Microbial Cyclosophoraose as a Catalyst for the Synthesis of Diversified Indolyl 4H-Chromenes *via* One-Pot Three Component reactions in Water

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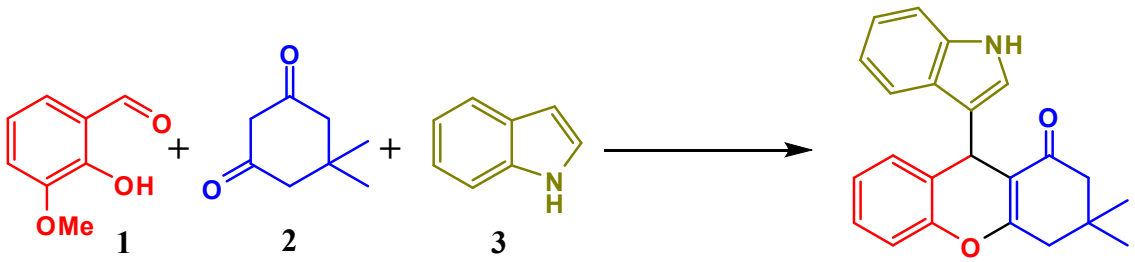
Contents

1. Green chemistry metrics calculations for initial reaction (single use of Cys) and initial reaction including solvent used for isolation of Cys for next reaction cycle (recovery of Cys):

Green chemistry calculations for Cys catalyzed synthesis of 9-(1H-indol-3-yl)-5-methoxy-3,3-dimethyl-2,3,4,9-tetrahydro-1H-xanthen-1-one (**4a**):



1 **2** **3** **4a**

Green chemistry metrics calculations for initial reaction:

E-factor = [0.152 g (2-hydroxy-3-methoxybenzaldehyde **1**) + 0.140 g (Dimedone **2**) + 0.117 g (indole **3**) - 0.345 g (product **4a**)]/ 0.345 g

E-factor = 0.18

Process mass intensity (PMI) = E-factor + 1

= 0.18 + 1

PMI = 1.18

Atom economy (AE) = MW of product ÷ ∑(MW of stoichiometric reactants) × 100

= 373.44 (4) ÷ [152.14 (**1**) + 140.17 (**2**) + 117.14 (**3**)] × 100

AE = 91.20%

Reaction mass efficiency (RME) = mass of product /∑(mass of stoichiometic reactants) × 100

= 0.345 g (**4a**)/ [0.15214 (**1**) + 0.14017 (**2**) + 0.11714 (**3**)] × 100

= [0.345/ 0.40945] × 100

RME = 84.25%

Green chemistry metrics calculations including solvent used for isolation of catalyst during work-up (isolation and reuse of catalyst):

E-factor = [0.152 g (2-hydroxy-3-methoxybenzaldehyde **1**) + 0.140 g (Dimedone **2**) + 0.117 g (indole **3**) + 15.8 g (Acetone i.e. used for isolation) - 0.345 g (product **4a**)]/ 0.345 g

E-factor = **45.98**

Process mass intensity (PMI) = E-factor + 1

= 45.98 + 1

PMI = **49.98**

Green chemistry metrics calculations for first reaction cycle (Reusability of catalyst):

E-factor = [0.152 g (2-hydroxy-3-methoxybenzaldehyde **1**) + 0.140 g (Dimedone **2**) + 0.117 g (indole **3**) - 0.341 g (product **4a**)]/ 0.341 g

E-factor = **0.19**

Process mass intensity (PMI) = E-factor + 1

= 0.18 + 1

PMI = **1.18**

Atom economy (AE) = MW of product ÷ ∑(MW of stoichiometric reactants) × 100

= 373.44 (4) ÷ [152.14 (**1**) + 140.17 (**2**) + 117.14 (**3**)] × 100

AE = 91.20%

Reaction mass efficiency (RME) = mass of product /∑(mass of stoichiometic reactants) × 100

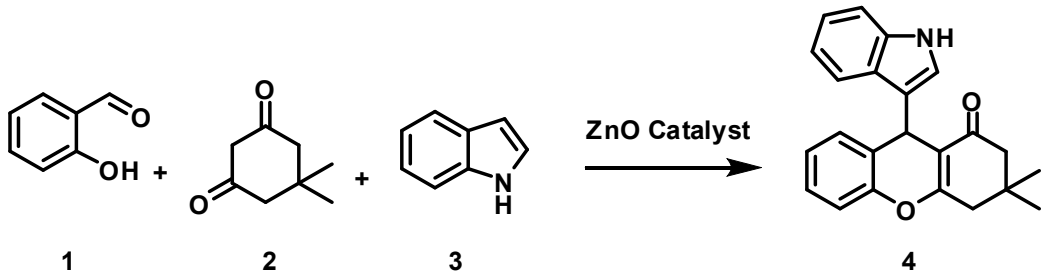
= 0.341 g (**4a**)/ [0.15214 (**1**) + 0.14017 (**2**) + 0.11714 (**3**)] × 100

= [0.345/ 0.40945] × 100

RME = 83.28%

2. **Green chemistry metrics calculations for Indolyl 4H-Chromenes for reported methods:**

1. **<u>J. Org. Chem., 2013, 78, 6170 (ZnO nano catalyst):</u>**



1 2 3 4

E-factor = [0.122 g (2-hydroxy-3-methoxybenzaldehyde **1**) + 0.140 g (Dimedone **2**) + 0.117 g (indole **3**) - 0.312 g (product **4a**)]/ 0.312 g

E-factor = **0.21**

Process mass intensity (PMI) = E-factor + 1

= 102.32 + 1

PMI = **1.21**

Atom economy (AE) = MW of product ÷ ∑(MW of stoichiometric reactants) × 100

= 343 (4) ÷ [122 (**1**) + 140 (**2**) + 117 (**3**)] × 100

AE = 90.50%

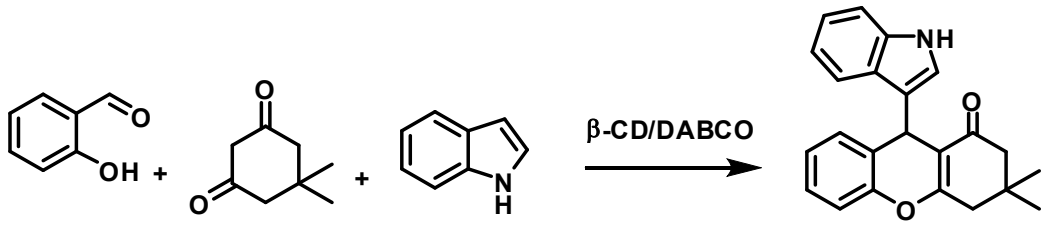
Reaction mass efficiency (RME) = mass of product /∑(mass of stoichiometic reactants) × 100

= 0.312 g (**4a**)/ [0.122 (**1**) + 0.140 (**2**) + 0.117 (**3**)] × 100

= [0.312/ 0.379] × 100

RME = 82.32%

2. **<u>Catal Lett., 2015, 145, 2020 (β-Cyclodextrin/DABCO):</u>**



1 2 3 4

E-factor = [0.122 g (2-hydroxy-3-methoxybenzaldehyde **1**) + 0.140 g (Dimedone **2**) + 0.117 g (indole **3**) + 0.022 g (DABCO) - 0.227 g (product **4a**)]/ 0.227 g

E-factor = **0.76**

Process mass intensity (PMI) = E-factor + 1

= 0.76 + 1

PMI = **1.76**

Atom economy (AE) = MW of product ÷ ∑(MW of stoichiometric reactants) × 100

= 343 (4) ÷ [122 (**1**) + 140 (**2**) + 117 (**3**)] × 100

AE = 90.50%

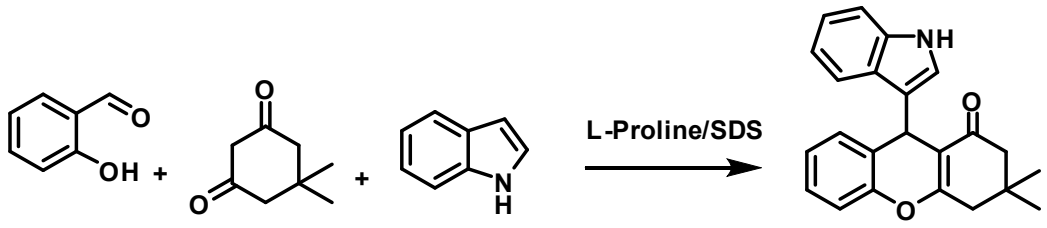
Reaction mass efficiency (RME) = mass of product /∑(mass of stoichiometic reactants) × 100

