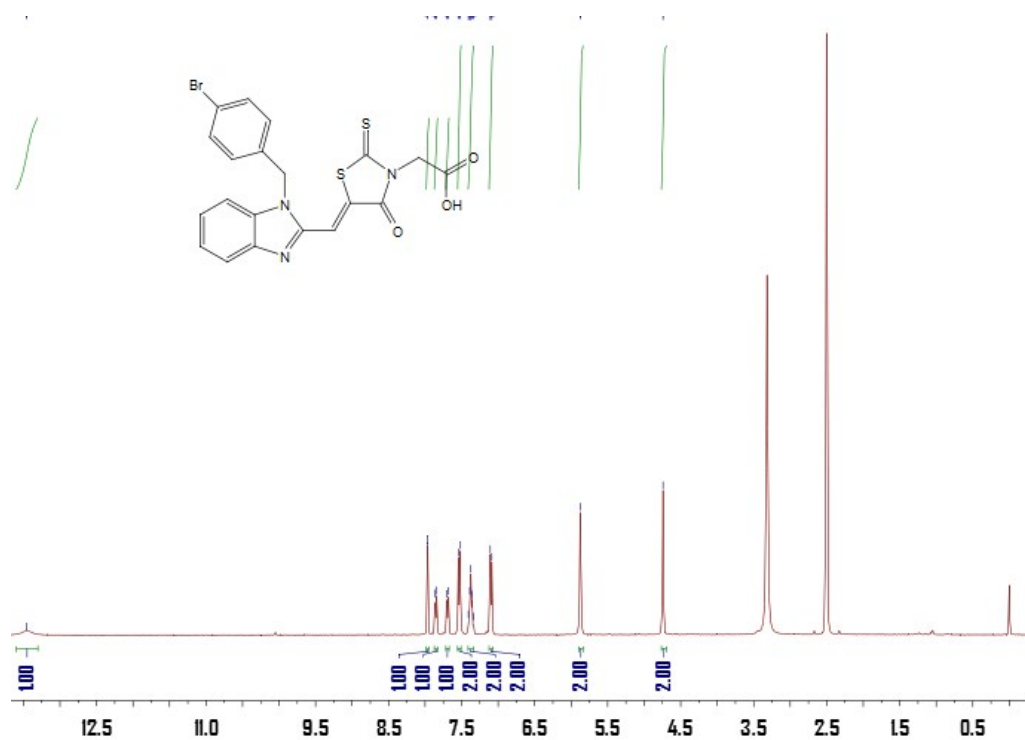
1-(2-Fluorobenzyl)-5-methoxy-1H-benzod[*h*]imidazole-2-carbaldehyde (7e)

Compound **4e** was used as reactant to give **7e**. While solid. Yield: 42%. ¹H NMR (400 MHz, CDCl₃) δ 10.11 (s, 1H), 7.35 (d, *J* = 9.1 Hz, 1H), 7.31 (d, *J* = 2.2 Hz, 1H), 7.26 – 7.22 (m, 1H), 7.13 – 7.05 (m, 2H), 7.01 (t, *J* = 7.5 Hz, 1H), 6.92 (t, *J* = 7.6 Hz, 1H), 5.91 (s, 2H), 3.88 (s, 3H).

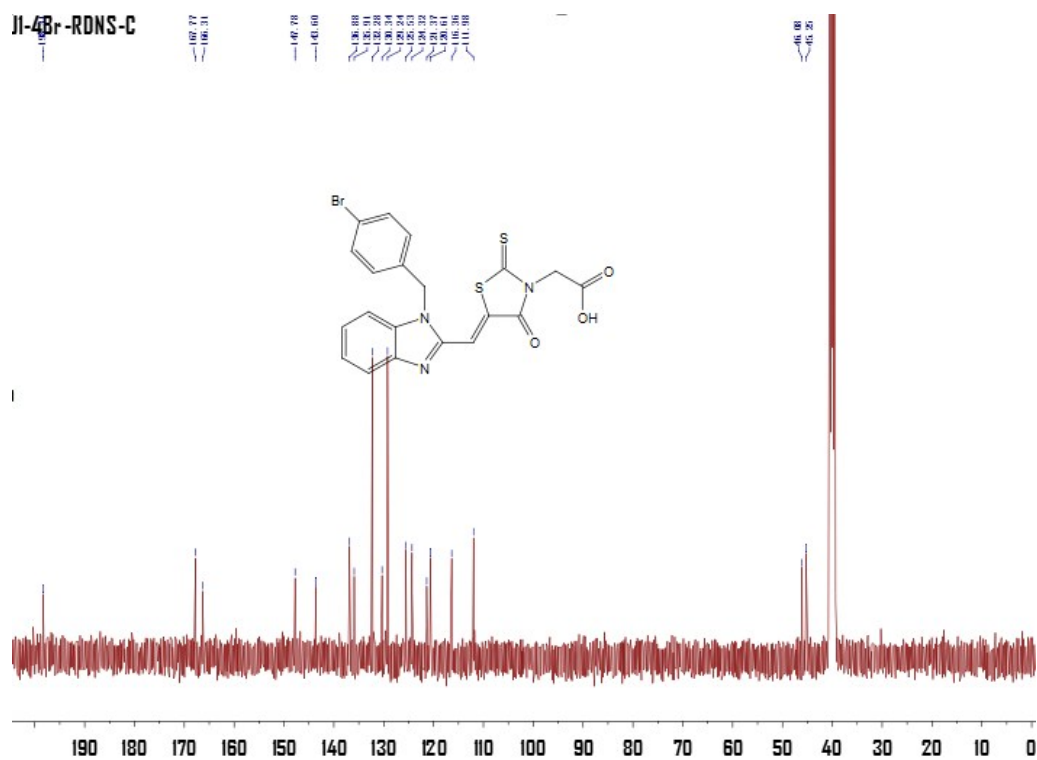
1-(2-Fluorobenzyl)-6-methoxy-1H-benzof[*d*]imidazole-2-carbaldehyde (7f)

Compound **4f** was used as reactant to give **7f**. While solid. Yield: 45%. ¹H NMR (400 MHz, CDCl₃) δ 10.07 (s, 1H), 7.81 (d, *J* = 9.0 Hz, 1H), 7.30 – 7.26 (m, 1H), 7.13 – 7.07 (m, 1H), 7.06 – 7.00 (m, 2H), 6.98 – 6.94 (m, 1H), 6.82 (d, *J* = 2.3 Hz, 1H), 5.90 (s, 2H), 3.85 (s, 3H).

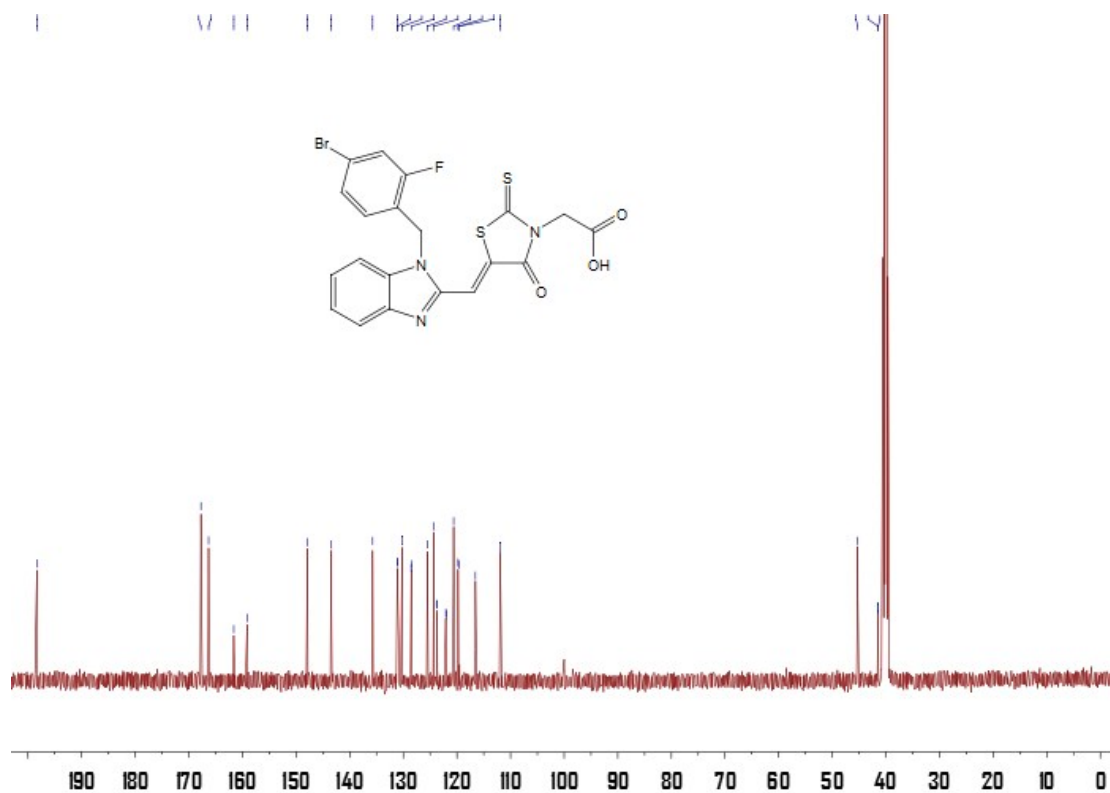
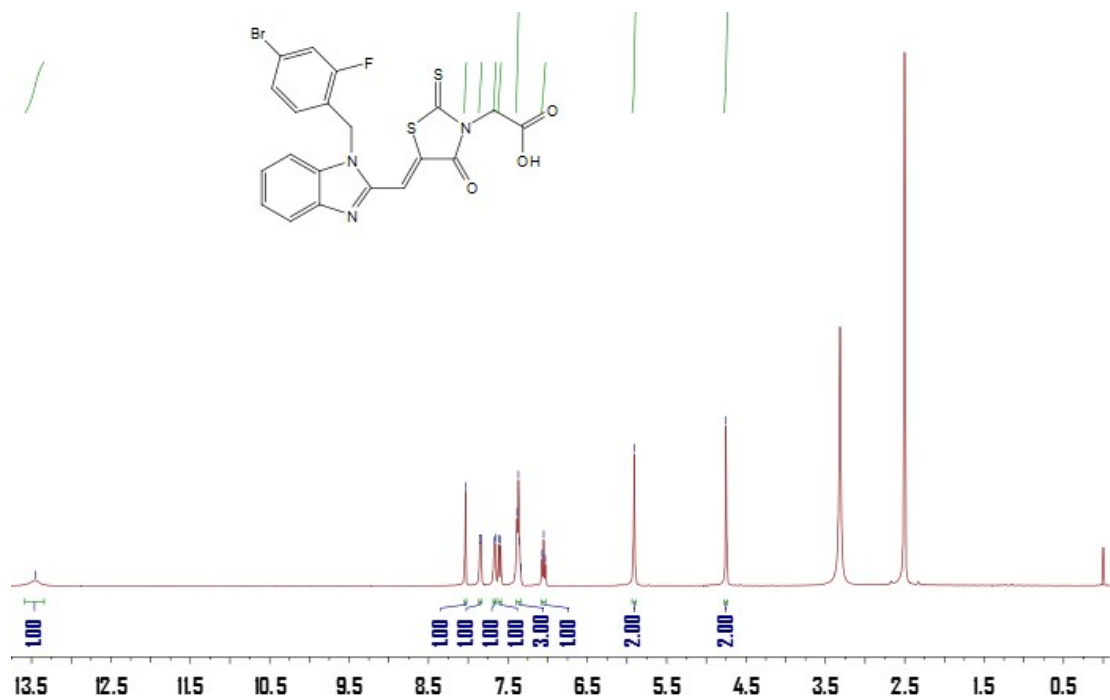
^1H NMR and ^{13}C NMR Spectrum of Target Compounds

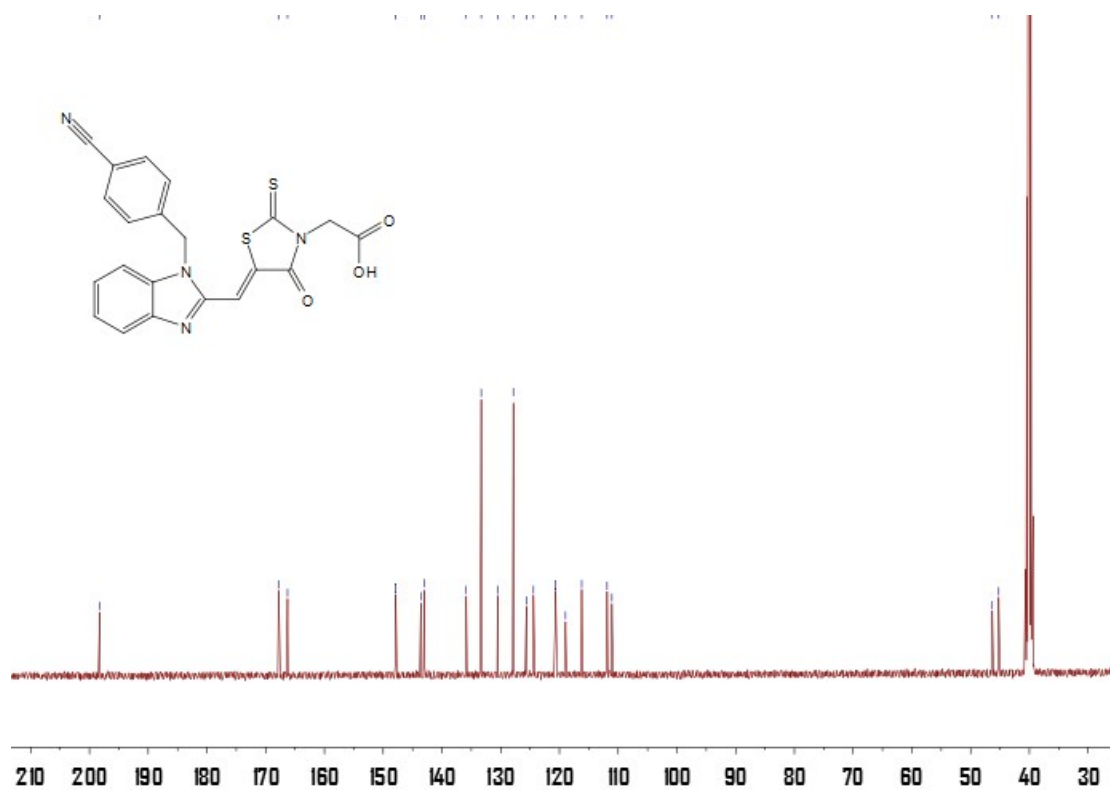
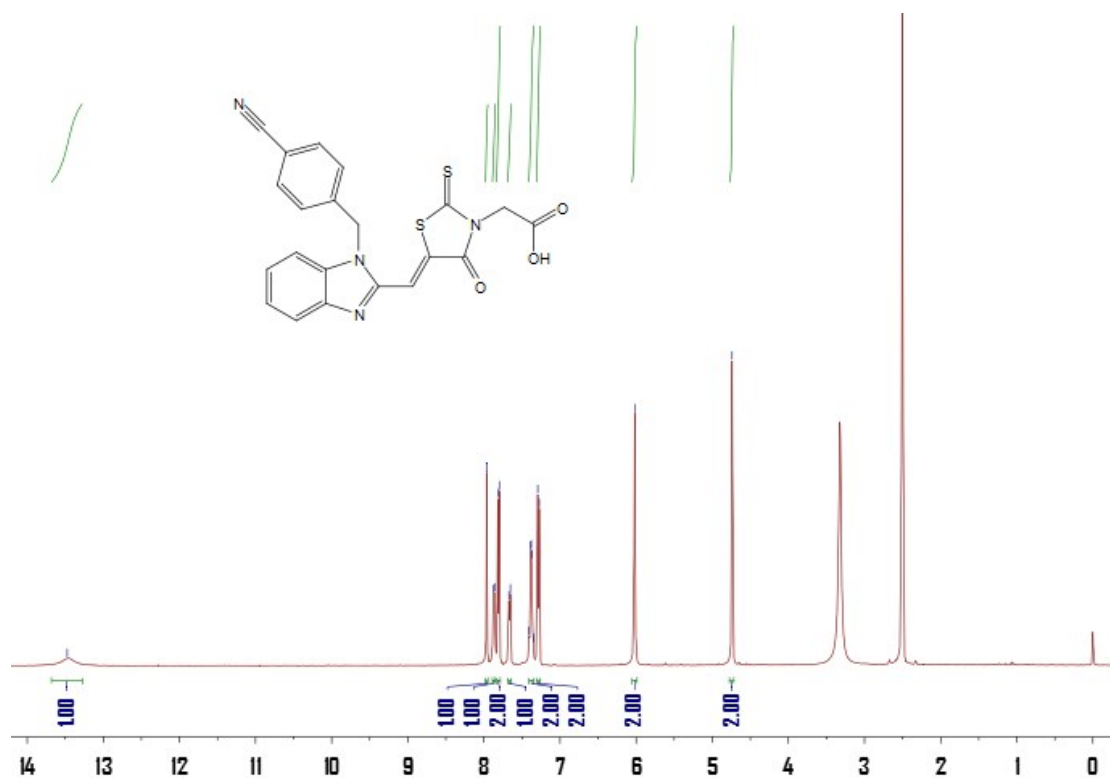


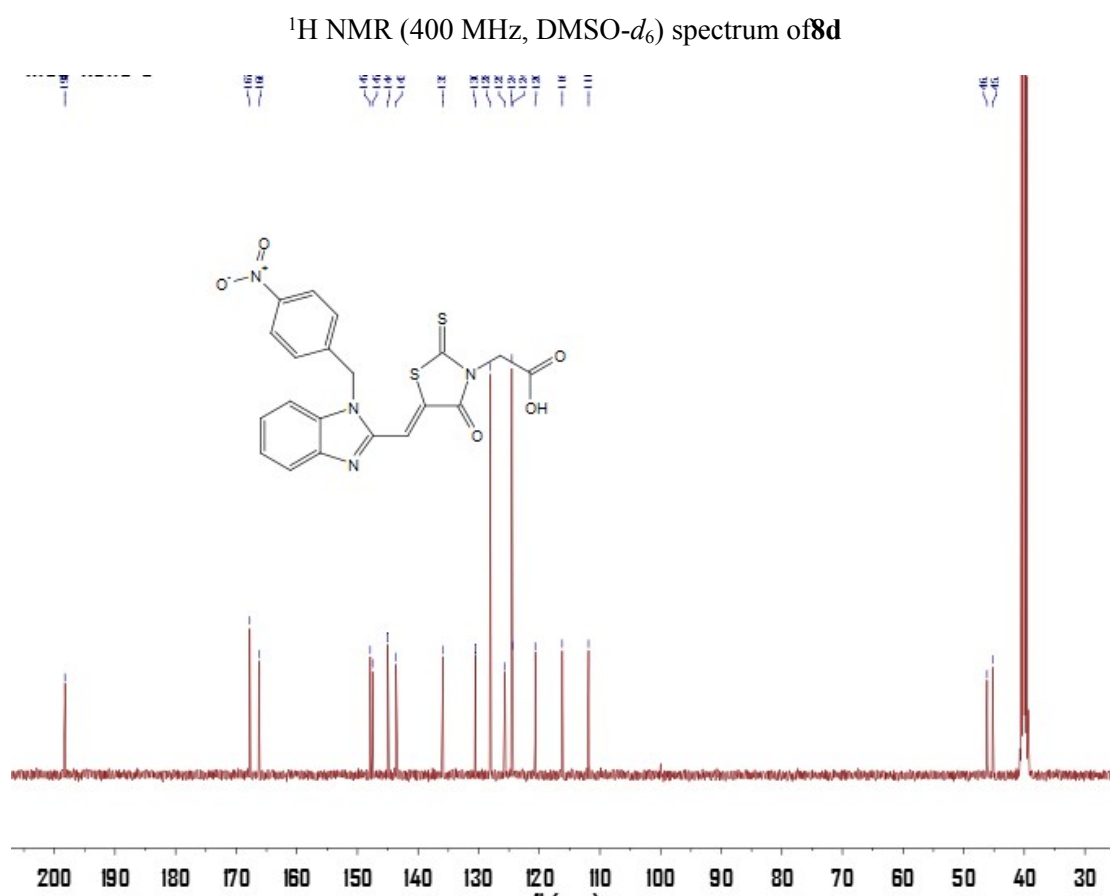
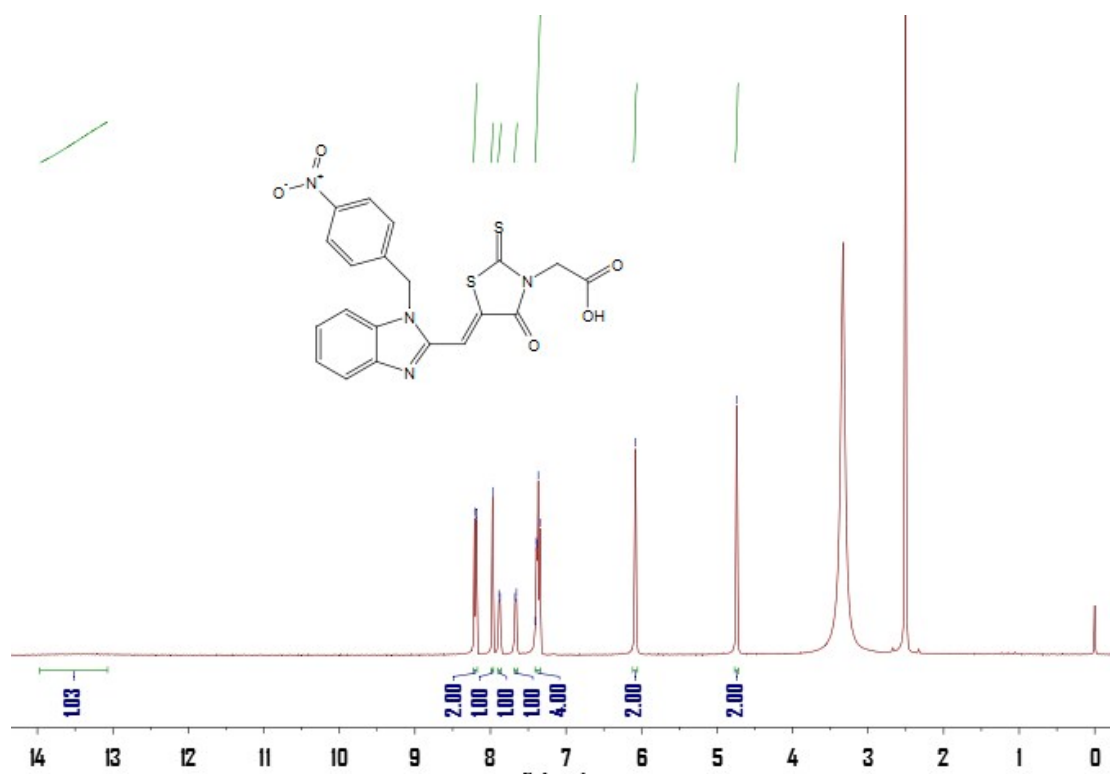
^1H NMR (400 MHz, $\text{DMSO-}d_6$) spectrum of **8a**