= 0.227 g (**4a**)/ [0.122 (**1**) + 0.14017 (**2**) + 0.11714 (**3**)] × 100

= [0.227/ 0.379] × 100

RME = 59.89%

3. **<u>Tetrahedron Lett., 2012, 53, 7067 (L-proline/SDS):</u>**



1 2 3 4

E-factor = [0.134 g (2-hydroxy-3-methoxybenzaldehyde **1**) + 0.154 g (Dimedone **2**) + 0.129 g (indole **3**) + 0.012 g (L-proline) + 0.023 g (SDS) + 33.33 g (ethyl acetate) - 0.326 g (product **4a**)]/ 0.326 g

E-factor = **102.32**

Process mass intensity (PMI) = E-factor + 1

= 102.32 + 1

PMI = **103.32**

Atom economy (AE) = MW of product ÷ ∑(MW of stoichiometric reactants) × 100

= 343 (4) ÷ [122 (**1**) + 140 (**2**) + 117 (**3**)] × 100

AE = 90.50%

Reaction mass efficiency (RME) = mass of product /∑(mass of stoichiometic reactants) × 100

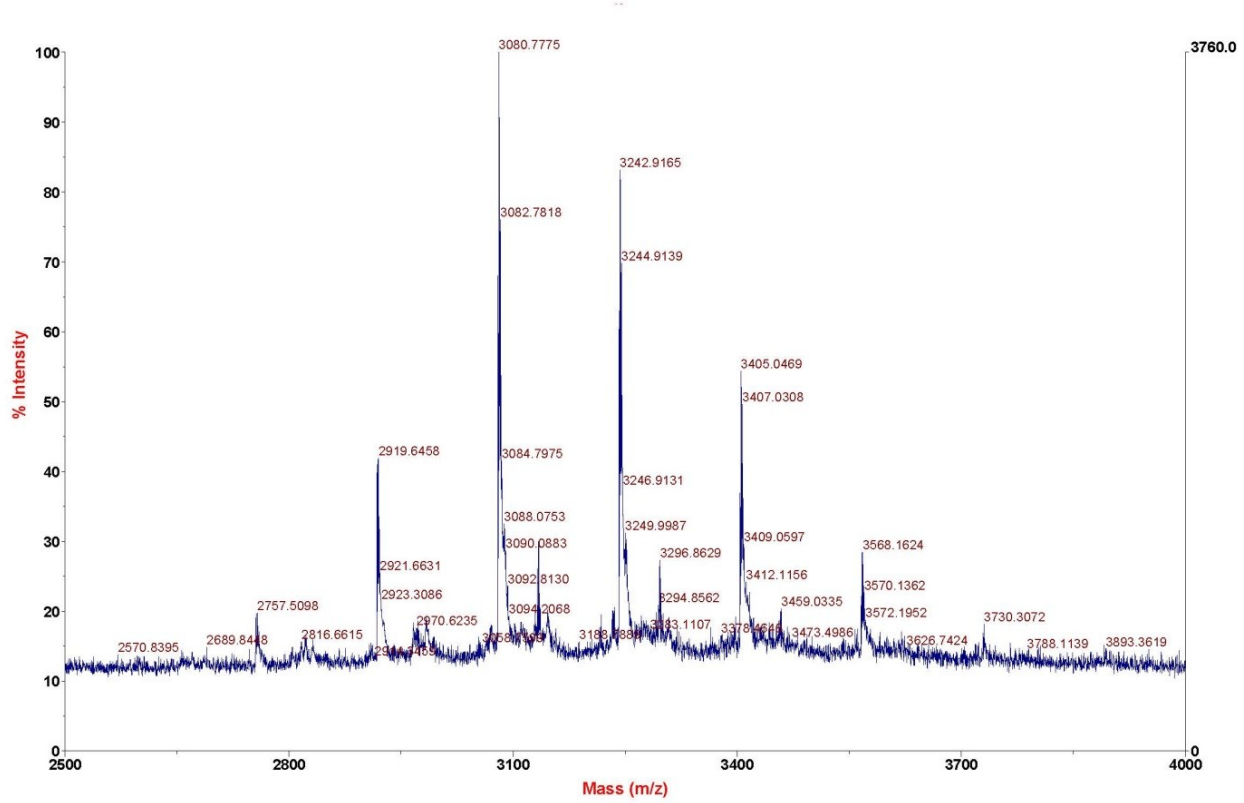
= 0.326 g (**4a**)/ [0.134 (**1**) + 0.154 (**2**) + 0.129 (**3**)] × 100

= [0.326/ 0.379] × 100

RME = 78.17%

3. Spectral Data:

3.1 MALDI TOF-MS spectrum cyclosophoraoses:

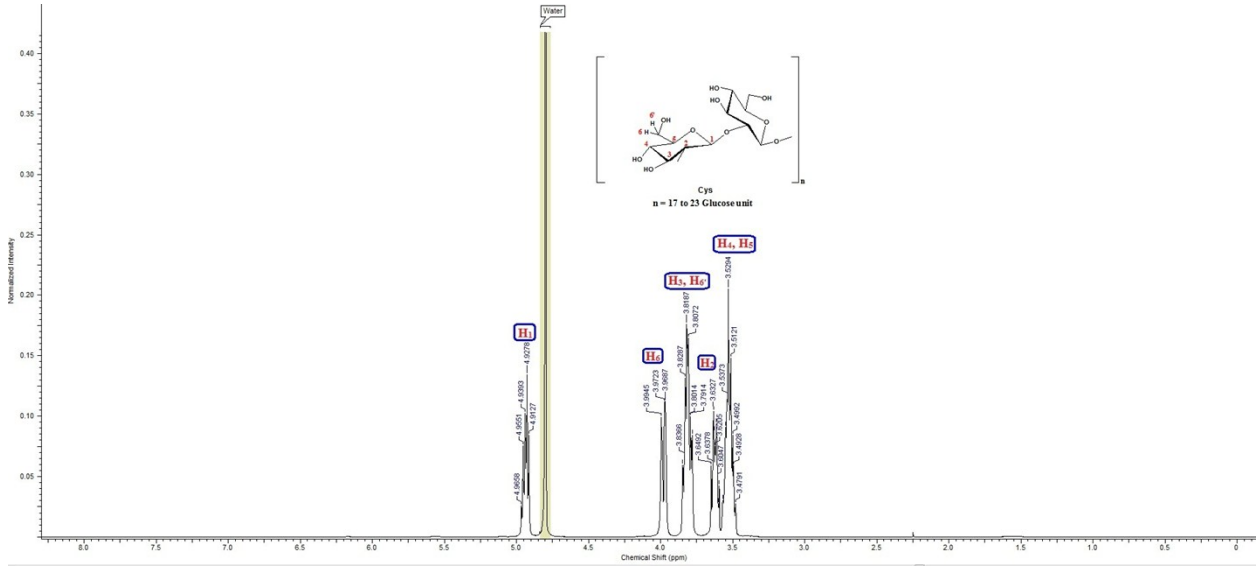


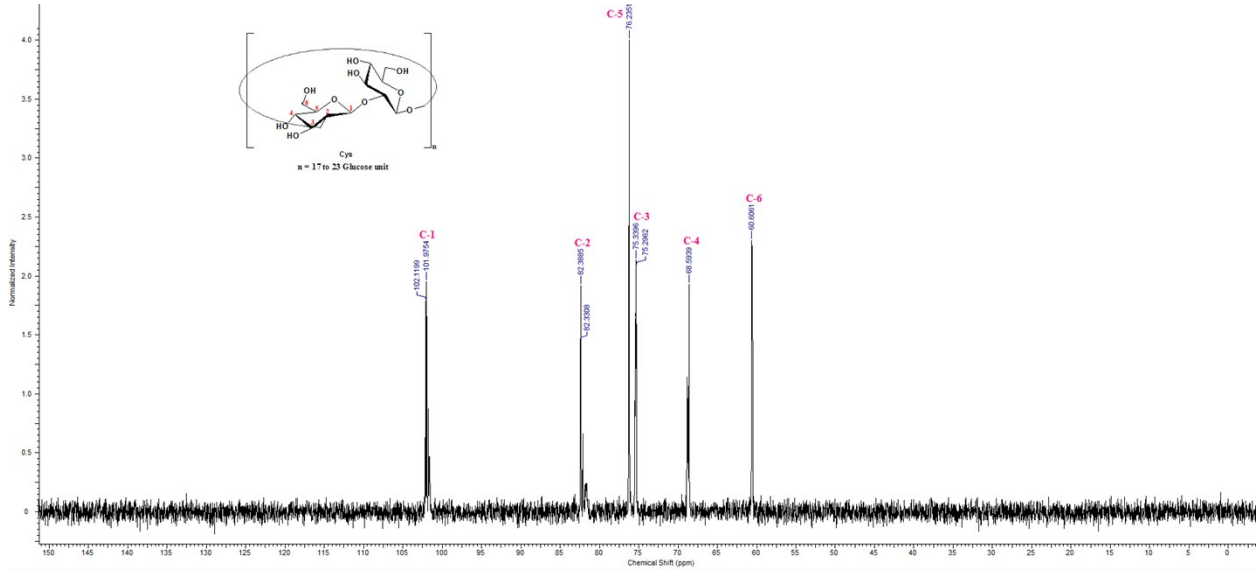
D:\...\VF39CYS_N_0002.dat
Acquired: 08:27:00, March 21, 2012

3.2 **Table 1. Calculation and measured mass unit of m/z of Cys from MALDI TOF-MS spectrum.**

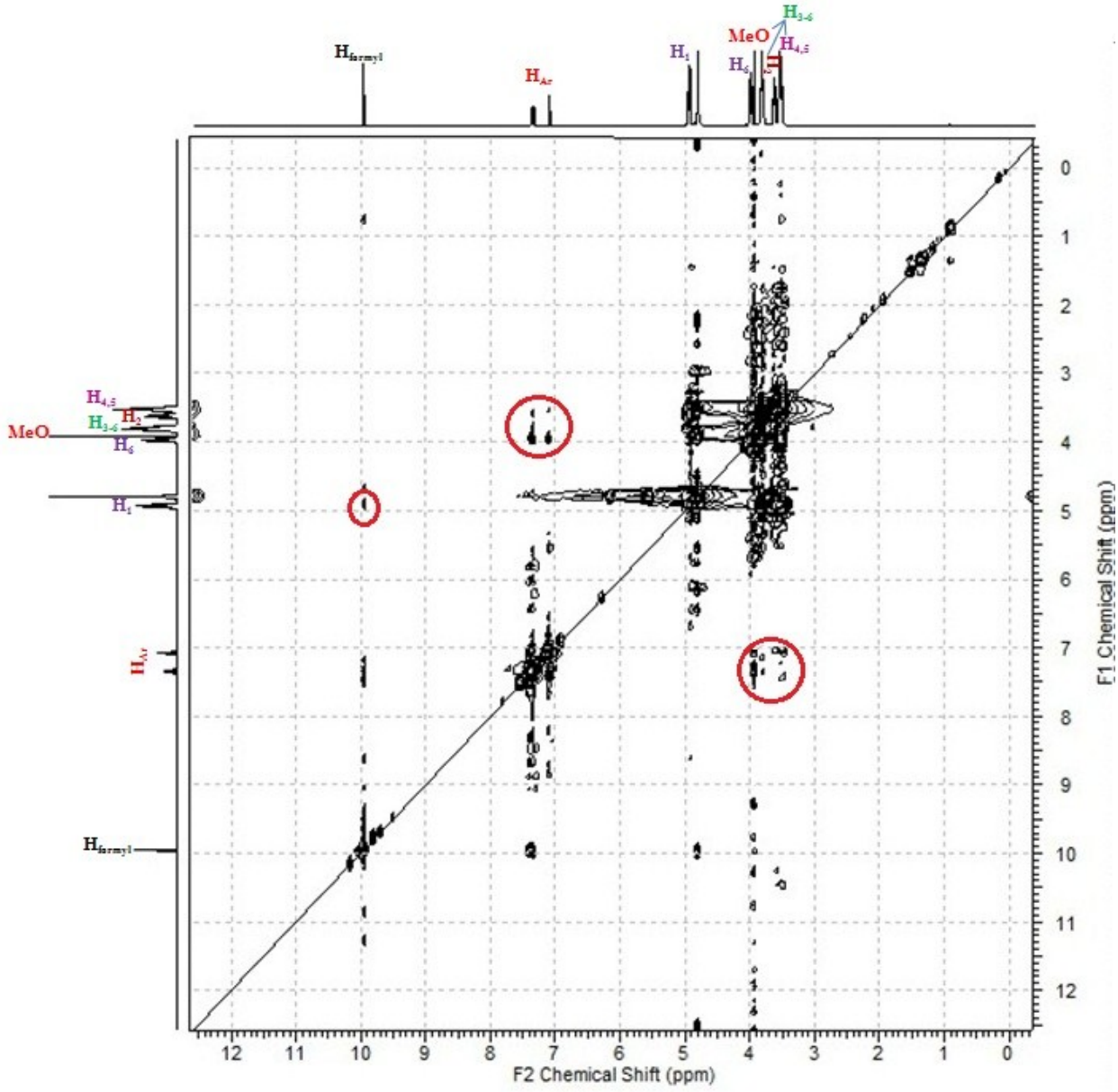
Glucose unit (DP)	Chemical formula	Molar mass (Expectation, g/mol)	m/z (MALDI-TOF)
17	$C_{102}H_{170}O_{85}$	2756.39	2757.5098
18	$C_{108}H_{180}O_{90}$	2918.53	2919.6458
19	$C_{114}H_{190}O_{95}$	3080.67	3080.7755
20	$C_{120}H_{200}O_{100}$	3242.81	3242.9165
21	$C_{126}H_{210}O_{105}$	3404.95	3405.0469
22	$C_{132}H_{220}O_{110}$	3567.09	3568.1624
23	$C138H_{230}O_{115}$	3729.23	3730.3072

3.3 *^{1}H and ^{13}C NMR of cyclosophoraoses (17-23 dp) in D_2O at 25 ^{o}C:*

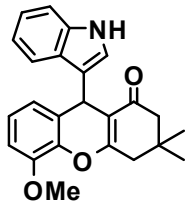
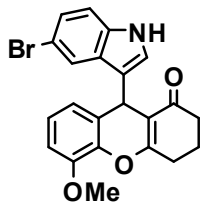
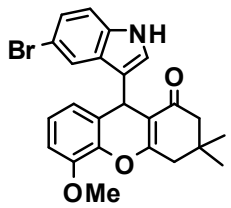


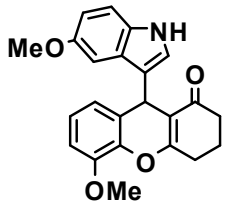
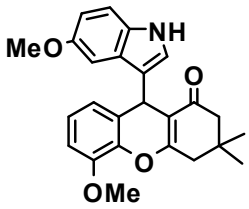


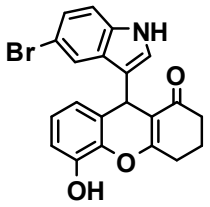
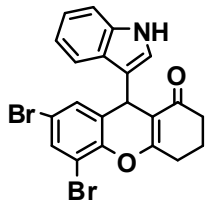
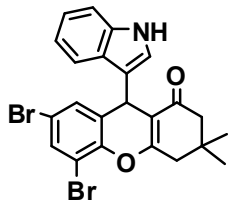
2.4 2D ROESY NMR spectrum of a mixture of 3-methoxysalicylaldehyde and cyclosophoraoses in D_2O (25 °C):

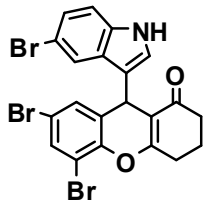
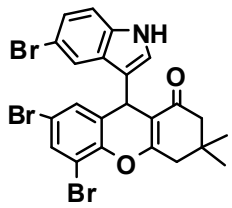
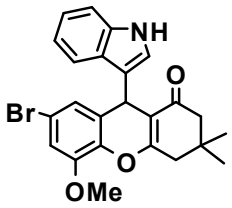


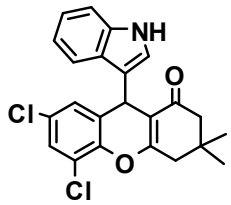
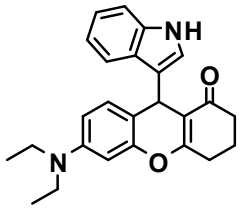
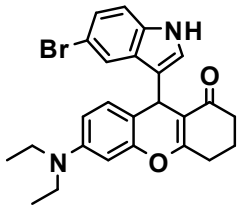
2.5 ^{1}H & ^{13}C NMR spectra of Indolyl 4H-chromenes derivatives (4a-4v).