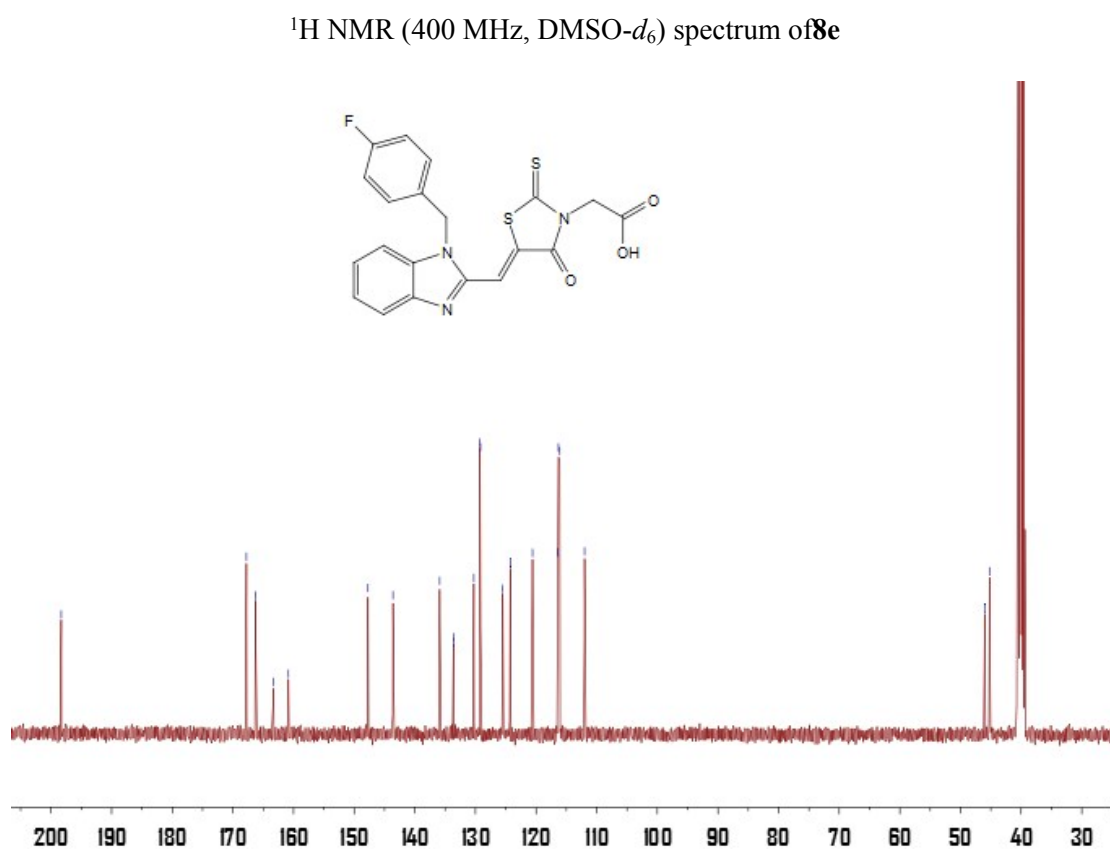
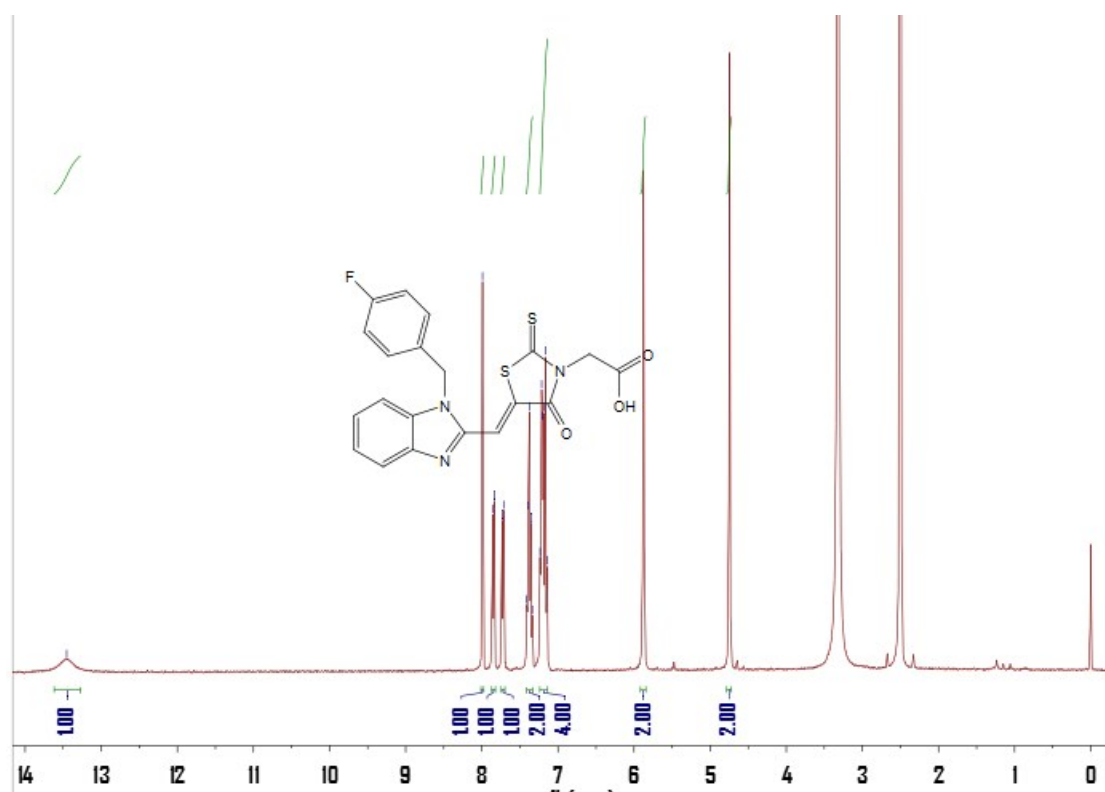


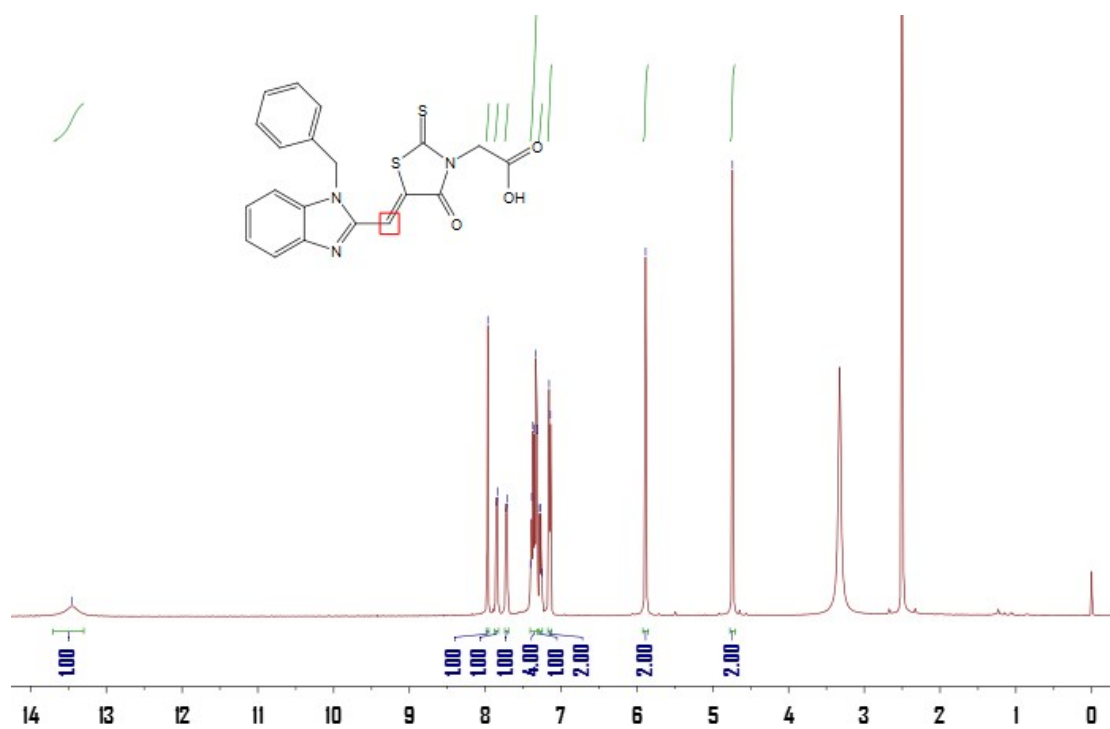
^{13}C NMR (400 MHz, $\text{DMSO-}d_6$) spectrum of **8a**



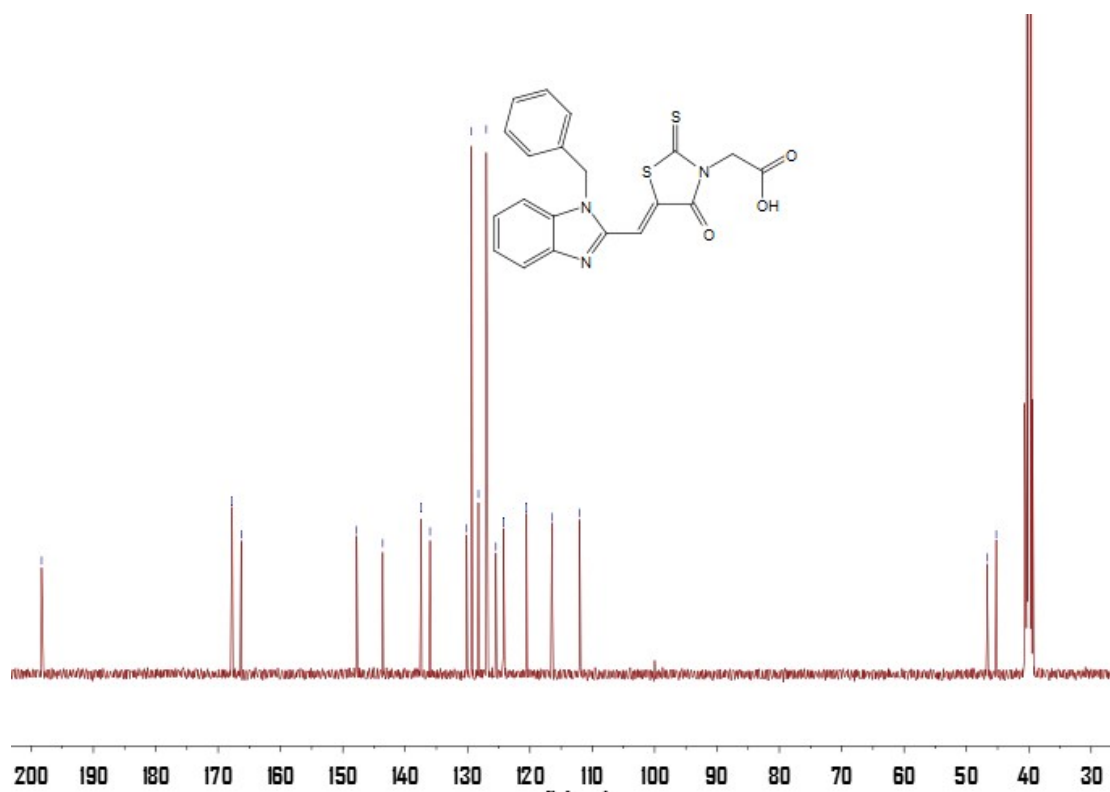




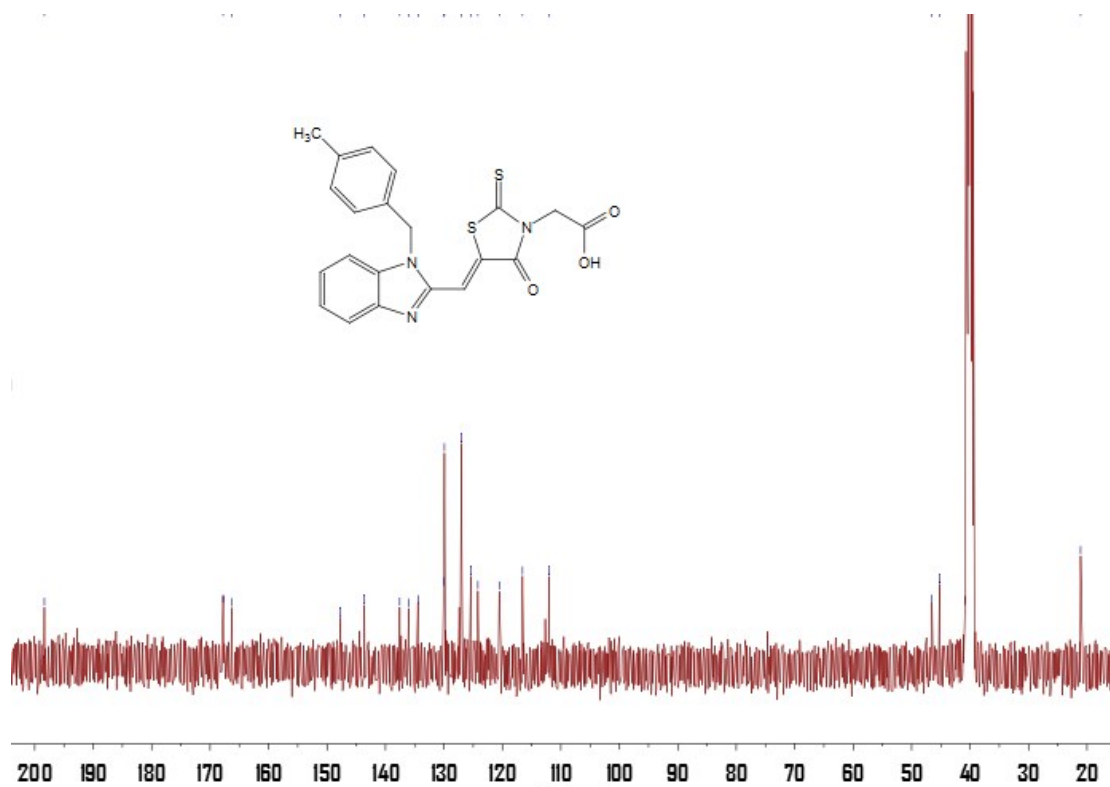
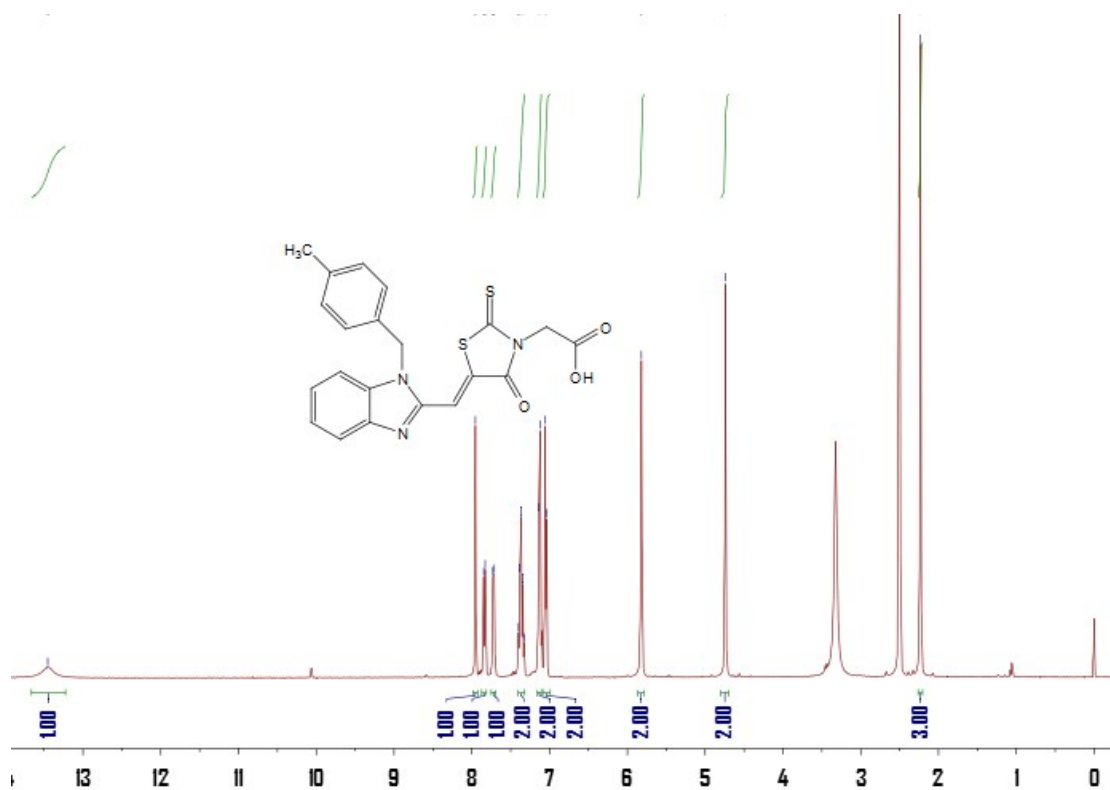


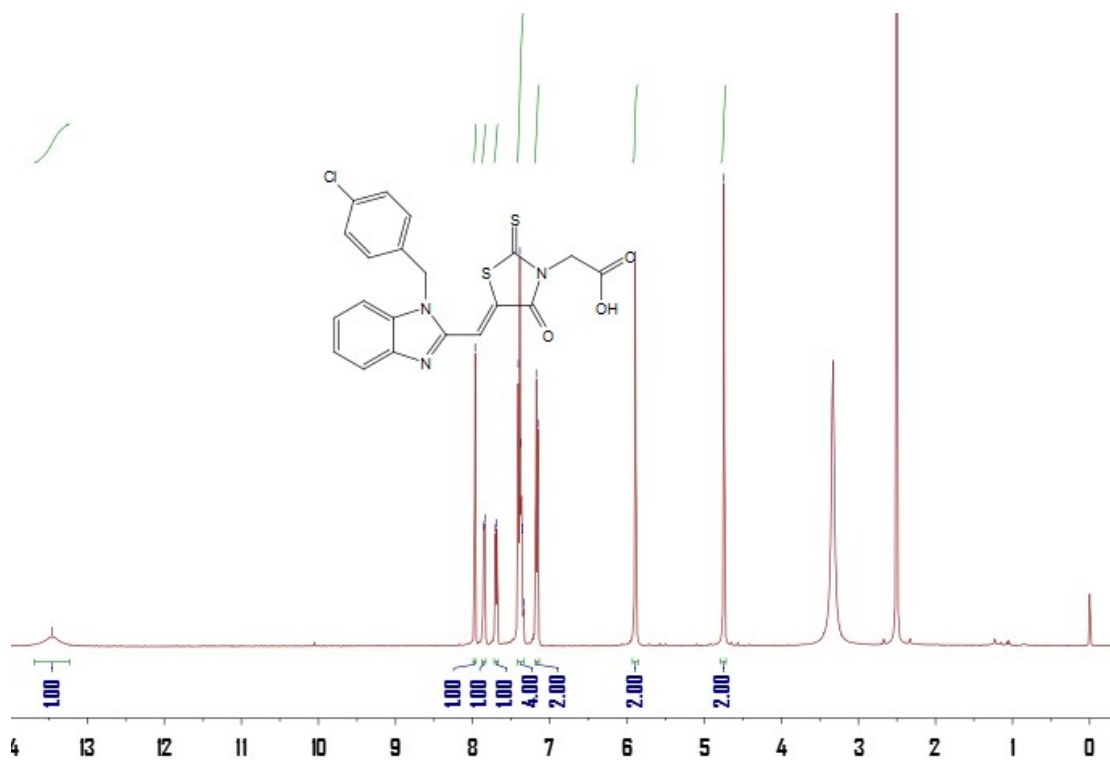


$^1\text{H NMR}$ (400 MHz, $\text{DMSO-}d_6$) spectrum of **8f**

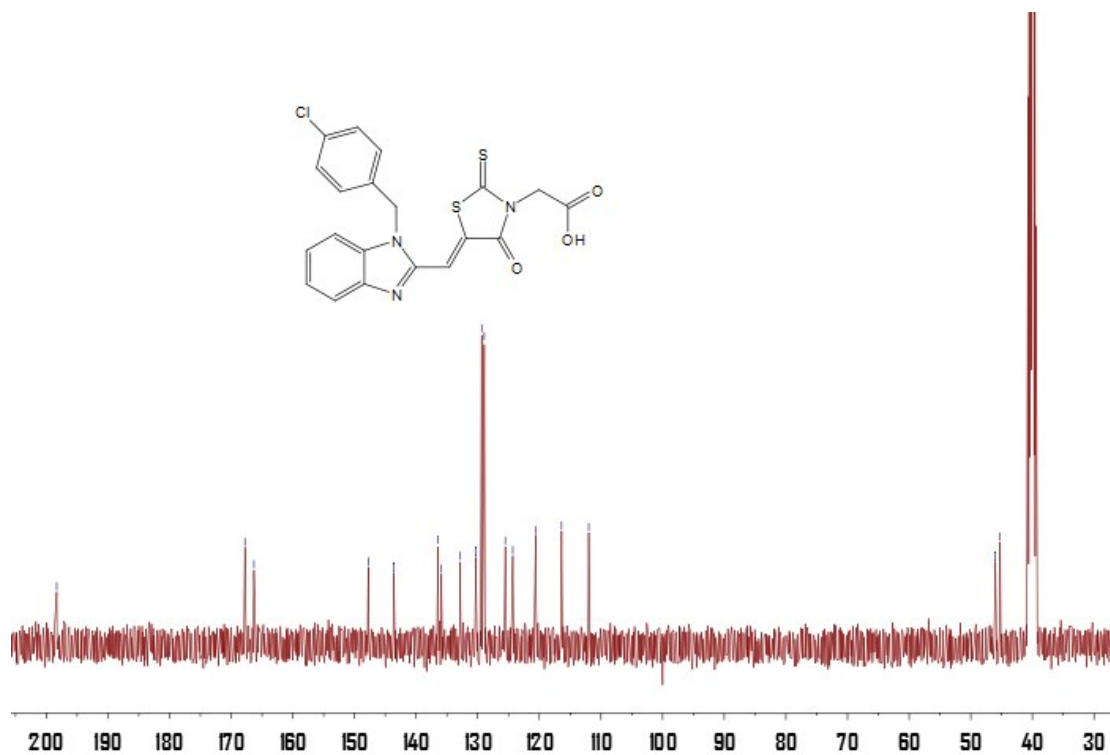


$^{13}\text{C NMR}$ (400 MHz, $\text{DMSO-}d_6$) spectrum of **8f**

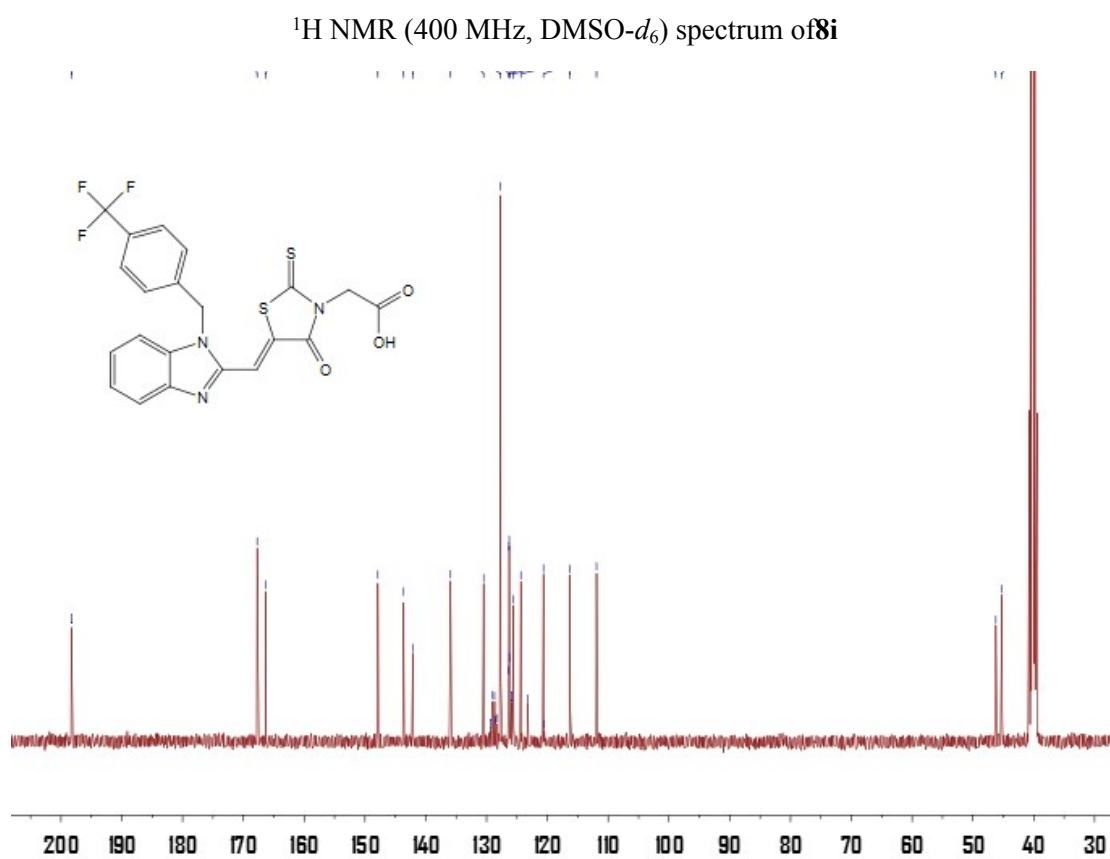
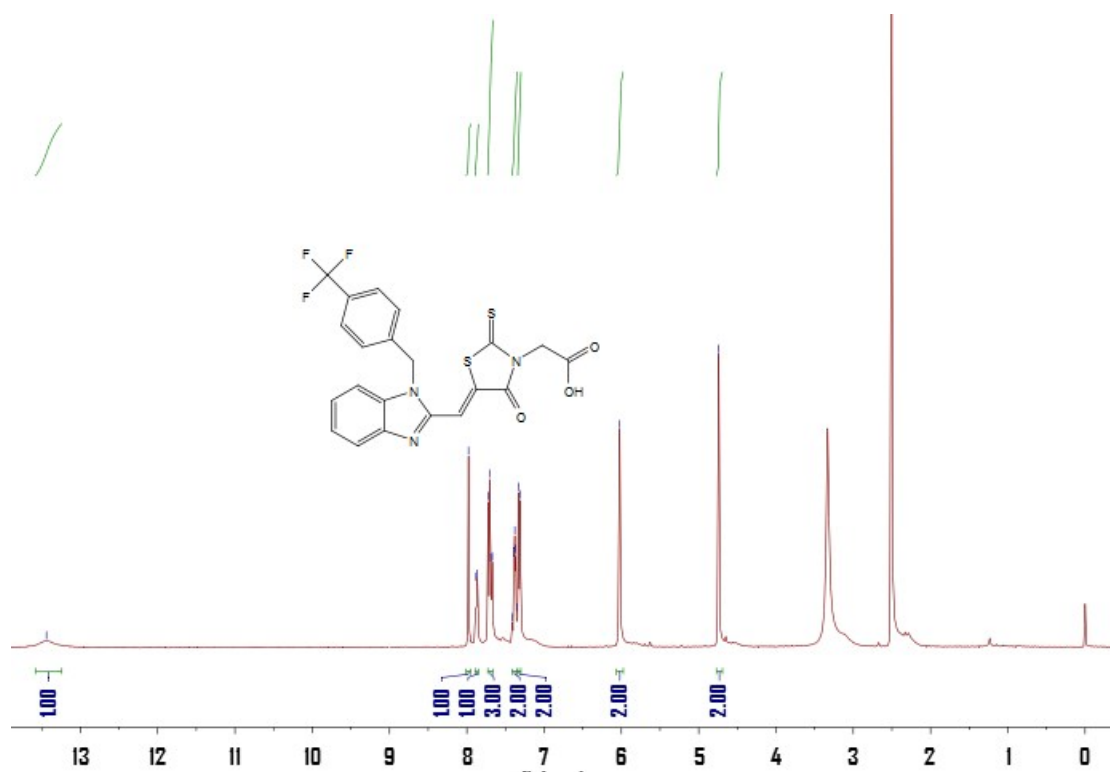


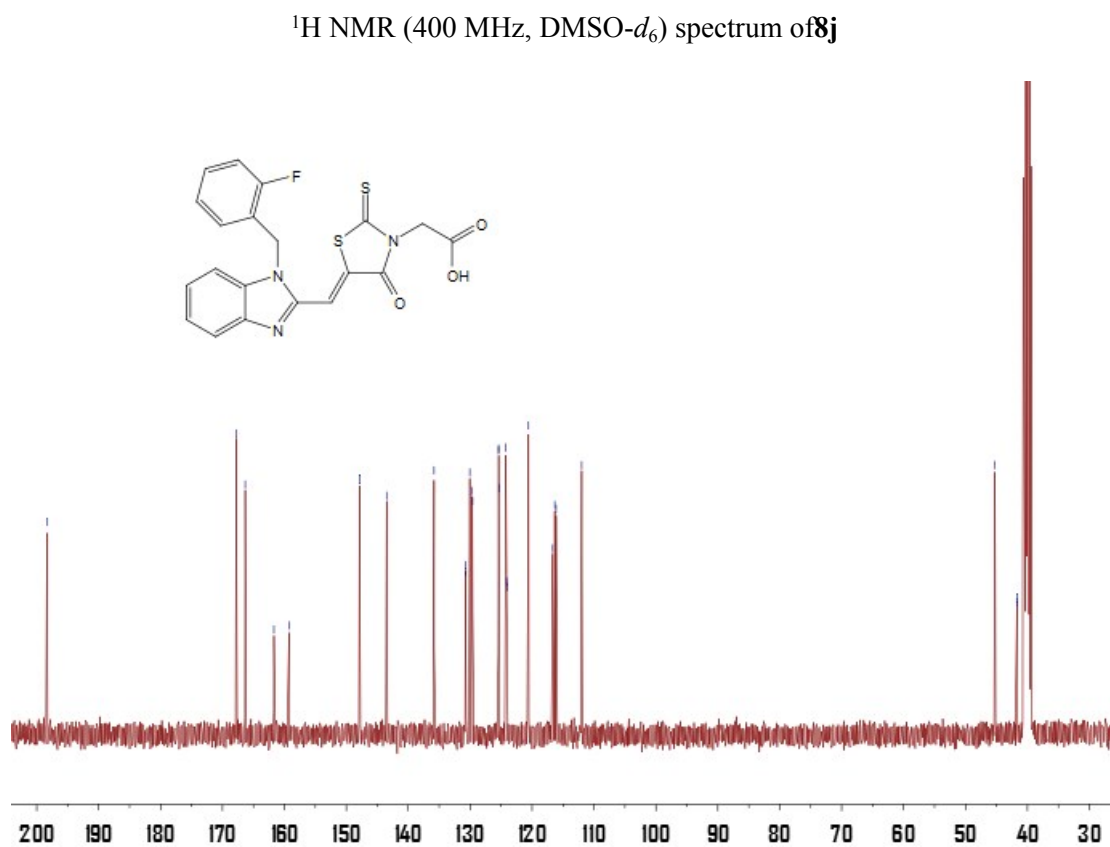
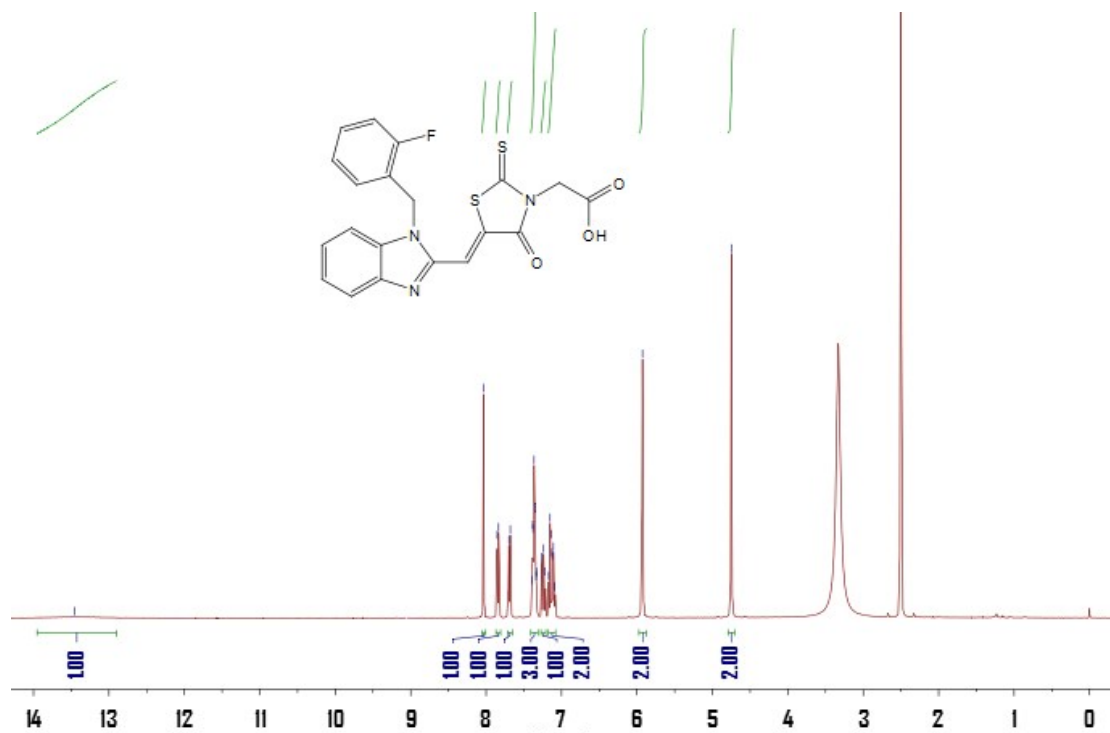


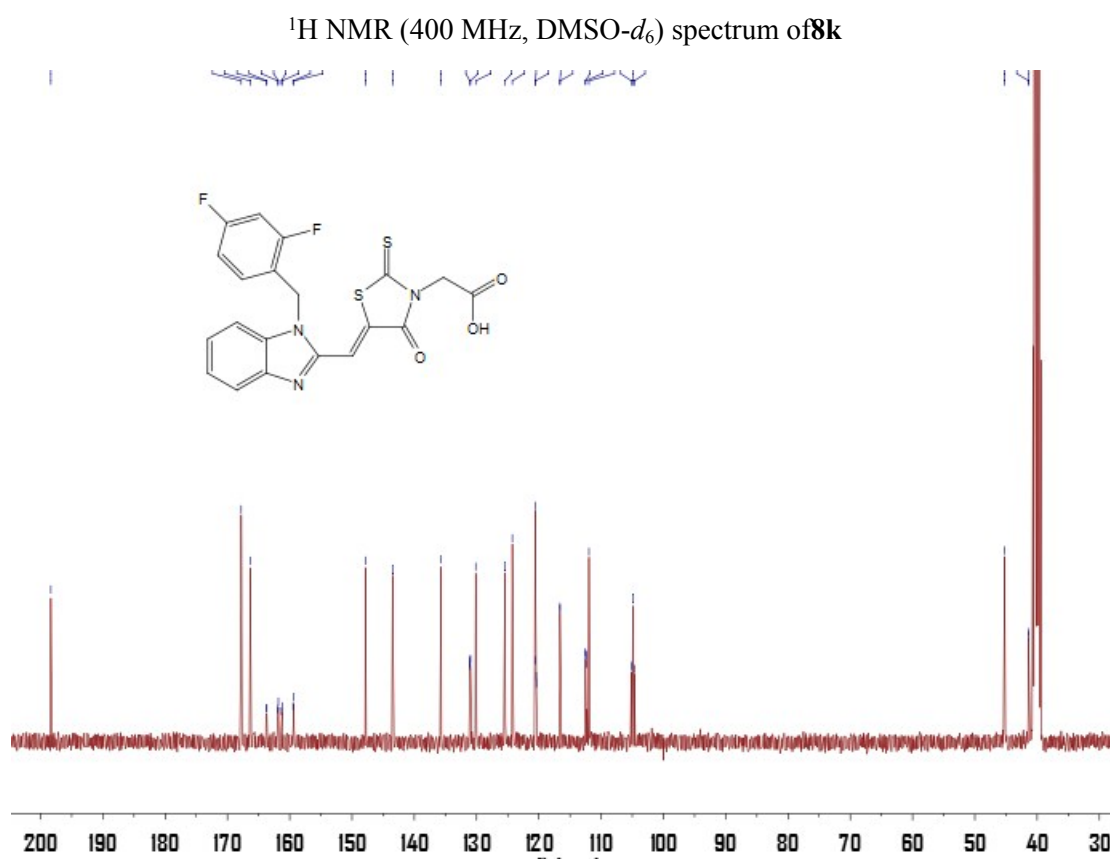
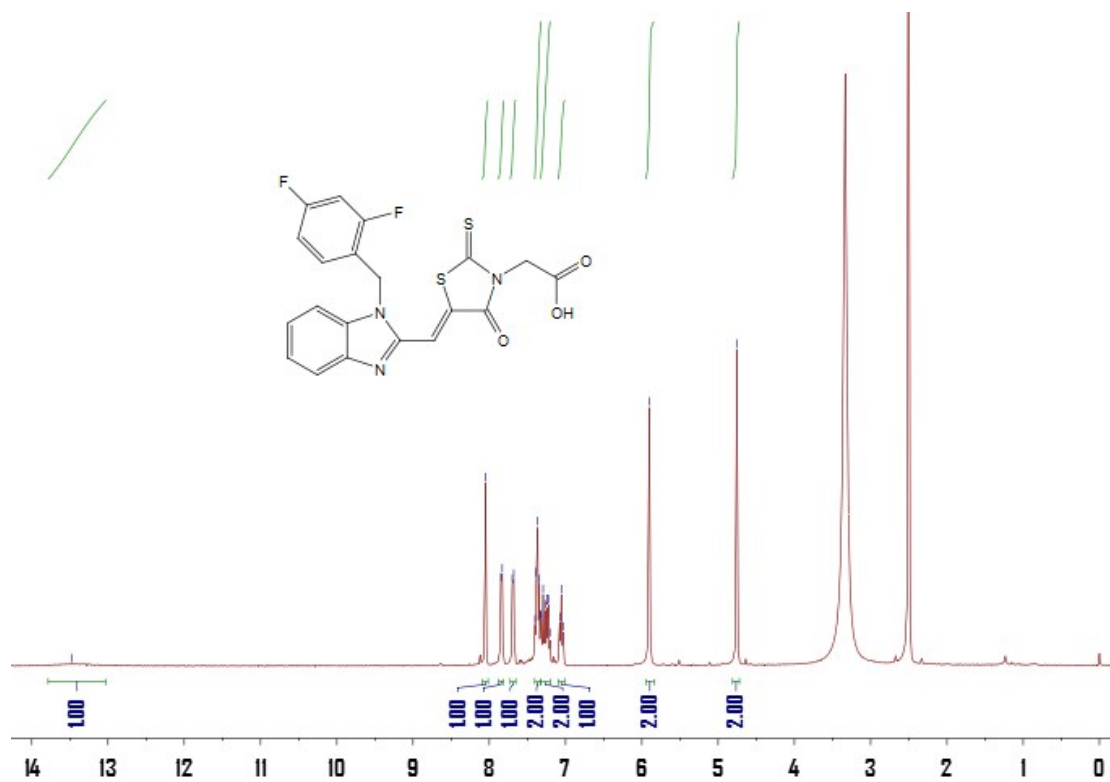
¹H NMR (400 MHz, DMSO-*d*₆) spectrum of **8h**