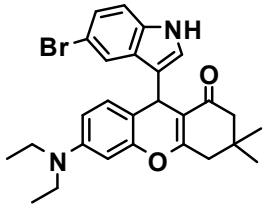
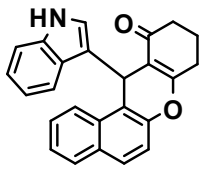
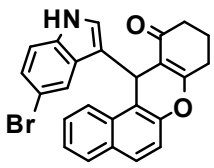
Entry	Spectral data
4a  *9-(1H-indol-3-yl)-5-methoxy-3,3-dimethyl-2,3,4,9-tetrahydro-1H-xanthen-1-one*:	^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 0.93 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 2.20 (q, 2H, J = 16.5 Hz, CH_2), 2.64 (q, 2H, J = 17.1 Hz, CH_2), 3.91 (s, 3H, OCH_3), 5.29 (s, 1H, CH), 6.73 (q, 2H, J = 7.8 Hz, ArH), 6.82 (t, 1H, J = 8.3 Hz, ArH), 6.96 (t, 1H, J = 7.6 Hz, ArH), 7.07-7.03 (m, 2H, ArH), 7.21 (d, 1H, J = 8.3 Hz, ArH), 7.44 (d, 1H, J = 7.8 Hz, ArH), 8.15 (s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C: 27.55, 29.44, 32.06, 41.48, 50.92, 56.04, 109.58, 111.17, 119.04, 119.27, 121.50, 122.39, 124.49, 125.64, 136.51, 147.48, 164.07, 197.33; HRMS m/z (ESI) calcd for $C_{24}H_{23}NO_3$ $[M+H^+]^+$ 373.1678; found 373.1662.
4b  *9-(5-bromo-1H-indol-3-yl)-5-methoxy-2,3,4,9-tetrahydro-1H-xanthen-1-one*	^{1}H NMR (500 MHz, DMSO-d_6) δ_H: 1.85-1.91 (m, 1H, CH_2), 1.97-2.01 (m, 1H, CH_2), 2.23-2.35 (m, 2H, CH_2), 2.67-2.78 (m, 2H, CH_2), 3.83 (s, 3H, OCH_3), 5.18 (s, 1H, CH), 6.85 (dd, 2H, J = 7.1, 2.2 Hz, ArH), 6.96 (t, 1H, J = 7.8 Hz, ArH), 7.11-7.13 (m, 2H, ArH), 7.25 (d, 1H, J = 8.8 Hz, ArH), 7.69 (unresolved doublet, 1H, ArH), 11.04 (s, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C: 20.12, 27.15, 28.04, 36.52, 55.71, 110.12, 111.18, 113.49, 120.71, 123.23, 124.51, 126.48, 127.15, 134.91, 147.32, 166.05, 196.17; HRMS m/z (ESI) calcd for $C_{22}H_{18}BrNO_3$ $[M+H^+]^+$ 423.0470; found 422.8450.
4c  9-(5-bromo-1H-indol-3-yl)-5-methoxy-3,3-dimethyl-2,3,4,9-tetrahydro-1H-	^{1}H NMR (500 MHz, DMSO-d_6) δ_H: 0.93 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 2.17 (q, 2H, J = 15.6 Hz, CH_2), 2.56 (s, 2H, CH_2), 3.83 (s, 3H, OCH_3), 5.15 (s, 1H, CH), 6.79-7.25 (m, 6H, ArH), 7.61 (s, 1H, ArH), 11.04 (s, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C: 26.53, 28.73, 31.62, 40.49, 50.15, 55.73, 110.14, 111.79, 113.43, 119.61, 120.80, 123.17, 124.48, 126.27, 127.02, 134.87, 138.35, 147.29, 164.06, 195.97.

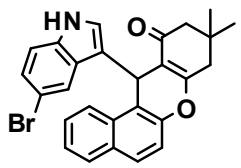
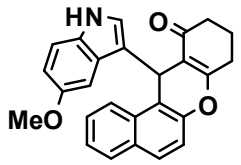
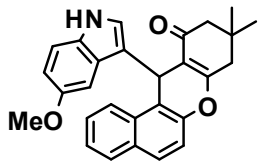
xanthen-1-one	
4d  *5-methoxy-9-(5-methoxy-1H-indol-3-yl)-2,3,4,9-tetrahydro-1H-xanthen-1-one*	^{1}H NMR (500 MHz, DMSO-d$_6$) δ_H: 1.86-1.90 (m, 1H, CH_2), 1.96-2.01 (m, 1H, CH_2), 2.24-2.32 (m, 2H, CH_2), 2.69-2.79 (m, 2H, CH_2), 3.70 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 5.14 (s, 1H, CH), 6.55 (dd, 2H, J = 7.5, 2.4 Hz, ArH), 6.84-6.86 (m, 2H, ArH), 6.93-6.96 (m, 2H, ArH), 7.05 (d, 1H, J = 2.4 Hz, ArH), 7.16 (d, 1H, J = 8.8 Hz, ArH), 10.64 (s, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d$_6$) δ_C: 20.15, 27.13, 28.38, 36.56, 40.01, 55.15, 55.68, 100.45, 109.95, 110.50, 112.03, 120.78, 123.28, 124.35, 125.57, 126.66, 147.26, 152.82, 165.90, 196.16; HRMS m/z (ESI) calcd for $C_{23}H_{21}NO_4$ $[M+H^+]^+$ 423.0470; found 422.8450.
4e  *5-methoxy-9-(5-methoxy-1H-indol-3-yl)-3,3-dimethyl-2,3,4,9-tetrahydro-1H-xanthen-1-one*	^{1}H NMR (500 MHz, DMSO-d$_6$) δ_H: 0.93 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 2.08 (d, 1H, J = 16.1 Hz, CH_2), 2.26 (d, 1H, J = 16.1 Hz, CH_2), 2.63 (s, 2H, CH_2), 3.69 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 5.12 (s, 1H, CH), 6.64 (dd, 1H, J = 2.4, 9.5 Hz, ArH), 6.80 (d, 1H, J = 7.8 Hz, ArH), 6.84-6.89 (m, 3H, ArH), 7.07 (d, 1H, J = 2.4 Hz, ArH), 7.15 (d, 1H, J = 8.8 Hz, ArH), 10.64 (s, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d$_6$) δ_C: 26.75, 28.74, 31.63, 40.49, 50.24, 55.12, 55.71, 100.39, 109.79, 110.59, 112.03, 119.28, 120.86, 123.18, 124.35, 125.48, 131.50, 138.54, 147.28, 152.74, 163.90, 195.98; HRMS m/z (ESI) calcd for $C_{25}H_{25}NO_4$ $[M+H^+]^+$ 403.1784; found 403.0254
4f  *7-hydroxy-9-(1H-indol-3-yl)-3,3-dimethyl-2,3,4,9-tetrahydro-1H-xanthen-1-*	^{1}H NMR (500 MHz, DMSO-d$_6$) δ_H: 0.90 (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 2.05 (d, 1H, J = 16.1 Hz, CH_2), 2.23 (d, 1H, J = 16.1 Hz, CH_2), 2.54-2.62 (m, 2H, CH_2), 5.08 (s, 1H, CH), 6.53-6.57 (m, 2H, ArH), 6.88 (t, 1H, J = 7.1 Hz, ArH), 6.95-7.00 (m, 2H, ArH), 7.13 (d, 1H, J = 2.4 Hz, ArH), 7.27 (d, 1H, J = 8.3 Hz, ArH), 7.38 (d, 1H, J = 7.8, ArH) 9.18 (s, 1H, OH), 10.78 (s, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d$_6$) δ_C: 26.69, 28.79, 31.55, 40.56, 50.27, 111.45, 114.34, 115.08, 116.81, 118.30, 120.65, 122.52, 126.43, 136.33, 141.89, 153.92, 164.21, 195.88.