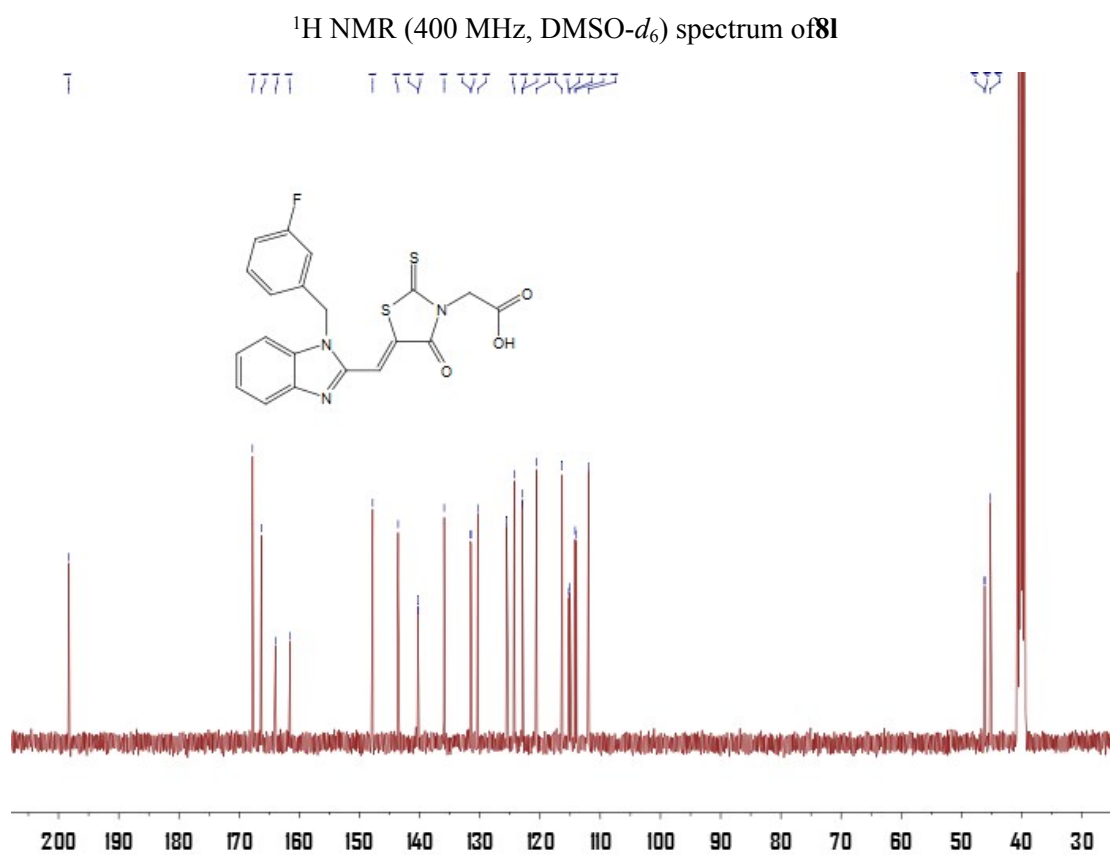
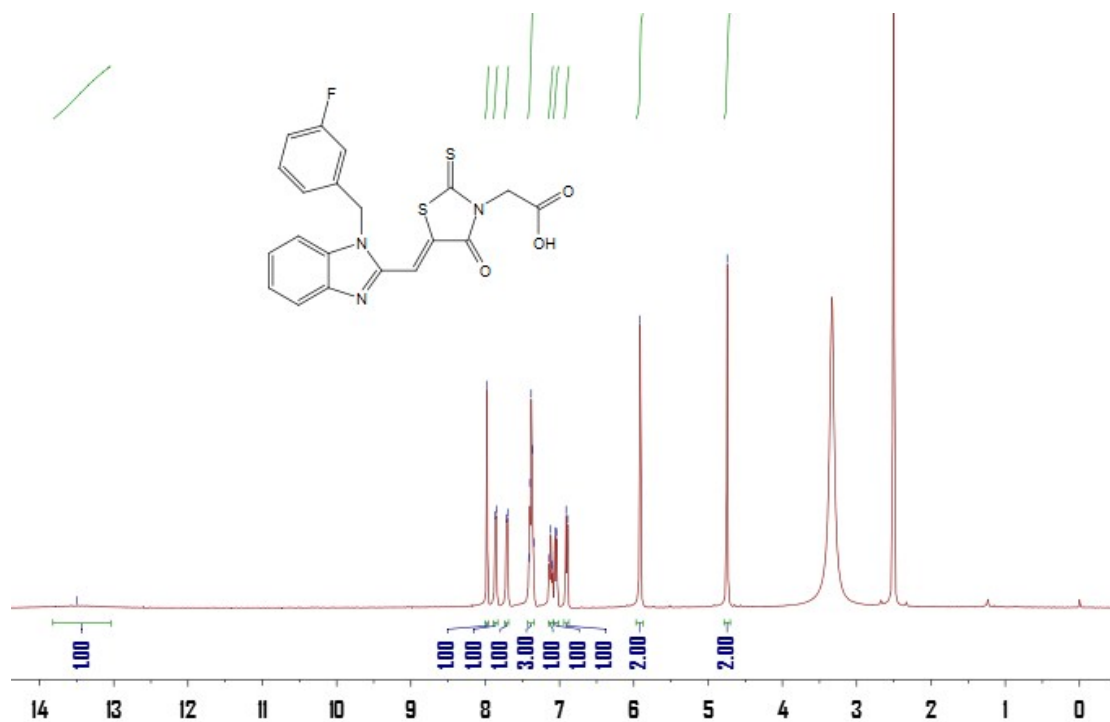


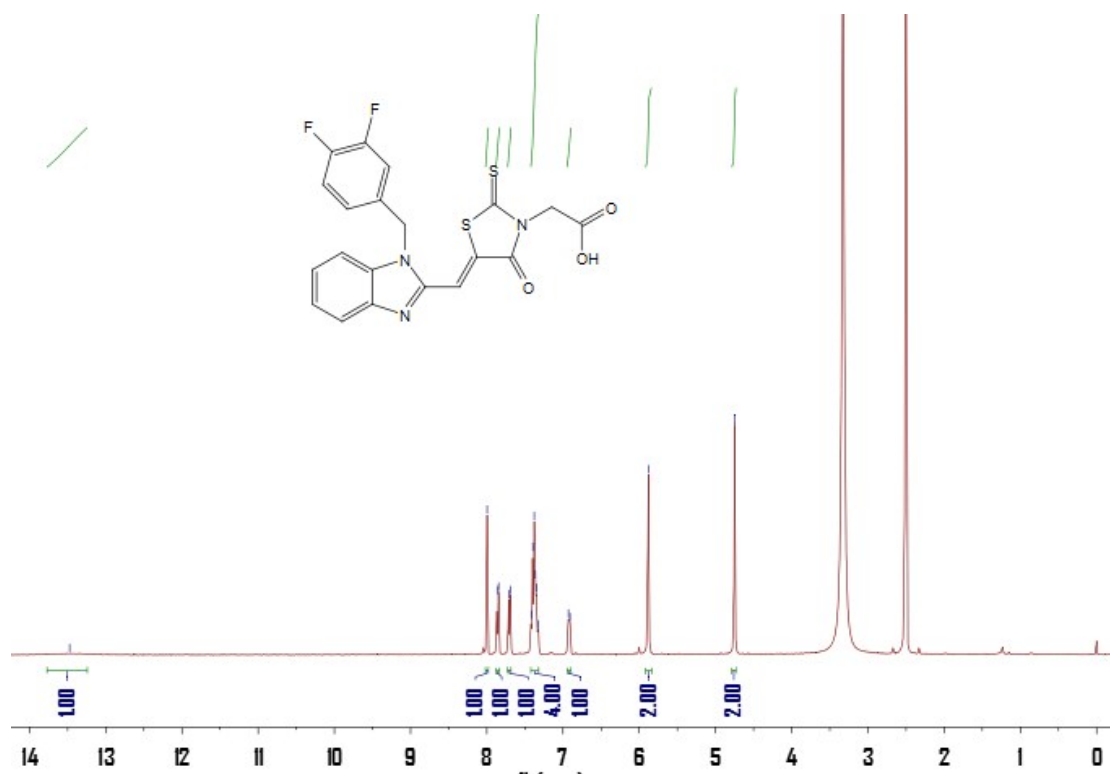
¹³C NMR (400 MHz, DMSO-*d*₆) spectrum of **8h**



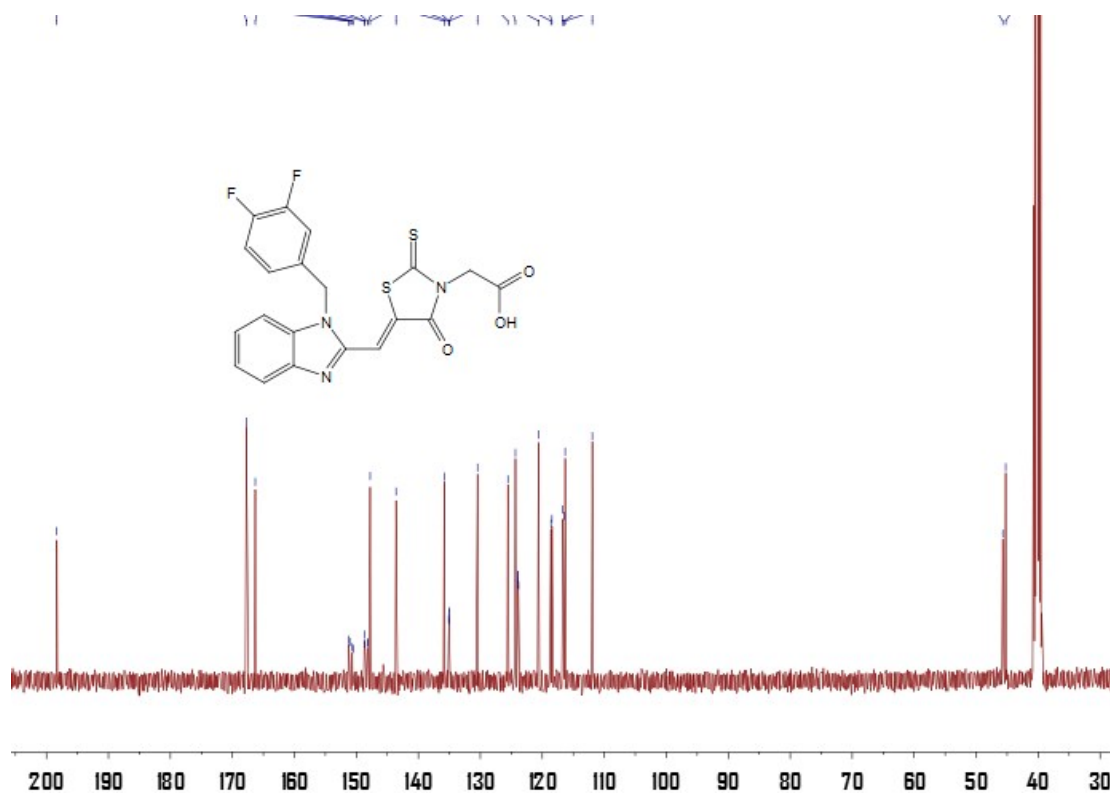




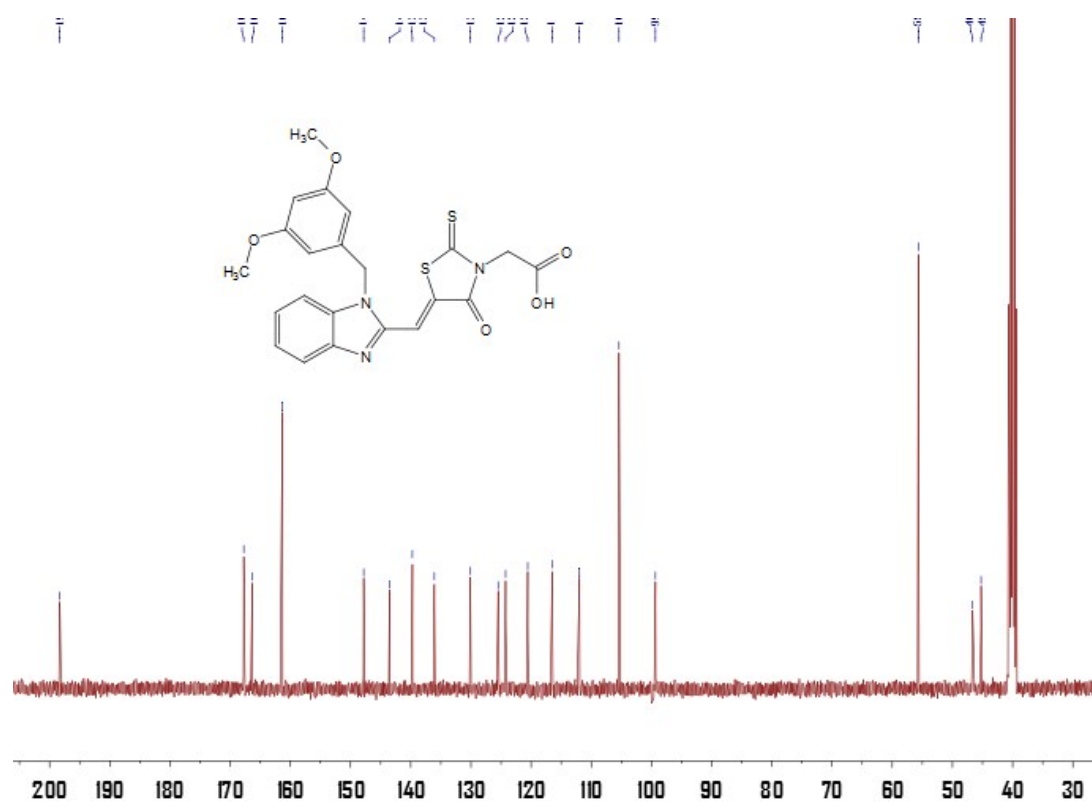
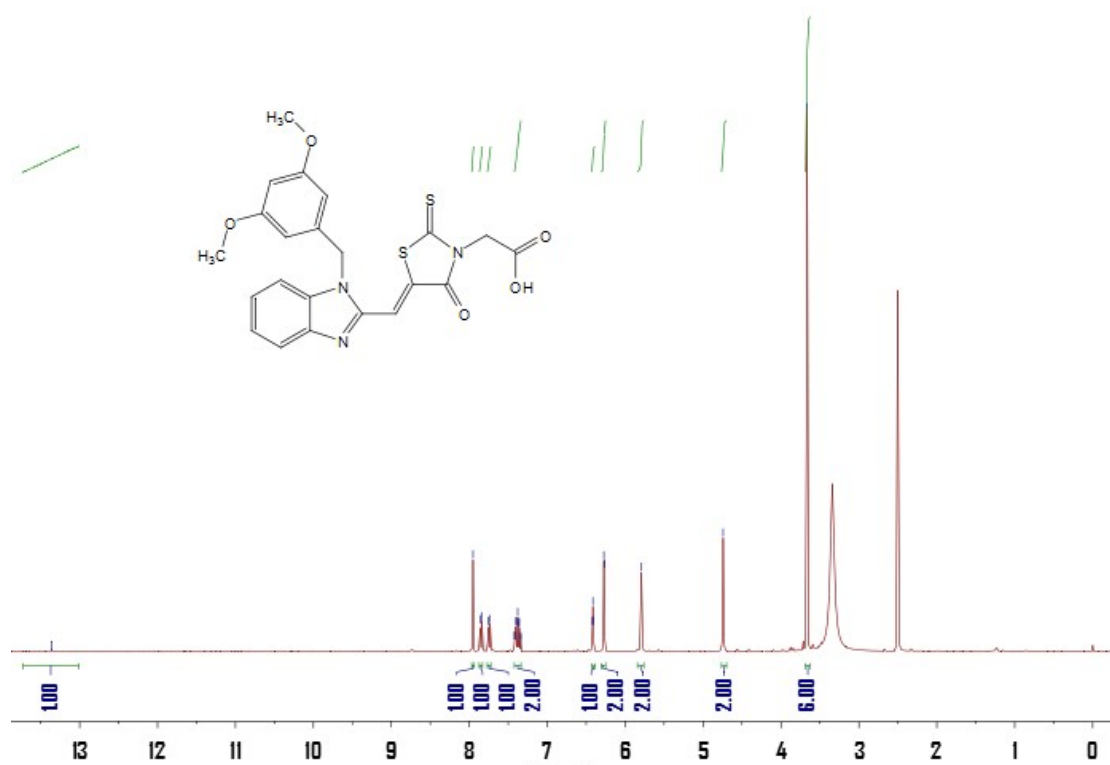


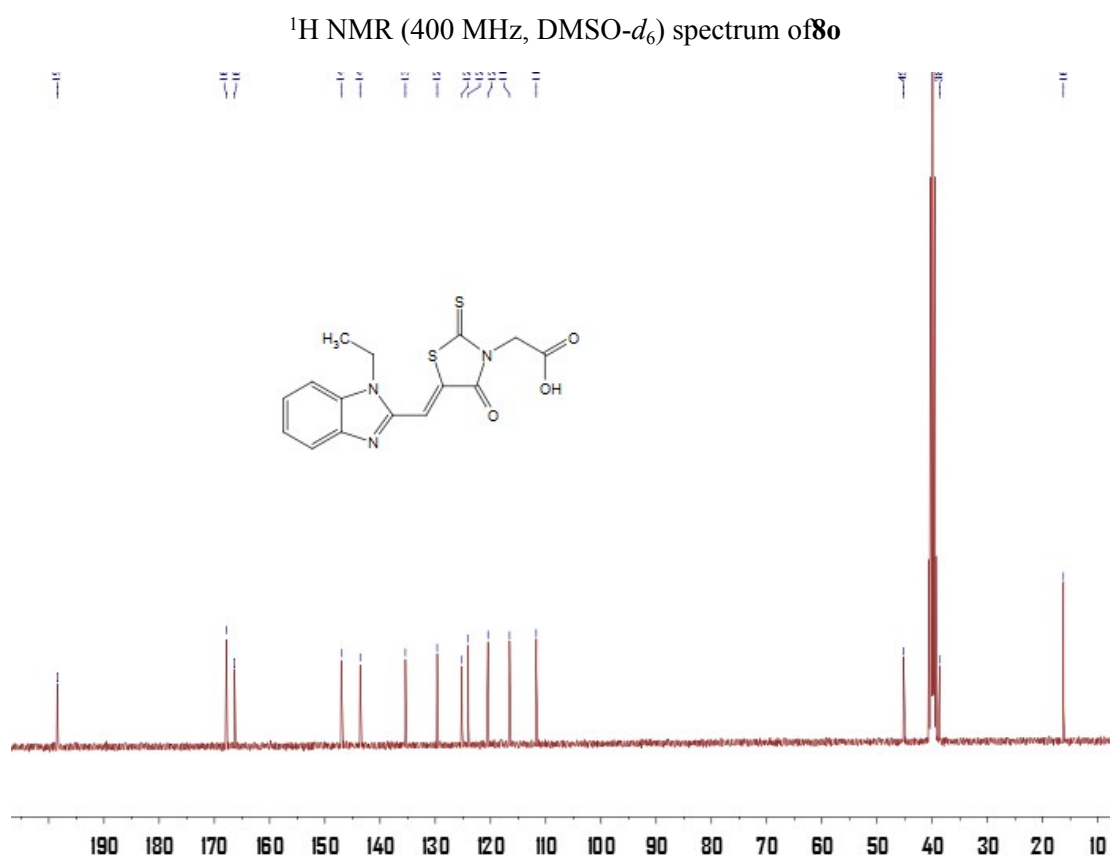
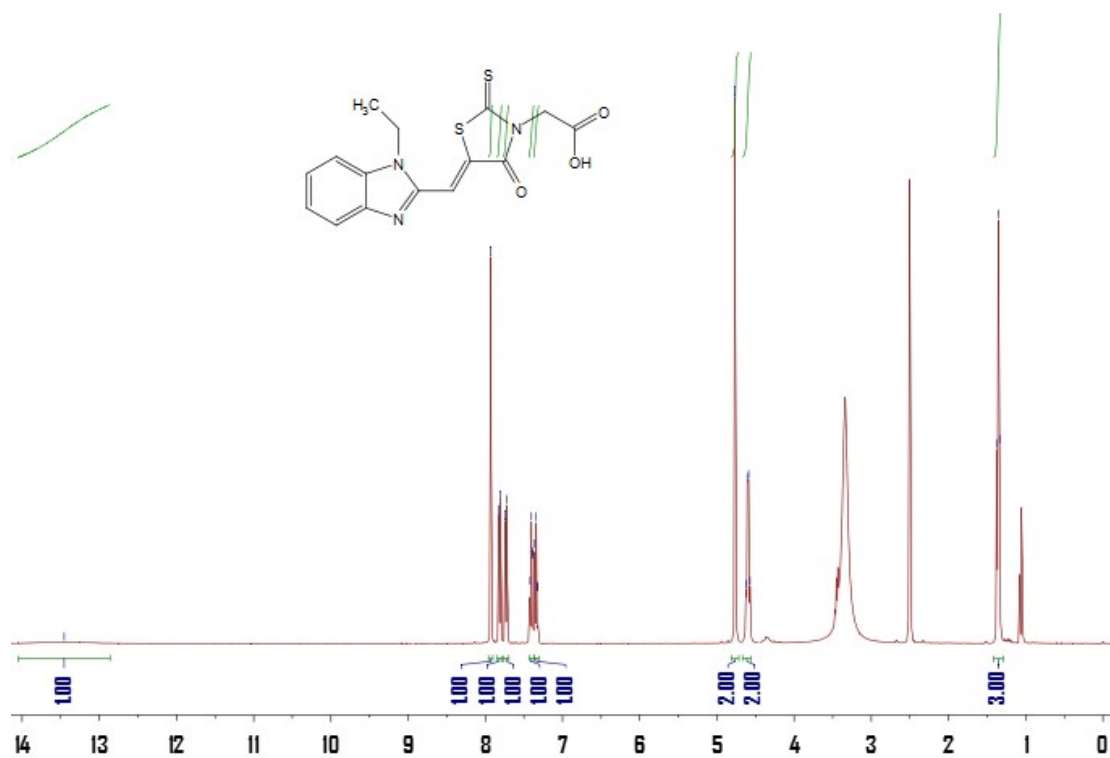


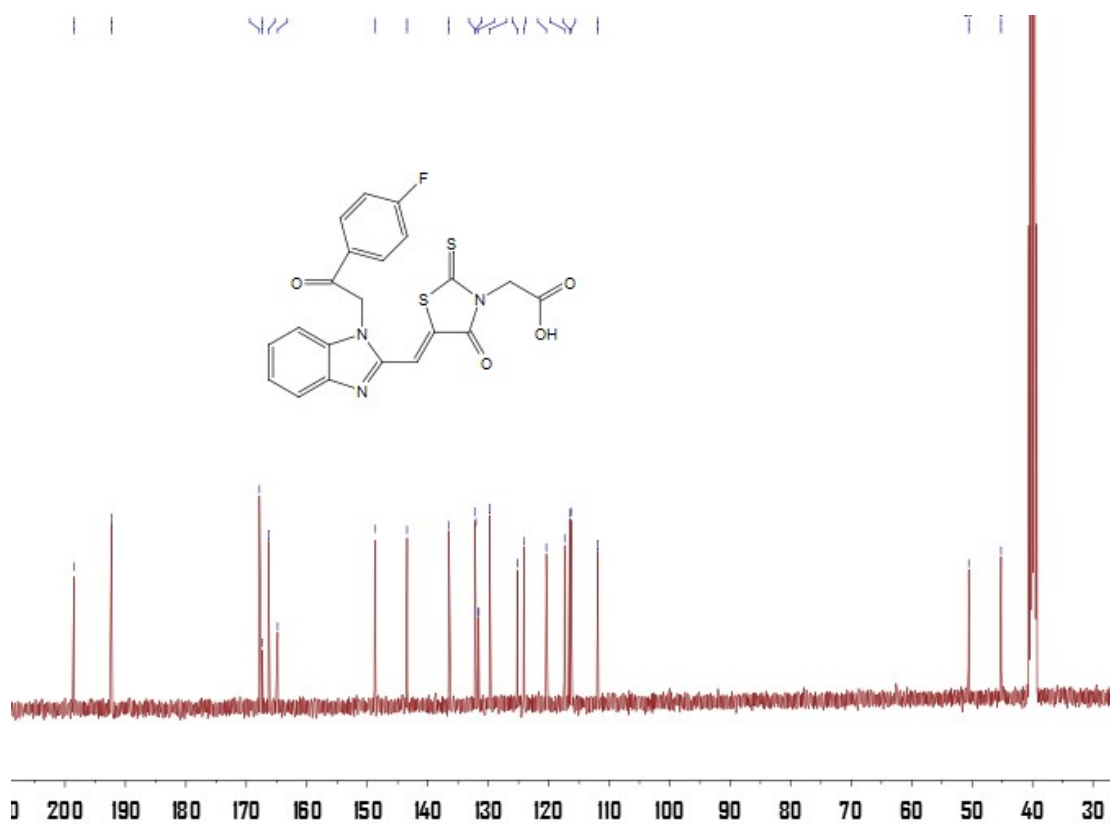
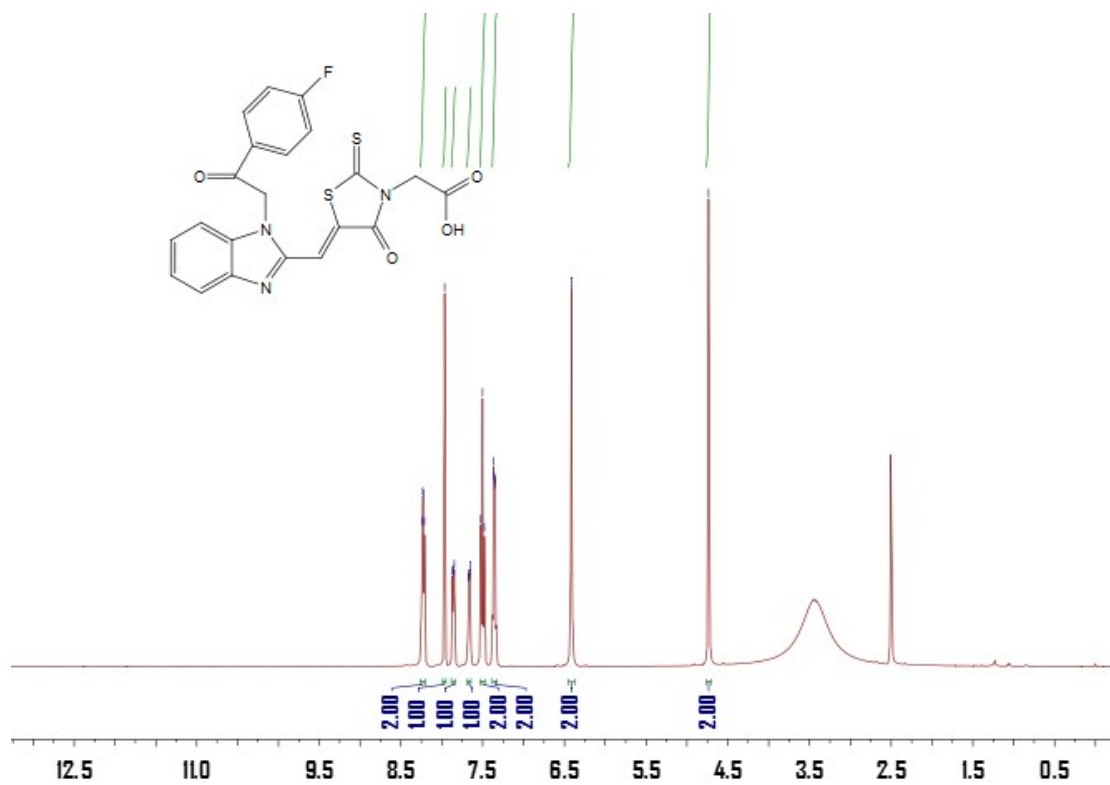
¹H NMR (400 MHz, DMSO-*d*₆) spectrum of **8m**

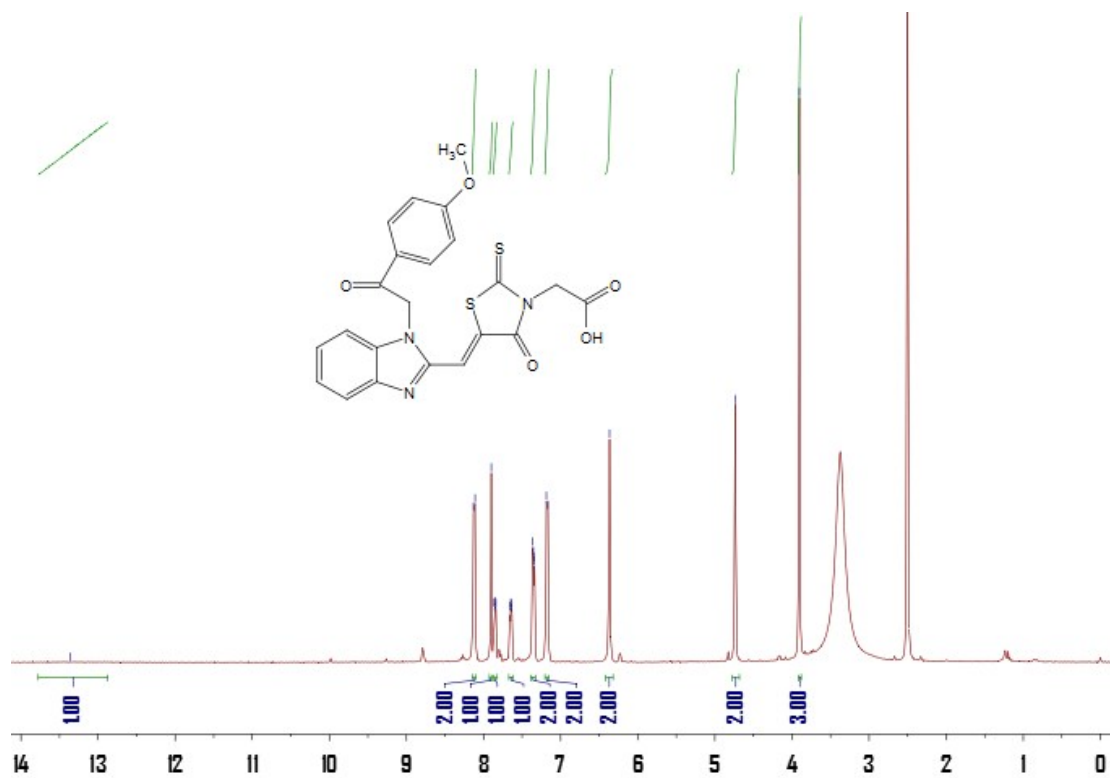


¹³C NMR (400 MHz, DMSO-*d*₆) spectrum of **8m**

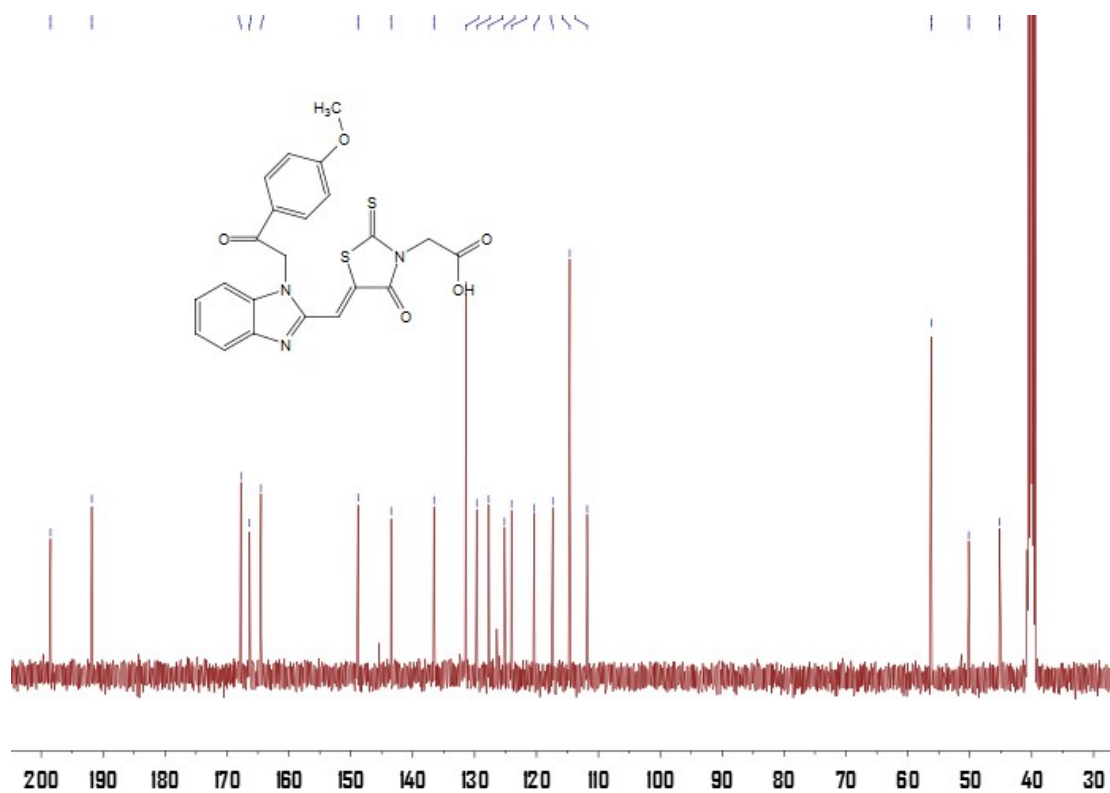




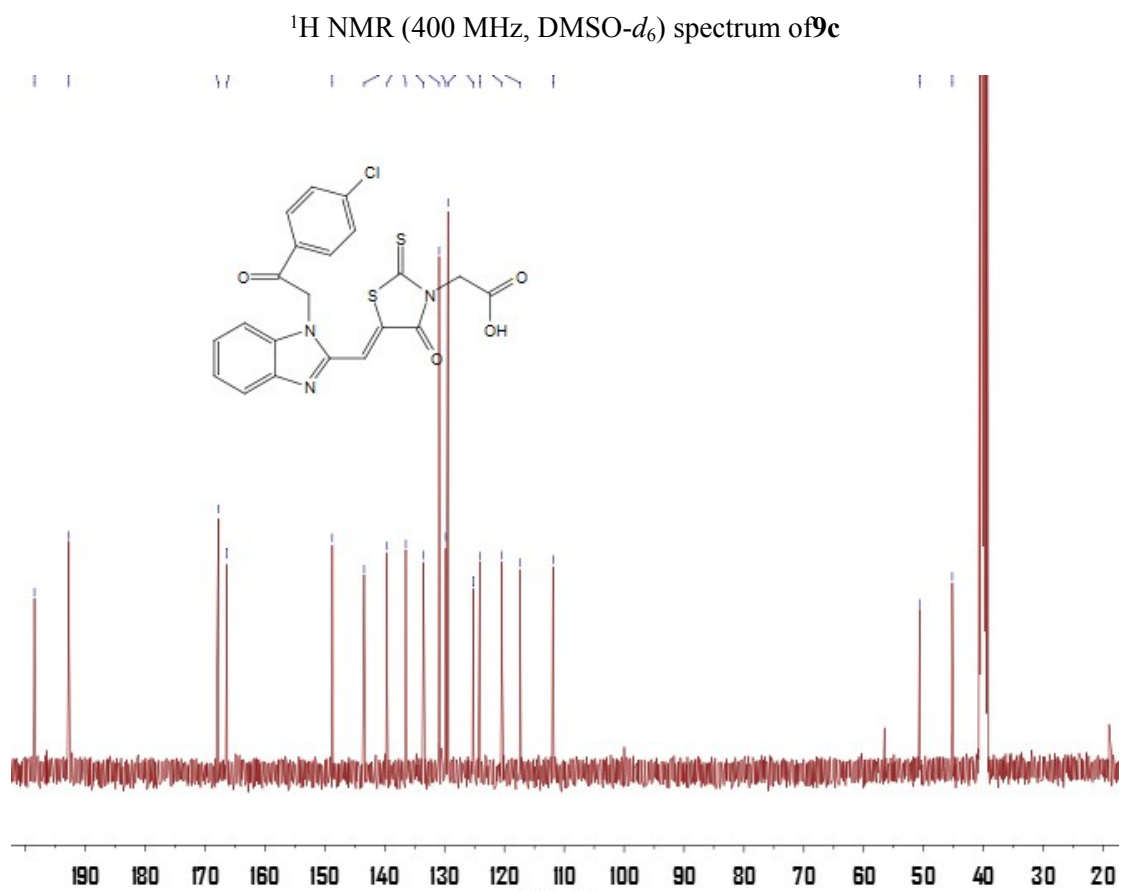
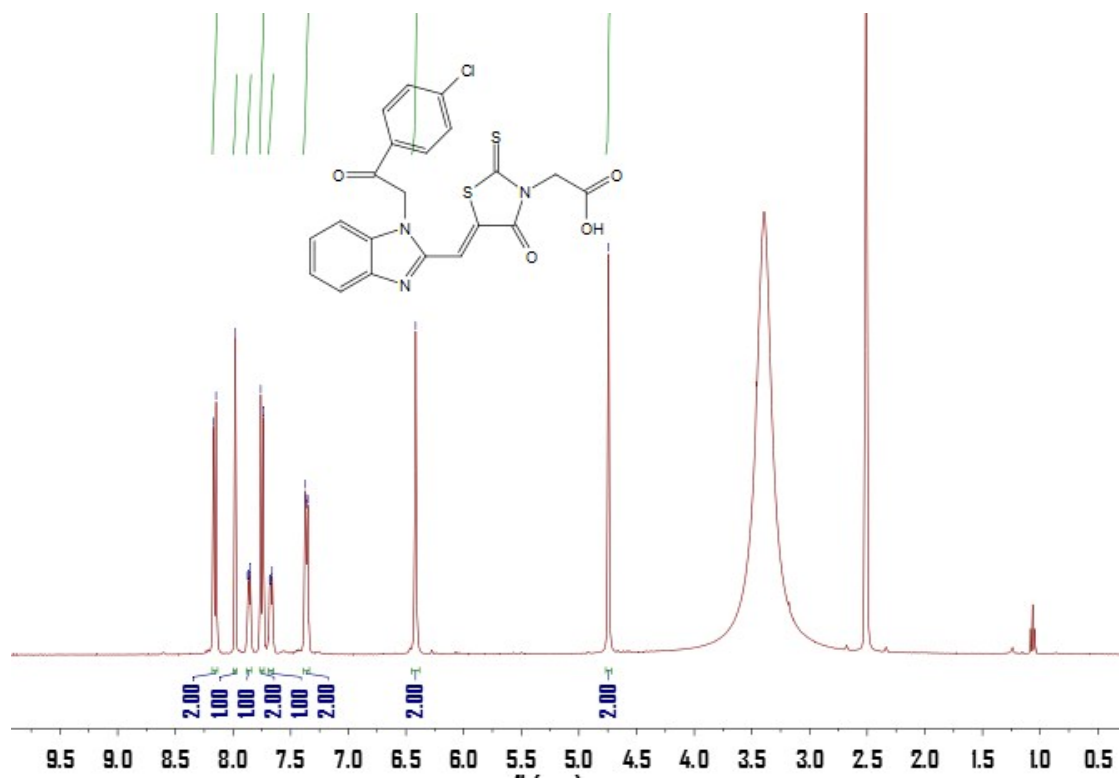