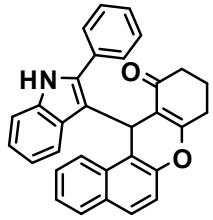
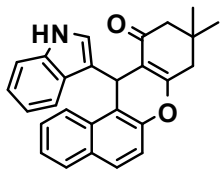
one	
4g  *9-(5-bromo-1H-indol-3-yl)-5-hydroxy-2,3,4,9-tetrahydro-1H-xanthen-1-one*	^{1}H NMR (500 MHz, DMSO-d$_6$) δ_H: 1.86-1.91 (m, 1H, CH_2), 1.97-2.01 (m, 1H, CH_2), 2.23-2.36 (m, 2H, CH_2), 2.66-2.79 (m, 2H, CH_2), 5.15 (s, 1H, CH), 6.67-6.72 (m, 2H, ArH), 6.82 (t, 1H, J = 7.8 Hz, ArH), 7.11-7.13 (m, 2H, ArH), 7.25 (d, 1H, J = 8.8 Hz, ArH), 7.67 (unresolved doublet, 1H, ArH), 9.70 (s, 1H, OH), 11.03 (s, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d$_6$) δ_C: 20.18, 27.18, 28.18, 36.56, 111.26, 113.45, 114.05, 119.14, 120.73, 123.17, 124.42, 126.63, 127.18, 134.93, 145.20, 166.18, 196.16; HRMS m/z (ESI) calcd for $C_{21}H_{16}BrNO_3$ $[M+H^+]^+$ 409.0314; found 409.0022.
4h  *5,7-dibromo-9-(1H-indol-3-yl)-2,3,4,9-tetrahydro-1H-xanthen-1-one*	^{1}H NMR (500 MHz, DMSO-d$_6$) δ_H: 1.88-1.95 (m, 1H, CH_2), 1.97-2.04 (m, 1H, CH_2), 2.24-2.37 (m, 2H, CH_2), 2.69-2.75 (m, 1H, CH_2), 2.61-2.89 (m, 1H, CH_2) 5.28 (s, 1H, CH), 6.96 (t, 1H, J = 7.9 Hz, ArH), 7.003 (t, 1H, J = 7.9 Hz, ArH), 7.19 (d, 1H, J = 2.2 Hz, ArH), 7.30 (d, 1H, J = 8.0 Hz, ArH), 7.49 (d, 1H, J = 8.0 Hz, ArH), 7.52 (d, 1H, J = 1.7 Hz, ArH), 7.71 (d, 1H, J = 2.2 Hz, ArH), 10.93 (s, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d$_6$) δ_C: 20.03, 26.87, 28.77, 36.47, 40.00,110.83, 111.71, 113.27, 116.16, 118.00, 118.79, 120.96, 123.20, 124.99, 129.86, 131.50, 132.70, 136.39, 145.23, 165.64, 195.95.
4i  *5,7-dibromo-9-(1H-indol-3-yl)-3,3-dimethyl-2,3,4,9-tetrahydro-1H-xanthen-1-one*	^{1}H NMR (500 MHz, DMSO-d$_6$) δ_H: 0.93 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 2.10 (d, 1H, J = 16.1 Hz, CH_2), 2.28 (d, 1H, J = 16.1 Hz, CH_2), 2.69-2.75 (m, 2H, CH_2), 5.26 (s, 1H, CH), 6.94 (t, 1H, J = 7.5 Hz, ArH), 7.02 (t, 1H, J = 7.5 Hz, ArH), 7.21 (d, 1H, J = 2.4 Hz, ArH), 7.30 (d, 1H, J = 8.3 Hz, ArH), 7.43 (d, 1H, J = 8.3, ArH), 7.44 (d, 1H, J = 1.9 Hz, ArH), 7.71 (d, 1H J = 2.4 Hz, ArH), 10.93 (s, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d$_6$) δ_C: 26.62, 28.57, 28.86, 31.65, 40.08, 50.11, 110.82, 111.68, 112.13, 116.13, 117.91, 118.68, 120.93, 123.08,

	124.87, 129.70, 131.56, 132.69, 136.31, 145.25, 163.56, 195.74.
4j  *5,7-dibromo-9-(5-bromo-1H-indol-3-yl)-2,3,4,9-tetrahydro-1H-xanthen-1-one*	^{1}H NMR (500 MHz, DMSO-d$_6$) δ_H: 1.90-1.95 (m, 1H, CH_2), 1.99-2.04 (m, 1H, CH_2), 2.26-2.38 (m, 2H, CH_2), 2.71-2.84 (m, 2H, CH_2), 5.29 (s, 1H, CH), 7.14-7.18 (m, 2H, ArH), 7.28 (d, 1H, J = 8.8 Hz, ArH), 7.55 (d, 1H, J = 2.4 Hz, ArH), 7.73 (d, 1H, J = 1.9 Hz, ArH), 7.80 (d, 1H, J = 1.45 Hz, ArH), 11.15 (s, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d$_6$) δ_C: 19.98, 26.85, 28.25, 36.40, 40.01, 110.88, 111.45, 113.61, 116.22, 118.22, 120.61, 123.47, 124.94, 126.67, 129.65, 131.46, 132.80, 134.88, 145.27, 165.69, 195.91.
4k  *5,7-dibromo-9-(5-bromo-1H-indol-3-yl)-3,3-dimethyl-2,3,4,9-tetrahydro-1H-xanthen-1-one*	^{1}H NMR (500 MHz, DMSO-d$_6$) δ_H: 0.94 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 2.12 (d, 1H, J = 16.4 Hz, CH_2), 2.30 (d, 1H, J = 16.0 Hz, CH_2), 2.67 (d, 2H, J = 3.5 Hz, CH_2), 5.28 (s, 1H, CH), 7.14-7.16 (m, 1H, ArH), 7.22 (d, 1H, J = 2.2 Hz, ArH), 7.27 (d, 1H, J = 8.4 Hz, ArH), 7.50 (d, 1H, J = 1.8 Hz, ArH), 7.70 (d, 1H J = 1.7 Hz, ArH), 7.73 (d, 1H, J = 2.2, ArH), 11.65 (s, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d$_6$) δ_C: 26.49, 28.64, 31.72, 40.14, 50.06, 110.96, 111.64, 112.26, 113.66, 116.31, 118.81, 120.61, 123.49, 124.87, 126.79, 129.49, 131.62, 132.89, 134.87, 145.25, 163.73, 195.80.
4l  *7-bromo-9-(1H-indol-3-yl)-5-methoxy-3,3-dimethyl-2,3,4,9-tetrahydro-1H-xanthen-1-one*	^{1}H NMR (500 MHz, DMSO-d$_6$) δ_H: 0.91 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 2.07 (d, 1H, J = 16.1 Hz, CH_2), 2.25 (d, 1H, J = 16.1 Hz, CH_2), 2.73 (br s, 2H, CH_2), 3.07 (s, 3H, OMe), 5.16 (s, 1H, CH), 6.91 (t, 1H, J = 7.3 Hz, ArH), 6.96 (d, 1H, J = 2.5 Hz, ArH), 6.99-7.04 (m, 2H, ArH), 7.19 (d, 1H, J = 2.4 Hz, ArH), 7.29 (d, 1H, J = 8.3, ArH), 7.40 (d, 1H, J = 8.3 Hz, ArH), 10.87 (s, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d$_6$) δ_C: 26.68, 28.66, 28.86, 31.62, 40.33, 50.18, 56.19, 111.60, 113.09, 115.79, 118.10, 118.53, 120.81, 122.91, 123.11, 125.05, 128.32, 136.33, 137.73, 148.24, 163.63, 195.85.