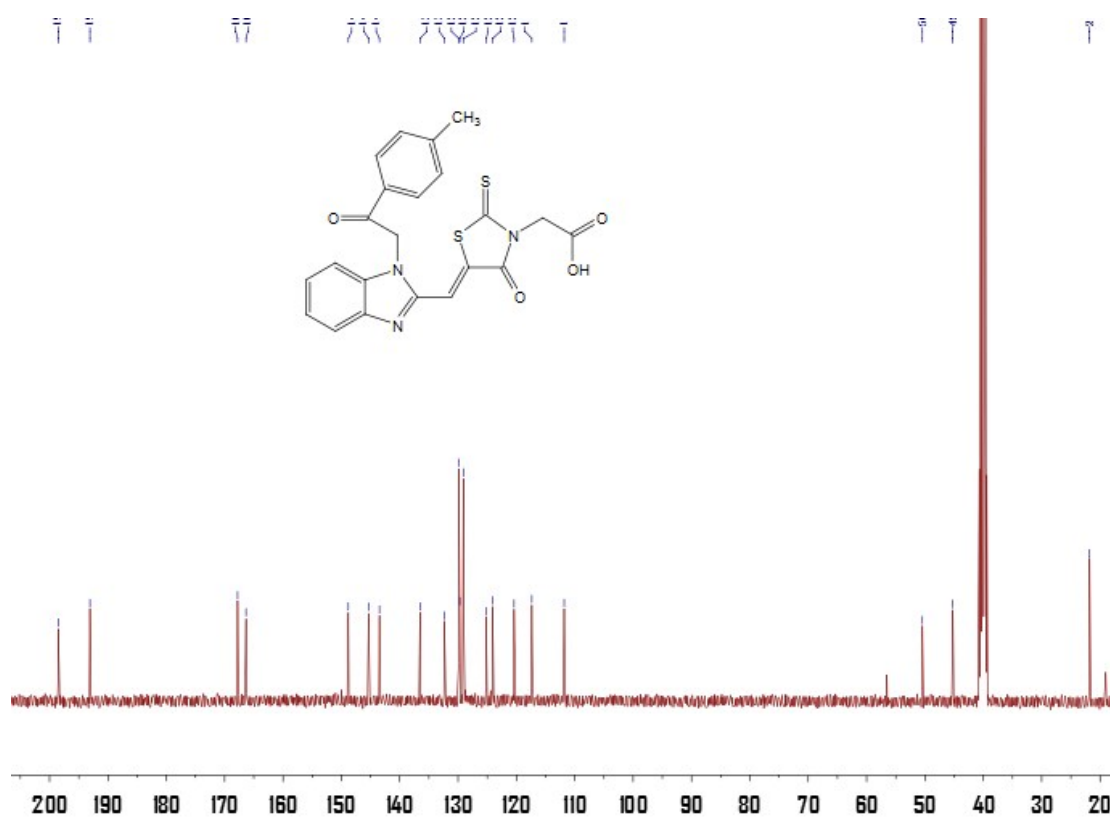
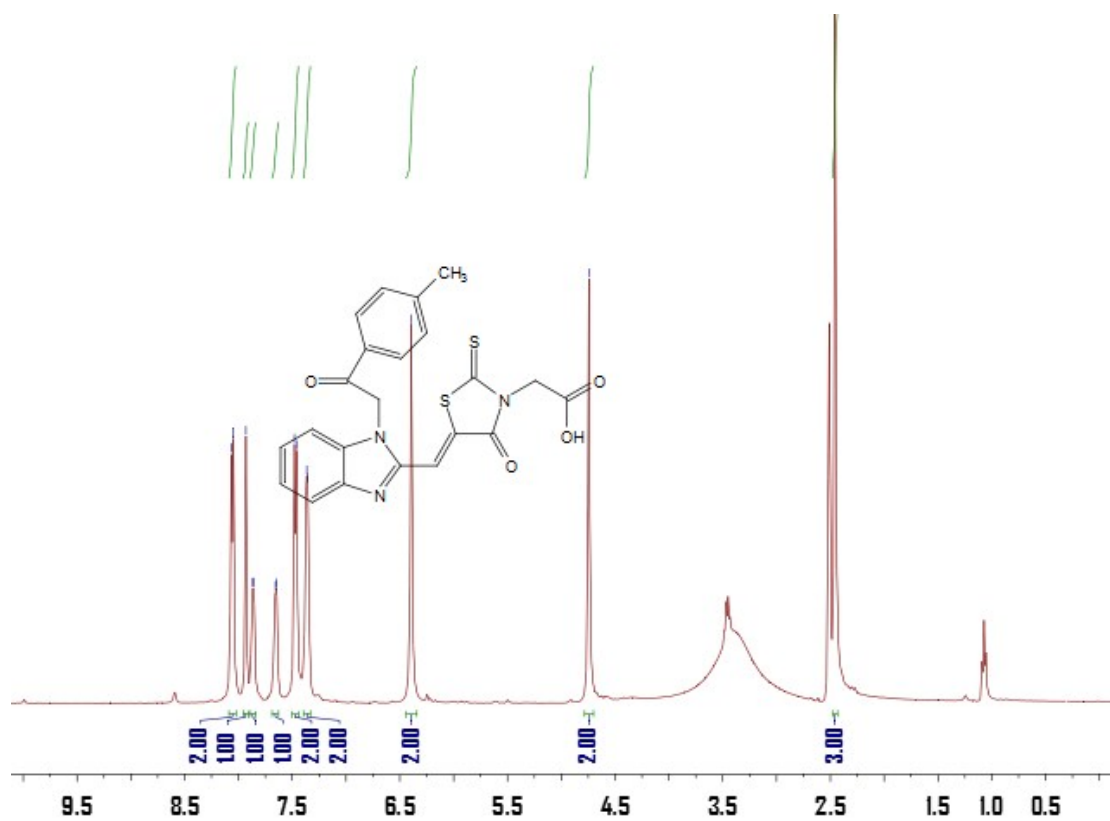


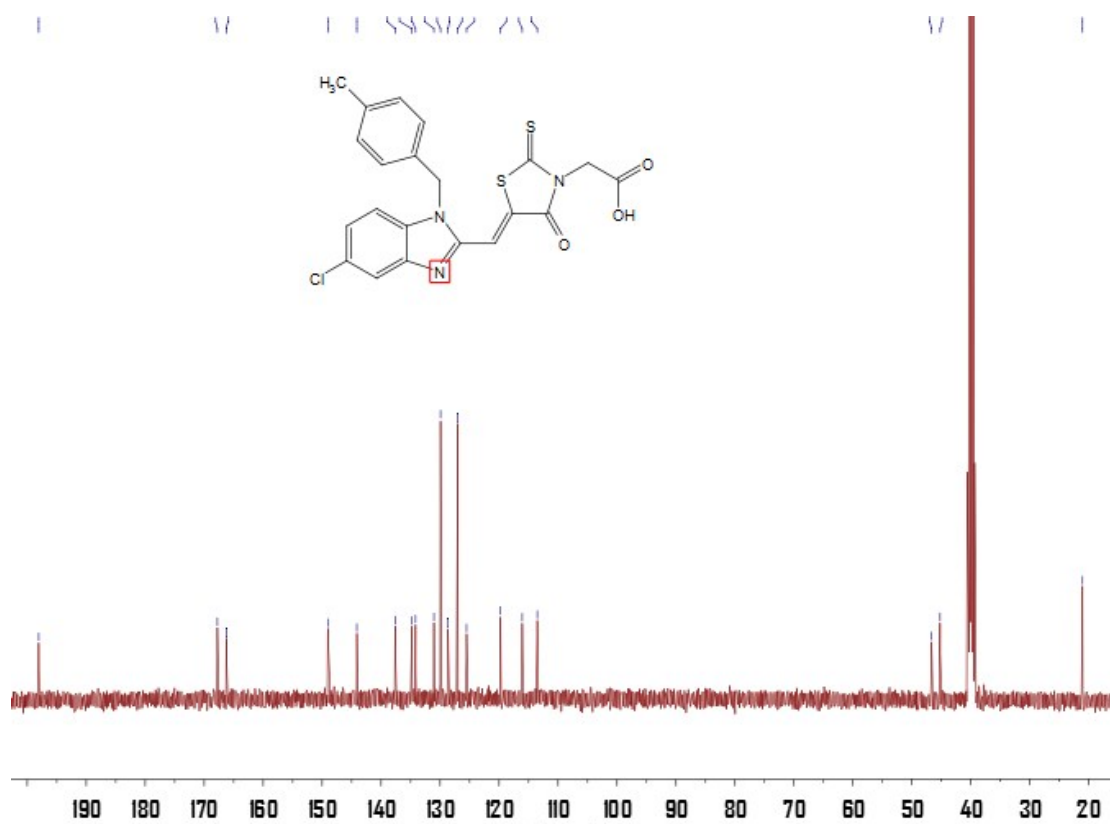
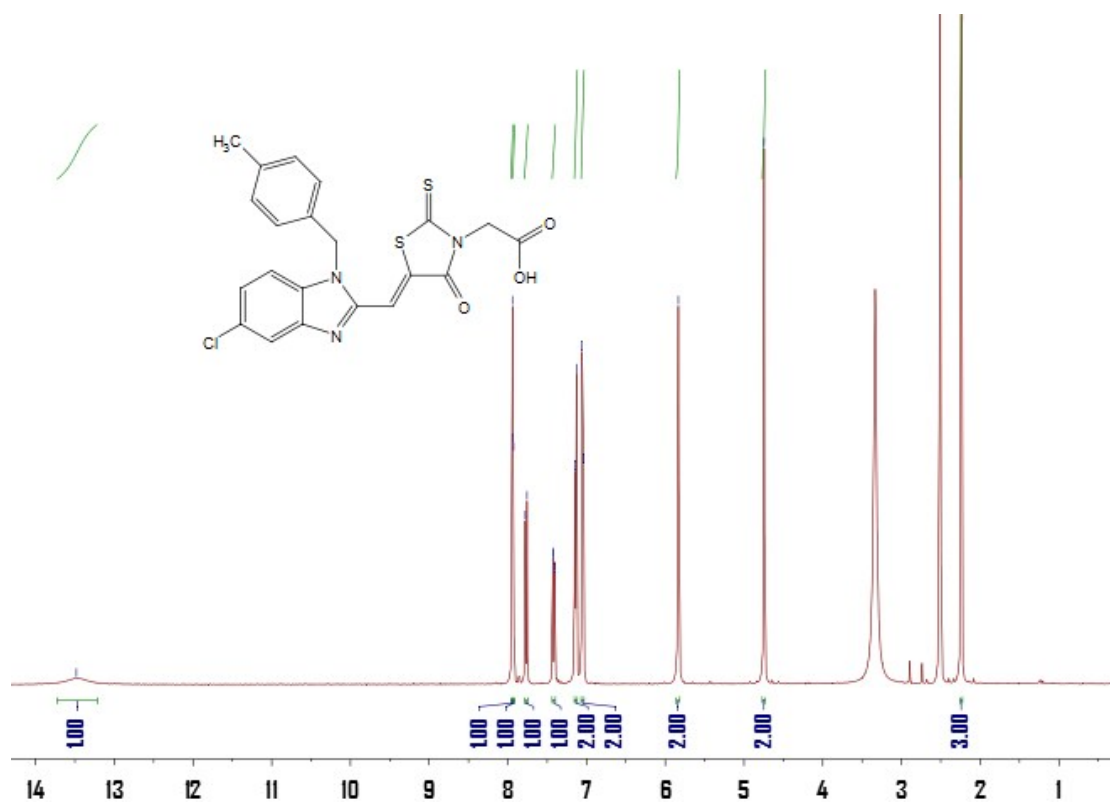
¹H NMR (400 MHz, DMSO-*d*₆) spectrum of **9b**

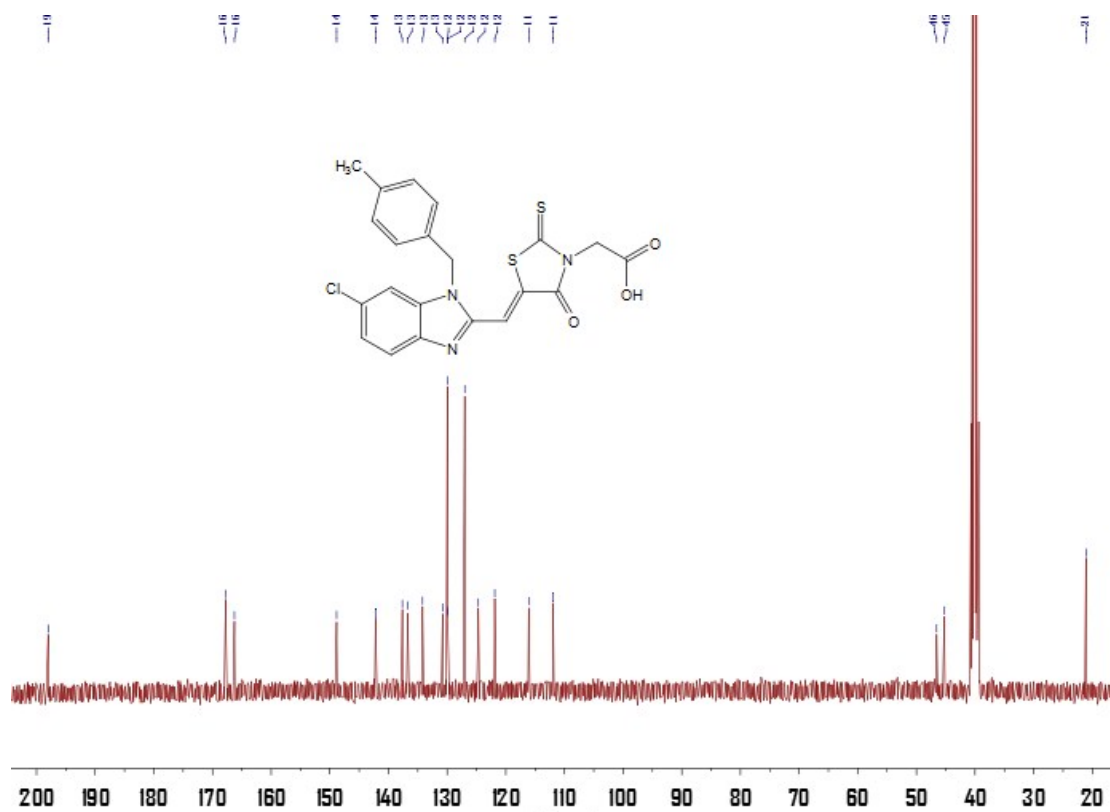
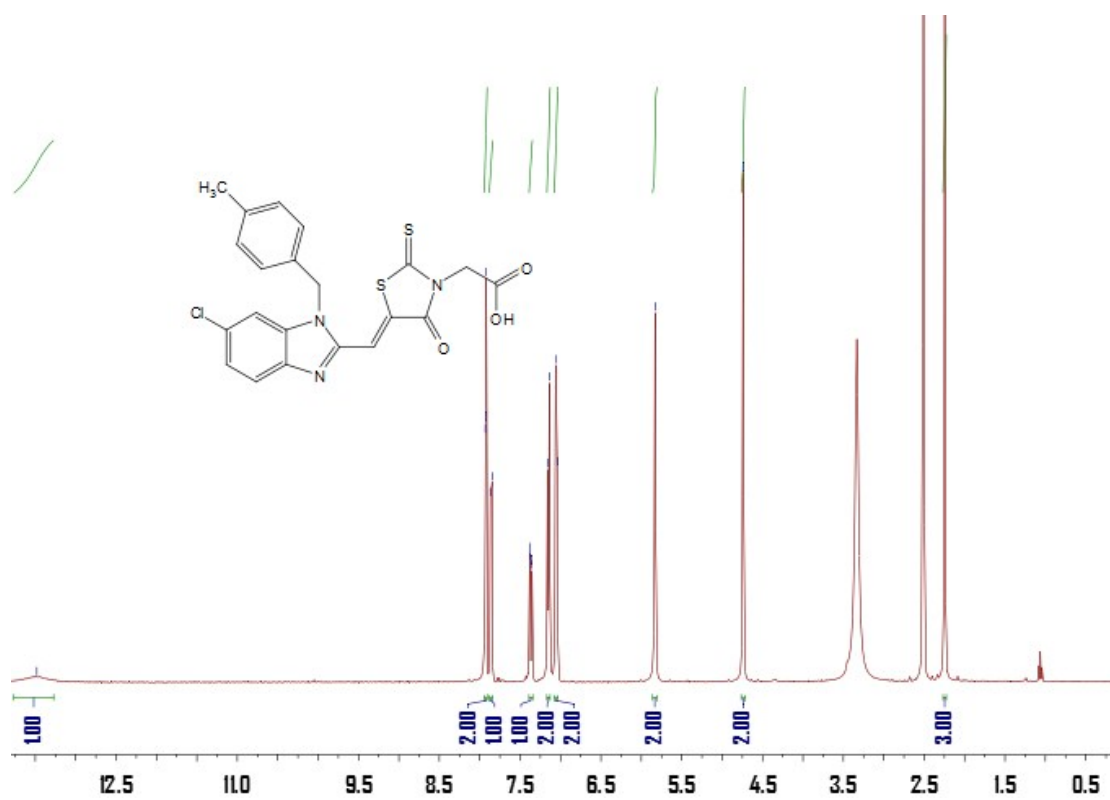


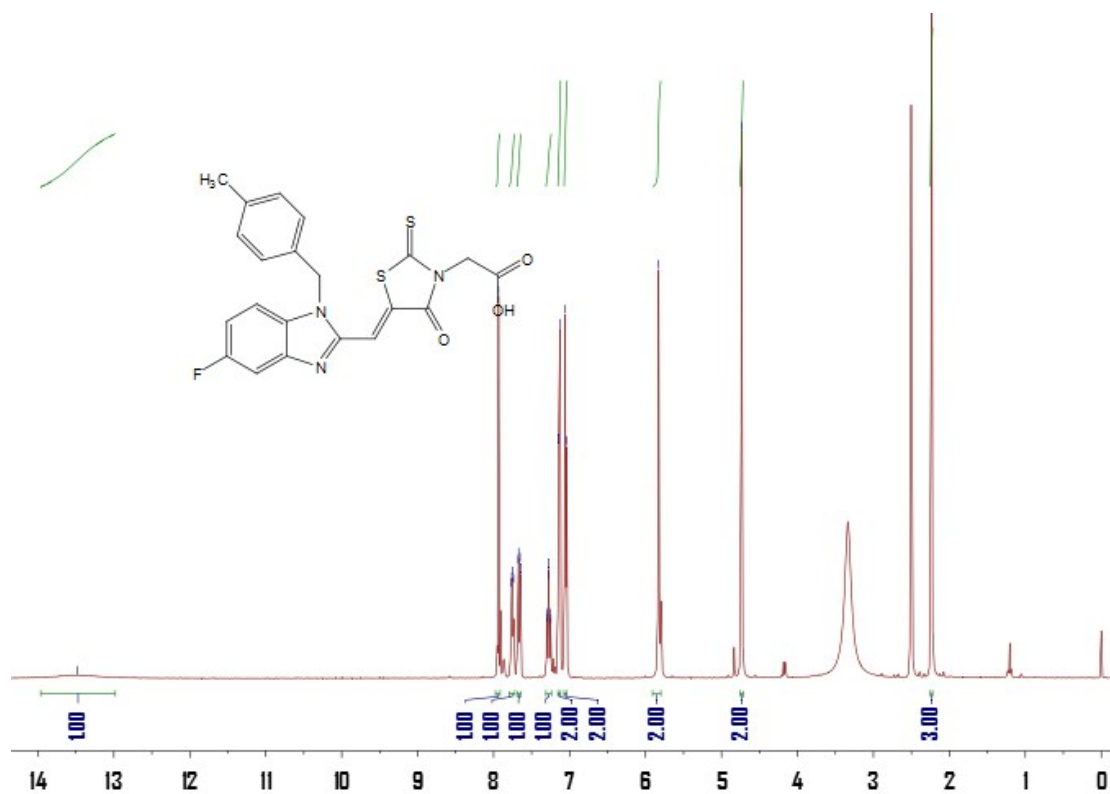
¹³C NMR (400 MHz, DMSO-*d*₆) spectrum of **9b**



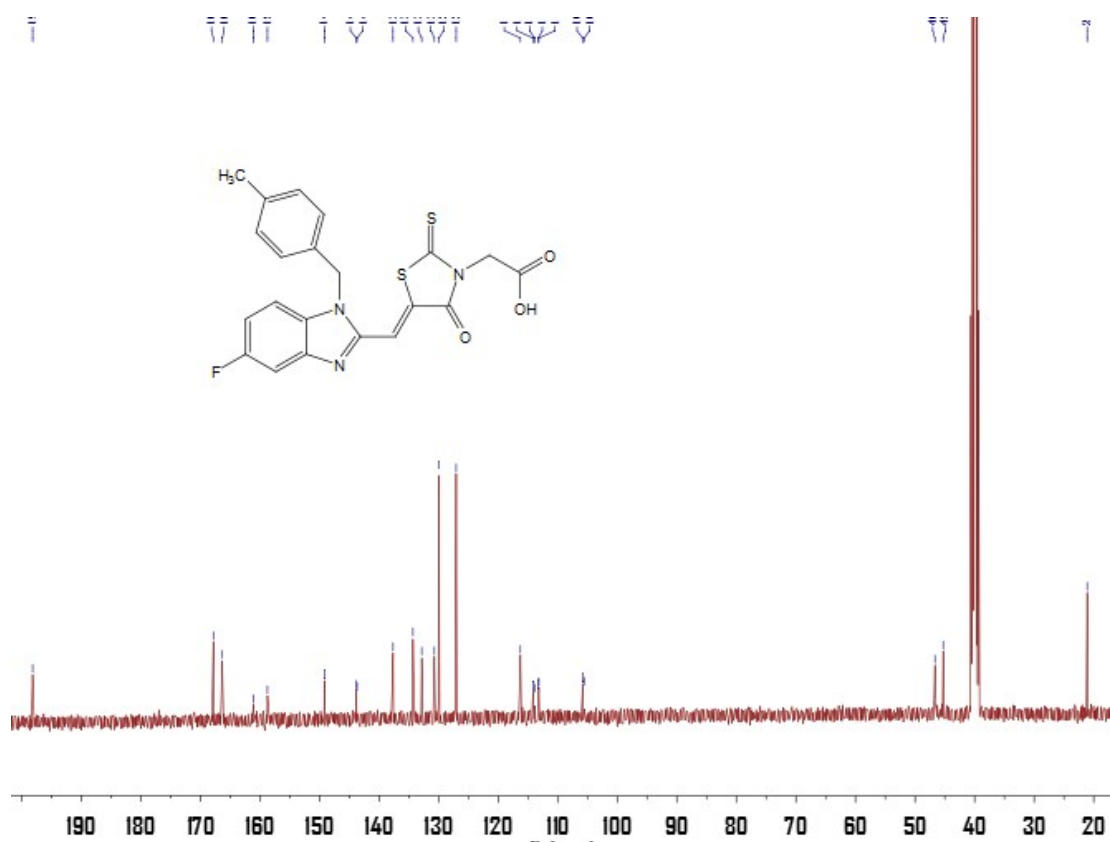




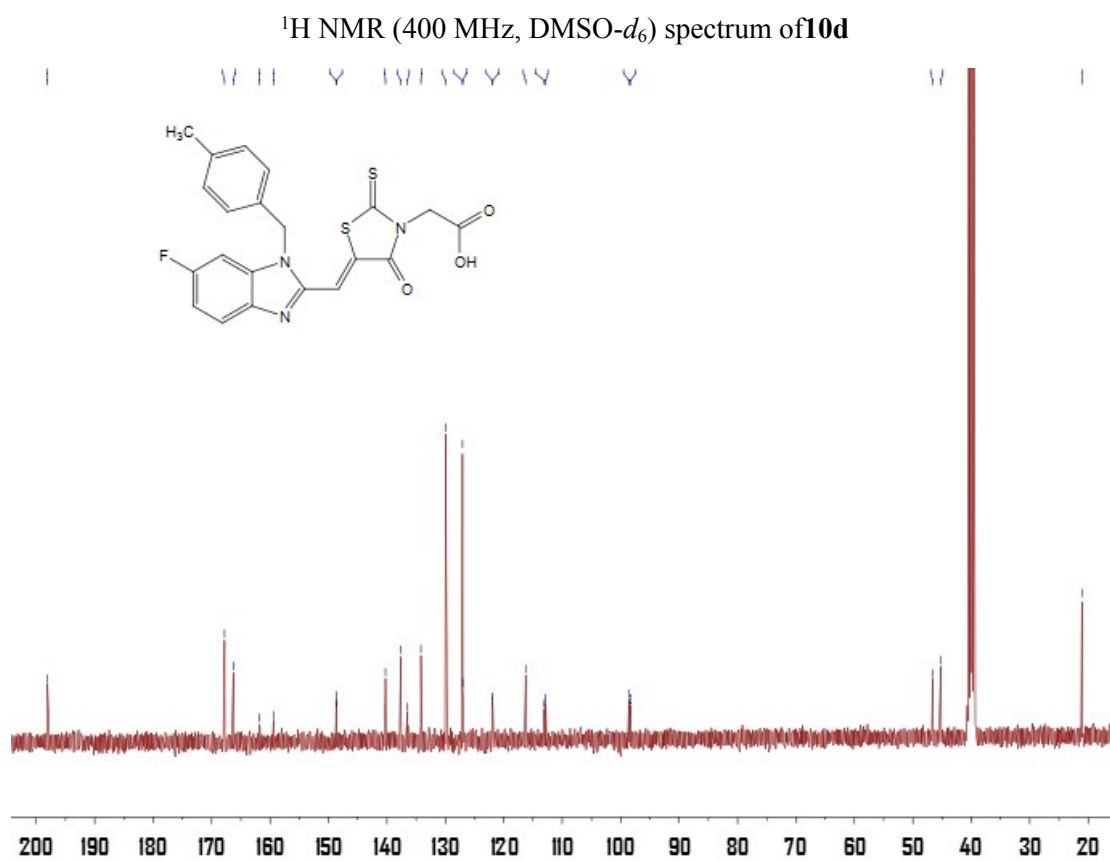
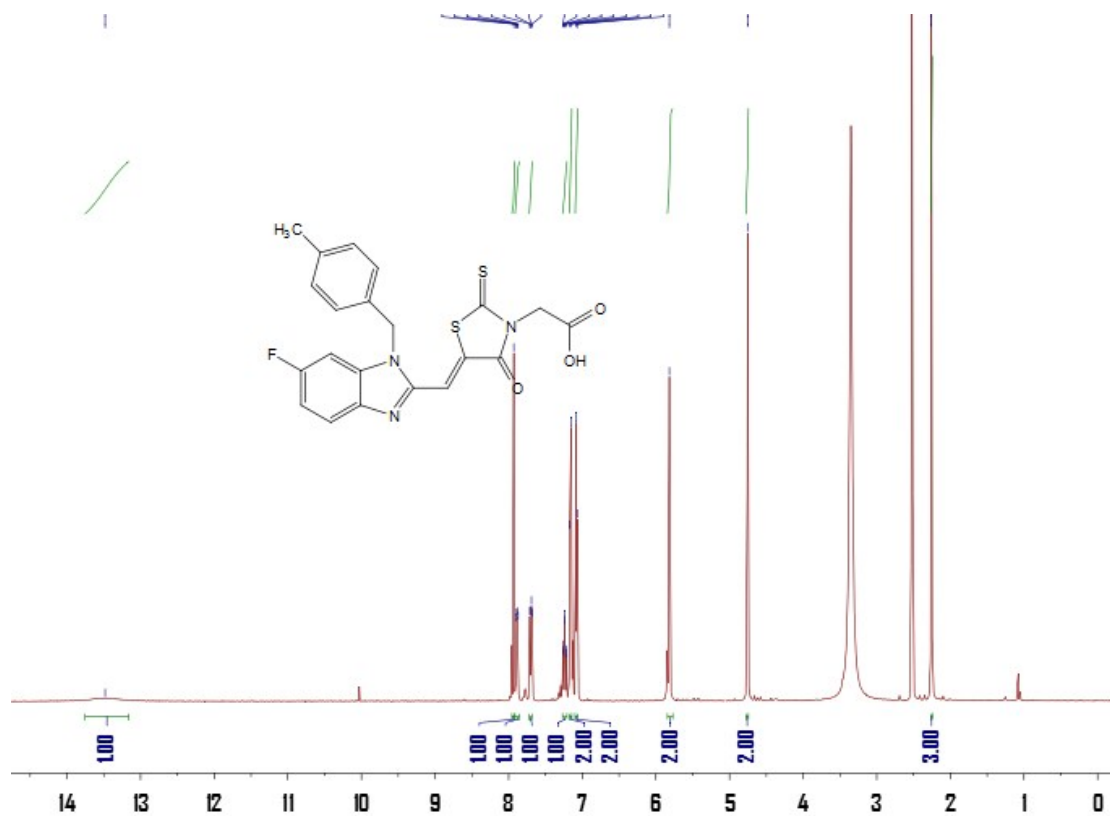


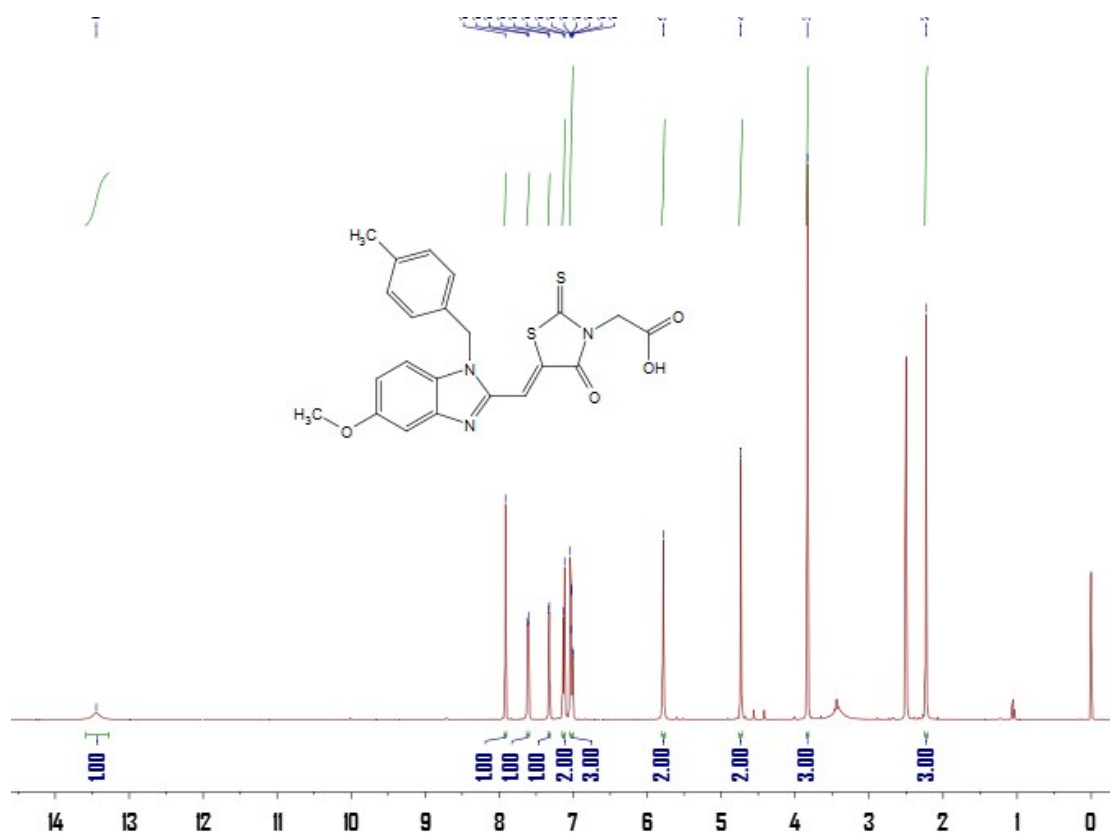


$^1\text{H NMR}$ (400 MHz, $\text{DMSO-}d_6$) spectrum of **10c**

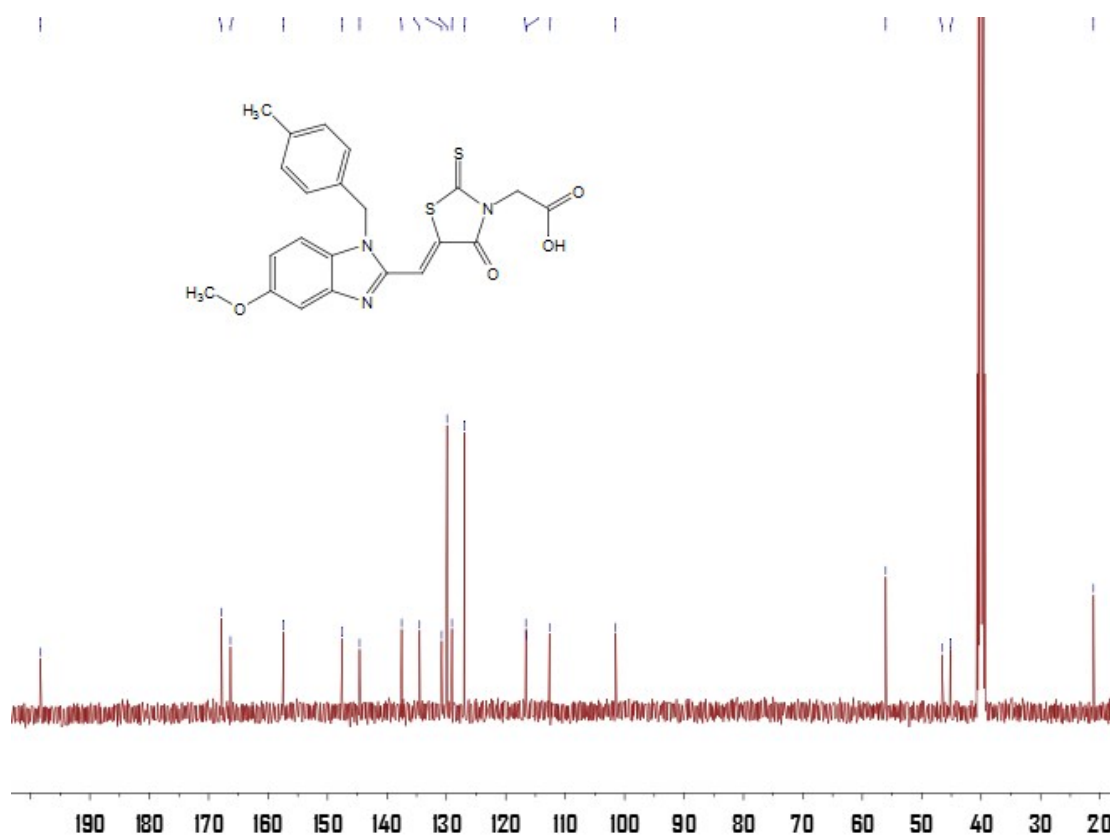


$^{13}\text{C NMR}$ (400 MHz, $\text{DMSO-}d_6$) spectrum of **10c**

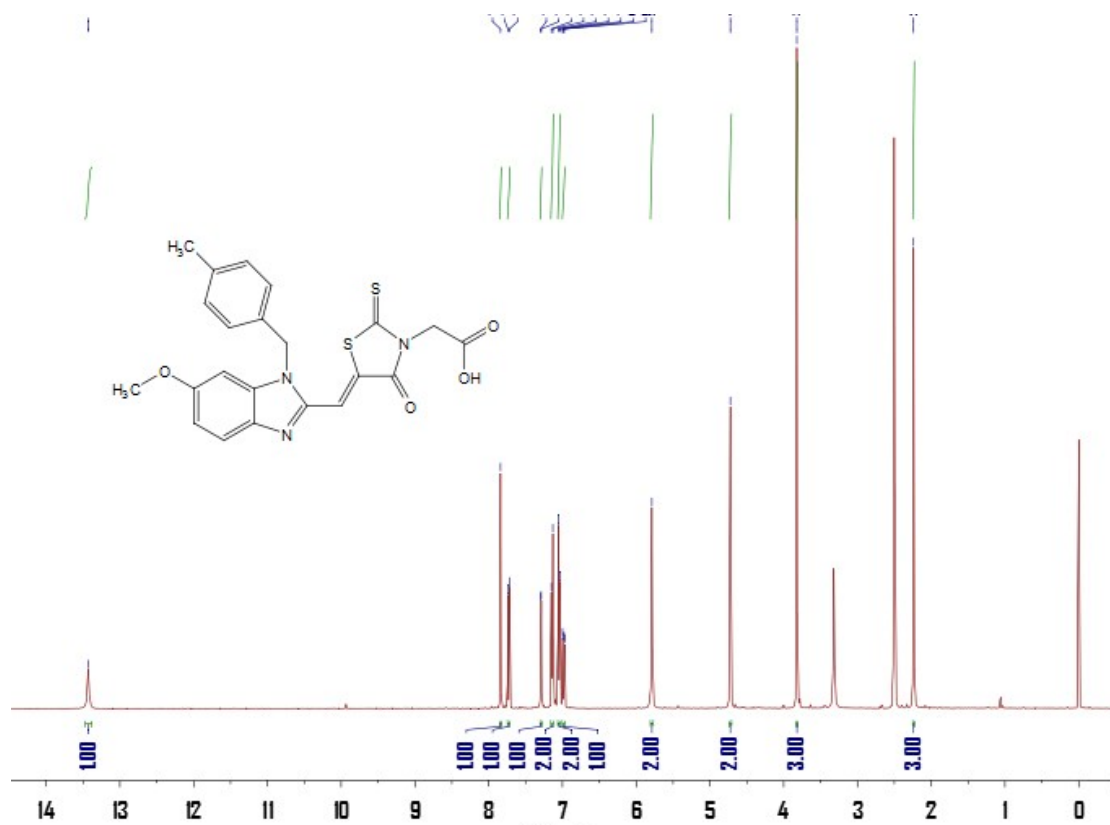




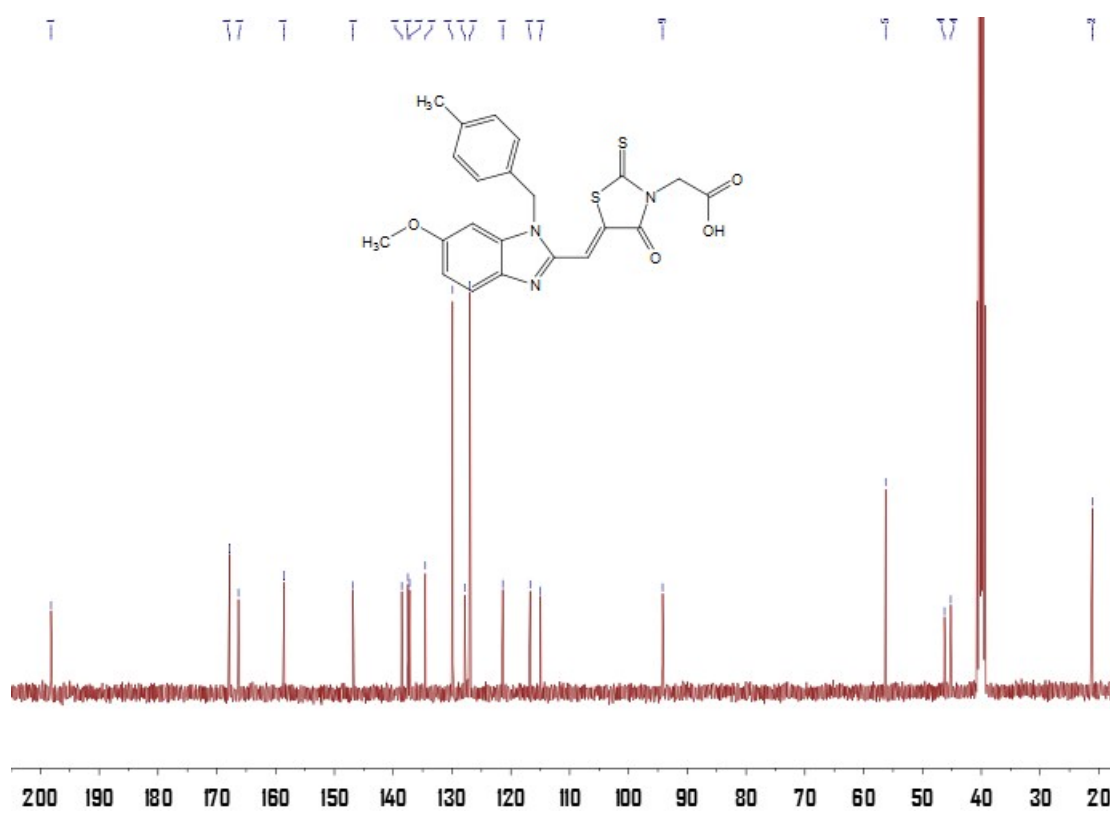
¹H NMR (400 MHz, DMSO-*d*₆) spectrum of **10e**