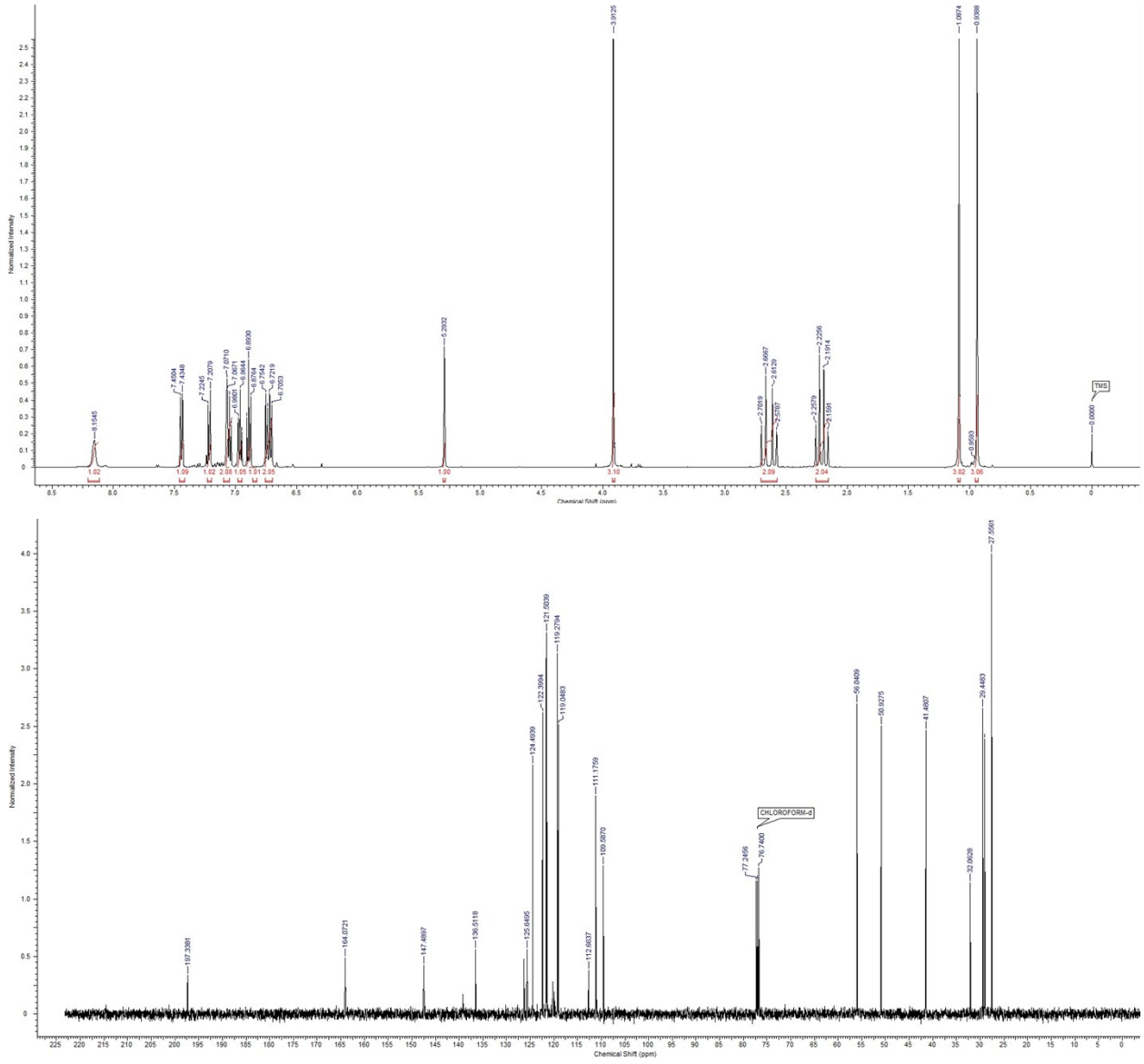
4m  *5,7-dichloro-9-(1H-indol-3-yl)-3,3-dimethyl-2,3,4,9-tetrahydro-1H-xanthen-1-one*	^{1}H NMR (500 MHz, DMSO-d$_6$) δ_H: 0.94 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 2.11 (d, 1H, J = 16.2 Hz, CH_2), 2.29 (d, 1H, J = 16.3 Hz, CH_2), 2.69 (d, 2H, J = 4.8 Hz, CH_2), 5.26 (s, 1H, CH), 6.93 (t, 1H, J = 7.9 Hz, ArH), 7.02 (t, 1H, J = 7.9 Hz, ArH), 7.21 (d, 1H, J = 2.6 Hz, ArH), 7.29-7.32 (m, 2H, ArH), 7.44 (d, 1H, J = 8.3 Hz, ArH), 7.51 (d, 1H, J = 2.2, ArH), 10.93 (s, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d$_6$) δ_C: 26.68, 28.63, 28.79, 31.70, 40.10, 50.15, 111.73, 112.00, 117.95, 118.53, 118.73, 120.99, 121.4542, 123.14, 124.90, 127.40, 128.14, 129.45, 136.36, 143.84, 163.54, 195.87; HRMS m/z (ESI) calcd for $C_{23}H_{19}Cl_2NO_2$ $[M+H^+]^+$ 411.0793; found 410.8457.
4n  *6-(diethylamino)-9-(1H-indol-3-yl)-2,3,4,9-tetrahydro-1H-xanthen-1-one*	^{1}H NMR (500 MHz, DMSO-d$_6$) δ_H: 1.01 (t, 6H, J = 6.8 Hz, 2CH_3), 1.81-1.88 (m, 1H, CH_2), 1.94-1.98 (m, 1H, CH_2), 2.19-2.32 (m, 2H, CH_2), 2.63-2.76 (m, 2H, CH_2), 3.20-3.28 (m, 4H, 2CH_2), 5.04 (s, 1H, CH), 6.32-6.35 (m, 2H, ArH), 6.88 (t, 1H, J = 7.0 Hz, ArH), 6.96-7.00 (m, 2H, ArH), 7.08 (d, 1H, J = 2.4 Hz, ArH), 7.26 (d, 1H, J = 8.3 Hz, ArH), 7.43 (d, 1H, J = 7.8 Hz, ArH), 10.73 (s, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d$_6$) δ_C: 12.28, 20.15, 27.24, 27.72, 36.63, 43.59, 98.02, 108.75, 111.37, 113.62, 118.43, 120.50, 122.26, 125.42, 129.90, 136.43, 146.87, 149.88, 166.10, 196.11; HRMS m/z (ESI) calcd for $C_{25}H_{26}N2O_2$ $[M+H^+]^+$ 386.1994; found 386.0568.
4o  *9-(5-bromo-1H-indol-3-yl)-6-(diethylamino)-2,3,4,9-tetrahydro-1H-xanthen-1-one*	^{1}H NMR (500 MHz, DMSO-d$_6$) δ_H: 1.02 (t, 6H, J = 7.07 Hz, 2CH_3), 1.83-1.66 (m, 1H, CH_2), 1.95-1.99 (m, 1H, CH_2), 2.22-2.33 (m, 2H, CH_2), 2.67-2.76 (m, 2H, CH_2), 3.23-3.26 (m, 4H, 2CH_2), 5.04 (s, 1H, CH), 6.35-6.38 (m, 2H, ArH), 6.98 (d, 1H, J = 8.8 Hz, ArH), 7.09-7.12 (m, 2H, ArH), 7.25 (d, 1H, J = 8.3 Hz, ArH), 7.59 (unresolved doublet, 1H, ArH), 10.98 (s, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d$_6$) δ_C: 12.25, 20.13, 27.23, 27.39, 36.57, 43.61, 98.01, 108.93, 108.93, 110.98, 111.68, 113.36, 113.63, 120.38, 120.81, 122.99, 124.15, 127.27,

	129.91, 134.94, 146.99, 149.89, 166.16, 196.14.
4p  *9-(5-bromo-1H-indol-3-yl)-6-(diethylamino)-3,3-dimethyl-2,3,4,9-tetrahydro-1H-xanthen-1-one*	^{1}H NMR (500 MHz, DMSO-d$_6$) δ_H: 0.9192 (s, 3H, CH_3), 1.01-1.04 (m, 9H, 3CH_3), 2.05 (d, 1H, J = 5.6 Hz, CH_2), 2.25 (d, 1H, J = 16.5 Hz, CH_2), 2.58 (q, 2H, CH_2), 3.24-3.28 (m, 4H, 2CH_2), 5.00 (s, 1H, CH), 6.34-6.37 (m, 2H, ArH), 6.94 (d, 1H, J = 8.8 Hz, ArH), 7.09 (dd, 2H, J = 1.7, 8.8 Hz, ArH), 7.15 (d, 1H, J = 2.4 Hz, ArH), 7.24 (d, 1H, J = 8.8 Hz, ArH), 7.53 (d, 1H, J = 1.9 Hz, ArH), 10.97 (s, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d$_6$) δ_C: 12.29, 26.59, 27.50, 28.74, 31.56, 40.63, 43.61, 50.22, 97.96, 108.93, 110.92, 111.53, 113.37, 120.28, 120.89, 122.98, 124.06, 127.15, 130.04, 134.95, 146.99, 149.88, 164.22, 196.00.
4q  *12-(1H-indol-3-yl)-9,10-dihydro-8H-benzo[a]xanthen-11(12H)-one*	^{1}H NMR (500 MHz, DMSO-d$_6$) δ_H: 1.71-1.79 (m, 1H, CH_2), 1.91-1.98 (m, 1H, CH_2), 2.23-2.37 (m, 2H, CH_2), 2.67-2.77 (m, 2H, CH_2), 5.89 (s, 1H, CH), 6.85 (t, 1H, J = 7.5 Hz, ArH), 6.93 (t, 1H, J = 7.8 Hz, ArH), 7.23 (d, 1H, J = 7.8 Hz, ArH), 7.30 (d, 1H, J = 2.4 Hz, ArH), 7.37 (t, 2H, J = 7.0 Hz, ArH), 7.41-7.46 (m, 2H, ArH), 7.84 (d, 2H, J = 8.8 Hz, ArH), 8.17 (d, 1H, J = 8.3 Hz, ArH), 10.84 (s, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d$_6$) δ_C: 20.03, 25.77, 26.84, 36.53, 110.92, 111.51, 116.90, 118.20, 118.49, 120.50, 123.27, 124.11, 124.67, 126.74, 128.56, 130.98, 136.11, 147.02, 165.07, 196.21.
4r  *12-(5-bromo-1H-indol-3-yl)-9,10-dihydro-8H-benzo[a]xanthen-11(12H)-one*	^{1}H NMR (500 MHz, DMSO-d$_6$) δ_H: 1.74-1.80 (m, 1H, CH_2), 1.93-1.97 (m, 1H, CH_2), 2.26-2.38 (m, 2H, CH_2), 2.70-2.73 (m, 2H, CH_2), 5.86 (s, 1H, CH), 7.07 (dd, 1H, J = 1.7, 8.5 Hz, ArH), 7.21-7.25 (m, 2H, ArH), 7.35-7.44 (m, 2H, ArH), 7.47 (d, 1H, J = 8.8 Hz, ArH), 7.62 (d, 1H, J = 1.4 Hz, ArH), 7.87 (d, 2H, J = 8.3 Hz, ArH), 8.06 (d, 1H, J = 8.3 Hz, ArH), 11.07 (s, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d$_6$) δ_C: 19.98, 25.42, 26.84, 36.44, 111.24, 113.48, 113.92, 116.81, 118.16, 120.77, 123.05, 124.77, 125.81, 126.88, 127.188, 128.40, 128.77,

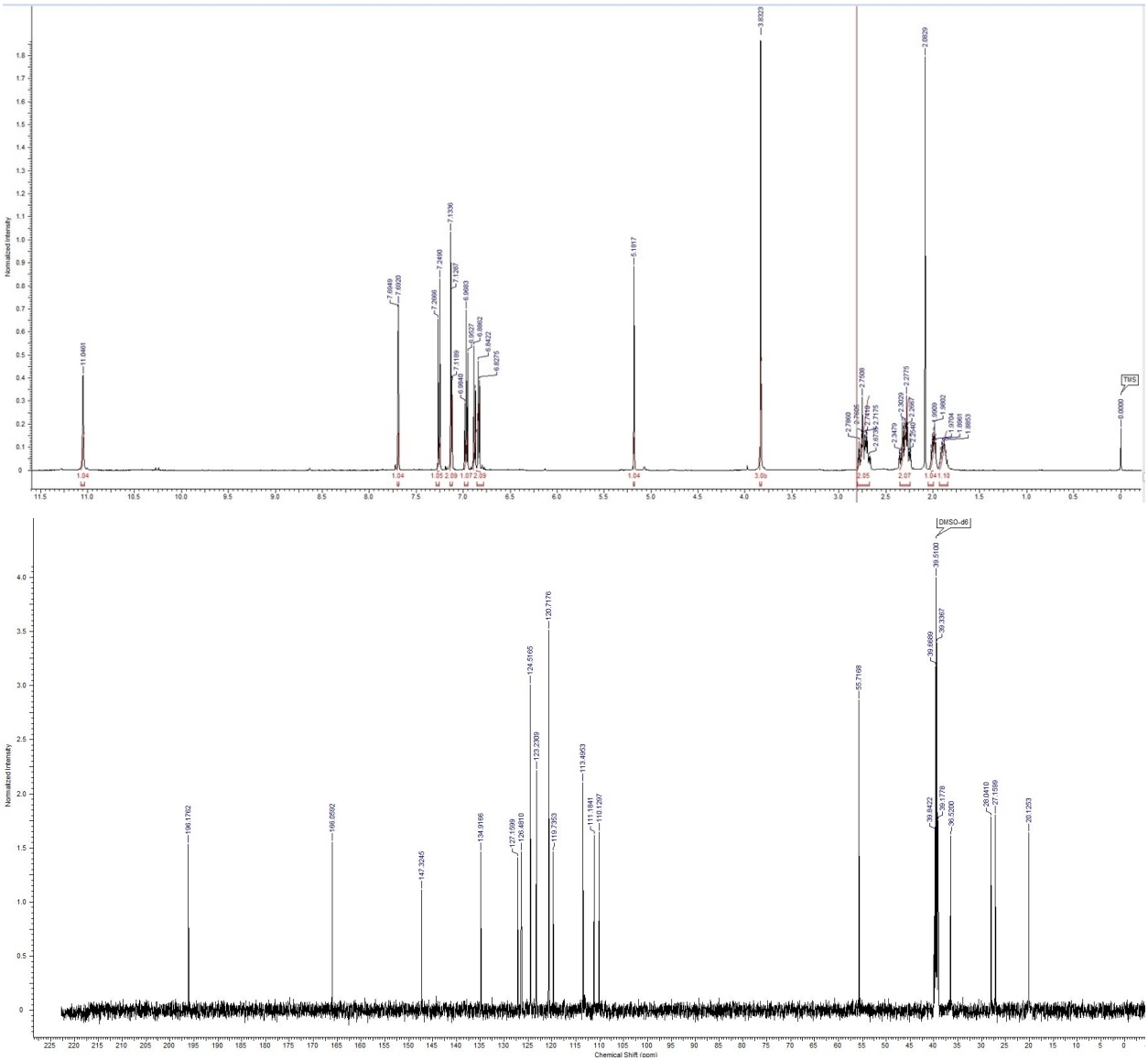
	130.87, 165.20, 196.26; HRMS m/z (ESI) calcd for $C_{25}H_{18}BrNO_2$ $[M+H^+]^+$ 443.0521; found 442.884.
4s  *12-(5-bromo-1H-indol-3-yl)-9,9-dimethyl-9,10-dihydro-8H-benzo[a]xanthen-11(12H)-one*	^{1}H NMR (500 MHz, DMSO-d_6) δ_H: 0.81 (s, 3H, CH_3), 1.04 (S, 3H, CH_3), 2.10 (d, 1H, J = 16.1 Hz, CH_2), 2.30 (d, 1H, J = 16.1 Hz, CH_2), 2.62 (q, 2H, CH_2), 5.83 (s, 1H, CH), 7.06 (dd, 1H, J = 1.9, 8.8 Hz, ArH), 7.20 (d, 1H J = 10.3 Hz, ArH), 7.34-7.48 (m, 3H, ArH), 7.57 (unresolved doublet, 1H, ArH), 7.86-7.88 (m, 3H, ArH), 8.14 (d, 1H, J = 8.8 Hz, ArH), 11.08 (s, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C: 25.55, 26.24, 28.70, 31.72, 40.23, 50.14, 111.15, 112.48, 113.46, 116.88, 117.81, 120.74, 122.98, 124.77, 126.85, 128.79, 130.90, 134.69, 146.96, 163.27, 196.01.
4t  *12-(5-methoxy-1H-indol-3-yl)-9,10-dihydro-8H-benzo[a]xanthen-11(12H)-one*	^{1}H NMR (500 MHz, DMSO-d_6) δ_H: 1.73-1.82 (m, 1H, CH_2), 1.92-1.99 (m, 1H, CH_2), 2.25-2.38 (m, 2H, CH_2), 2.68-2.78 (m, 2H, CH_2), 3.65 (s, 3H, OCH_3), 5.85 (s, 1H, CH), 6.60 (dd, 1H, J = 2.4, 8.3 Hz, ArH), 6.84 (d, 1H, J = 2.4 Hz, ArH), 7.11 (d, 1H, J = 8.8 Hz, ArH), 7.24 (d, 1H, J = 2.4 Hz, ArH), 7.36 (t, 1H, J = 7.1 Hz, ArH), 7.42-7.46 (m, 2H, ArH), 7.85 (d, 2H, J = 8.3 Hz, ArH), 8.16 (d, 1H, J = 8.3 Hz, ArH), 10.67 (s, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C: 20.05, 25.71, 36.53, 54.99, 100.37, 110.30, 112.03, 113.75, 116.74, 117.20, 123.31, 124.68, 126.75, 128.57, 131.01, 131.30, 141.12, 152.77, 165.10, 196.26.
4u  *12-(5-methoxy-1H-indol-3-yl)-9,9-dimethyl-9,10-dihydro-8H-benzo[a]xanthen-11(12H)-one*	^{1}H NMR (500 MHz, DMSO-d_6) δ_H: 0.82 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 2.09 (d, 1H, J = 16.1 Hz, CH_2), 2.30 (d, 1H, J = 16.1 Hz, CH_2), 2.65 (q, 2H, CH_2), 5.82 (s, 1H, CH), 6.58 (dd, 1H, J = 2.4, 8.8 Hz, ArH), 6.81 (s, 1H, ArH), 7.09 (d, 1H, J = 8.8 Hz, ArH), 7.31 (d, 1H, J = 2.4 Hz, ArH), 7.36 (t, 1H, J = 7.3 Hz, ArH), 7.43-7.46 (m, 2H, ArH), 7.85 (d, 2H, J = 8.8 Hz, ArH), 8.22 (d, 1H, J = 8.8 Hz, ArH), 10.67 (s, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C: 25.84, 26.45, 28.79, 31.73, 40.21,