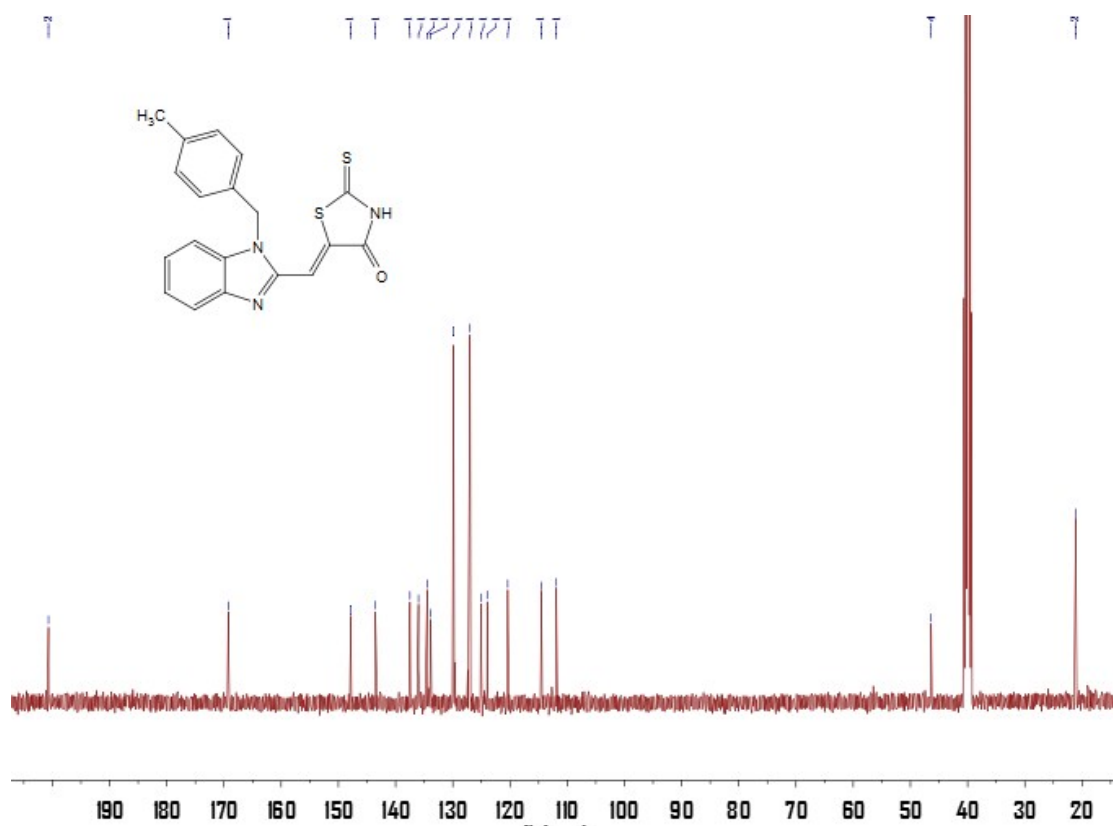
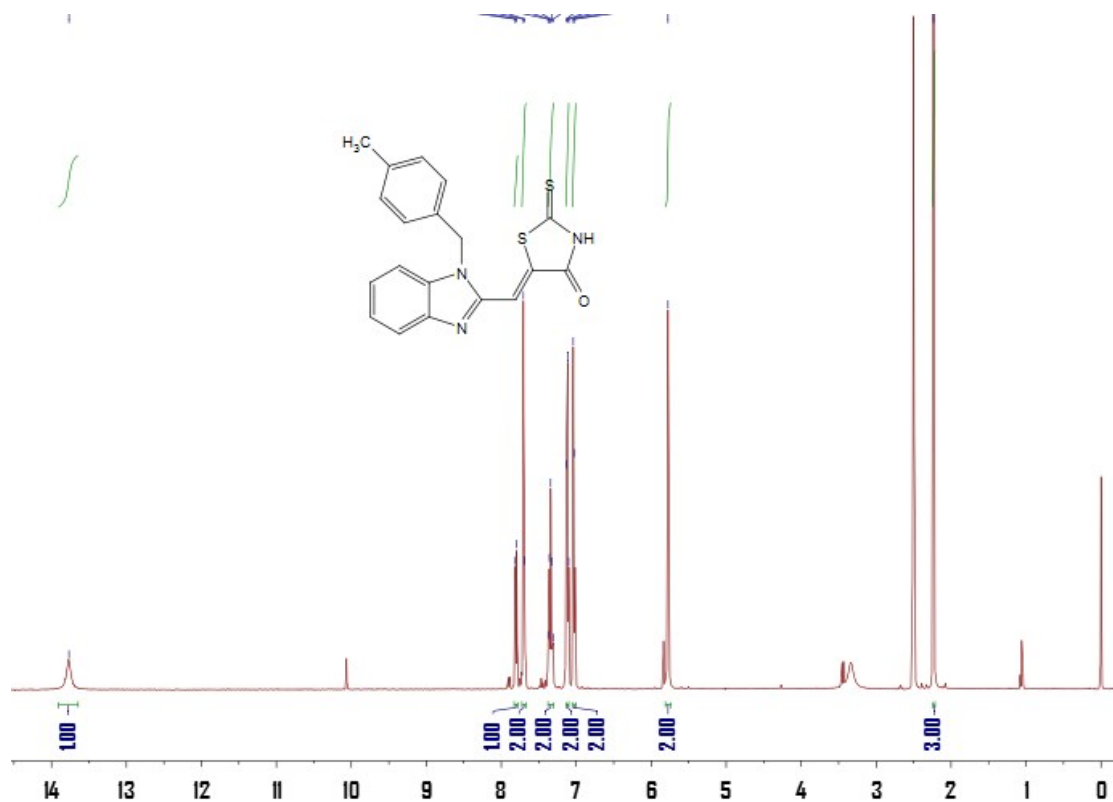
¹³C NMR (400 MHz, DMSO-*d*₆) spectrum of **10e**

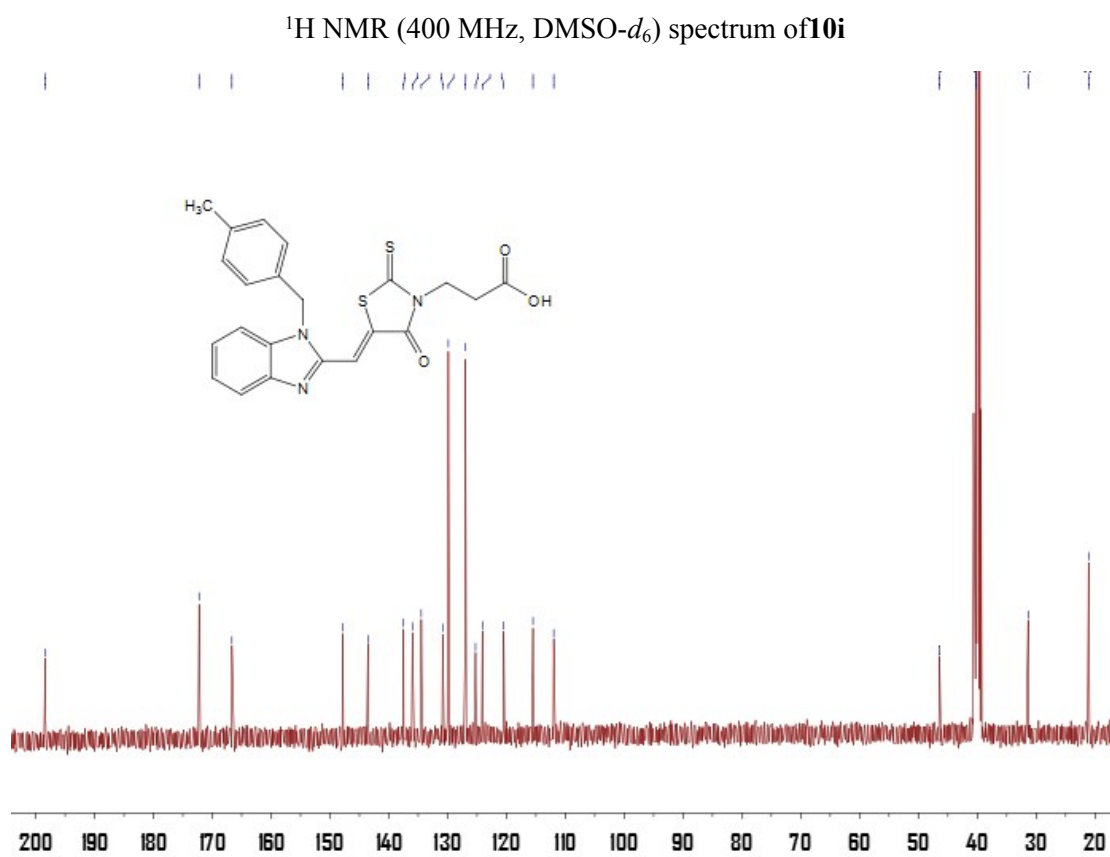
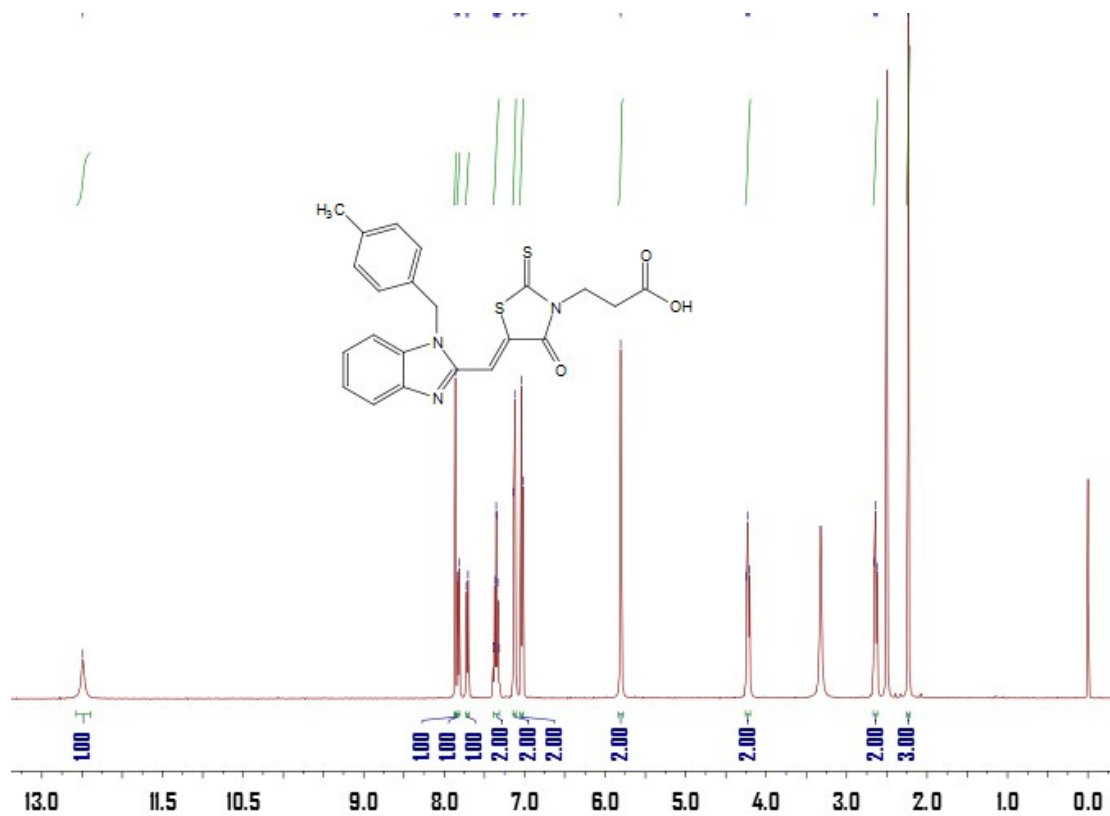


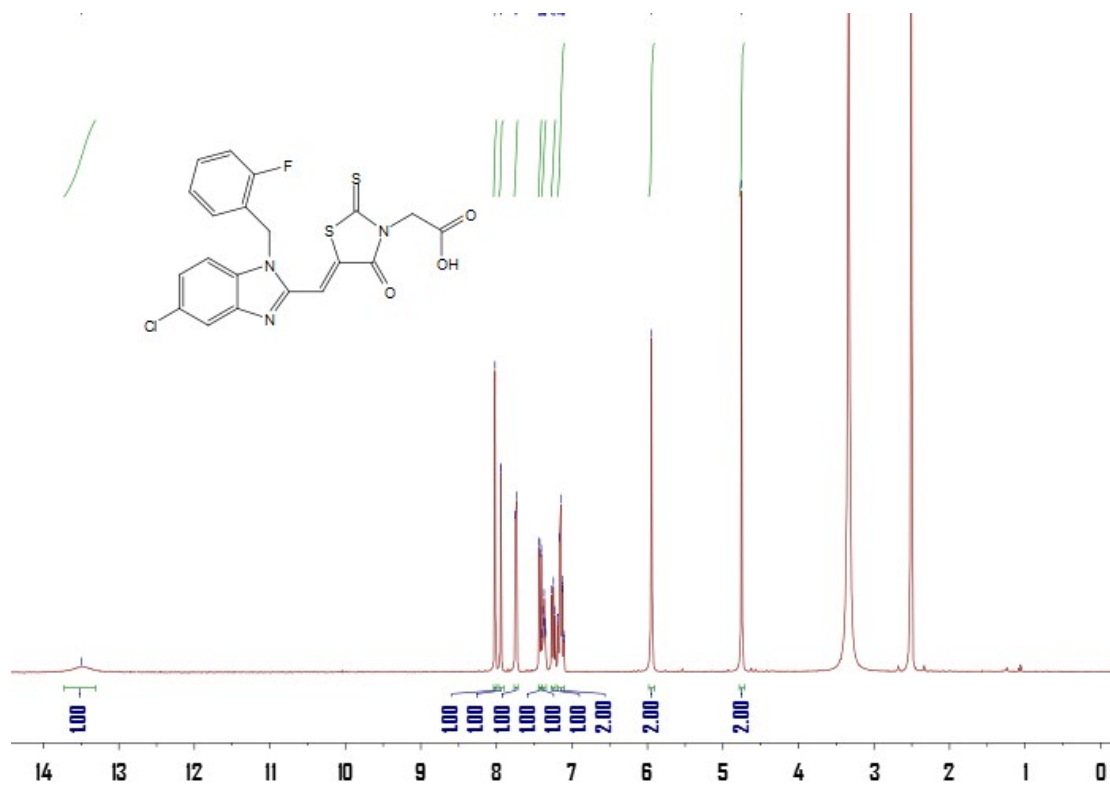
¹H NMR (400 MHz, DMSO-*d*₆) spectrum of **10f**



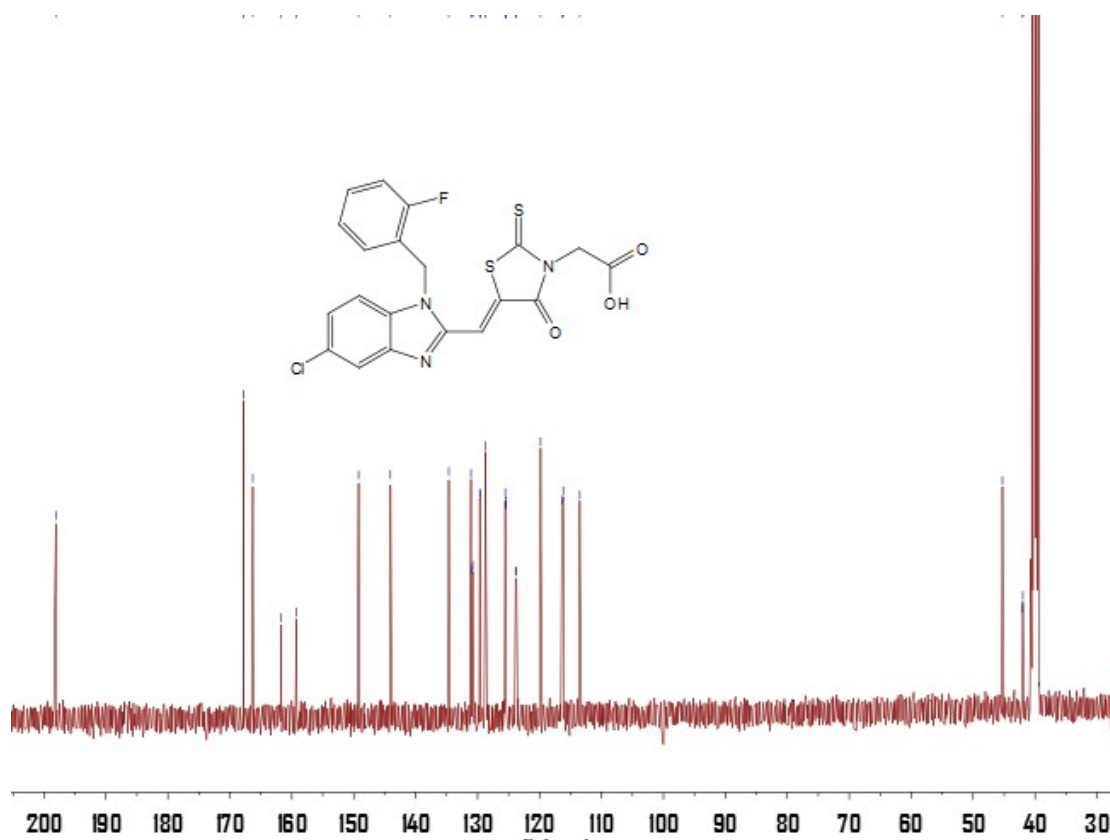
¹³C NMR (400 MHz, DMSO-*d*₆) spectrum of **10f**







¹H NMR (400 MHz, DMSO-*d*₆) spectrum of **11a**



¹³C NMR (400 MHz, DMSO-*d*₆) spectrum of **11a**