	50.22, 54.99, 100.22, 110.38, 112.03, 112.32, 116.80, 117.29, 123.40, 124.68, 125.20, 128.37, 128.57, 131.27, 147.00, 152.66, 163.17, 196.03.
4v  *12-(2-phenyl-1H-indol-3-yl)-9,10-dihydro-8H-benzo[a]xanthen-11(12H)-one*	^{1}H NMR (500 MHz, DMSO-d$_6$) δ_H: 0.91 (s, 3H, CH_3), 1.10 (s, 3H, CH_3), 2.18 (d, 1H, J = 16.1 Hz, CH_2), 2.42 (d, 1H, J = 16.1 Hz, CH_2), 2.75 (q, 2H, CH_2), 5.93 (s, 1H, CH), 6.80-6.86 (M, 2H, ArH), 6.94 (t, 2H, J = 7.5 Hz, ArH), 7.11 (d, 1H, J = 7.8 Hz, ArH), 7.22 (d, 2H, J = 7.8 Hz, ArH), 7.36 (d, 2H, J = 8.8 Hz, ArH), 7.58 (t, 1H, J = 7.3 Hz, ArH), 7.69-7.74 (m, 5H, ArH), 11.22 (s, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d$_6$) δ_C: 25.87, 26.48, 28.93, 31.59, 40.59, 50.53, 112.35, 111.55, 116.96, 117.13, 118.16, 118.73, 120.97, 123.60, 124.50, 125.88, 126.46, 128.08, 128.37, 128.50, 128.74, 129.45, 130.81, 133.91, 135.86, 146.21, 164.58, 197.40.
4w  *12-(1H-indol-3-yl)-9,9-dimethyl-9,10-dihydro-8H-benzo[a]xanthen-11(12H)-one*	^{1}H NMR (500 MHz, DMSO-d$_6$) δ_H: 0.80 (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 2.08 (d, 1H, J = 16.1 Hz, CH_2), 2.29 (d, 1H, J = 16.1 Hz, CH_2), 2.62 (q, 2H, CH_2), 5.86 (s, 1H, CH), 6.83 (t, 2H, J = 7.0 Hz, ArH), 6.92 (t, 1H, J = 7.0 Hz, ArH), 7.21 (d, 2H, J = 7.8 Hz, ArH), 7.35-7.37 (m, 3H, ArH), 7.44 (d, 2H, J = 9.1 Hz, ArH), 7.84 (d, 1H, J = 8.7 Hz, ArH), 8.21 (d, 1H, J = 8.7 Hz, ArH), 10.84 (s, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d$_6$) δ_C: 26.37, 28.80, 31.75, 40.21, 50.24, 111.53, 112.51, 116.99, 118.21, 118.40, 120.50, 123.38, 124.14, 124.70, 125.32, 126.75, 128.40, 131.03, 163.18, 196.03.

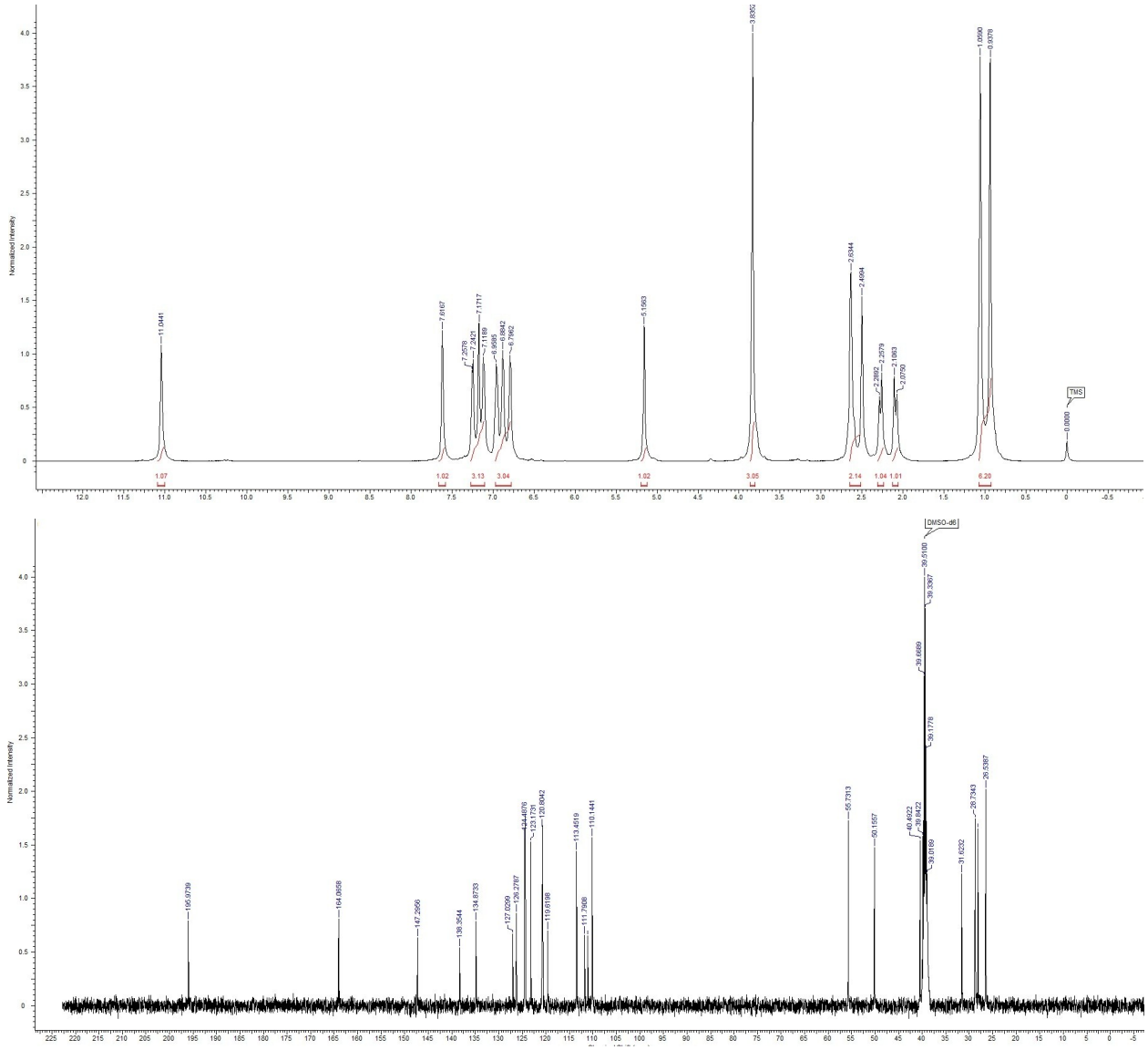
[1]H and [13]C NMR of H9-(1H-indol-3-yl)-5-methoxy-3,3-dimethyl-2,3,4,9-tetrahydro-1H-xanthen-1-one (**4a**):



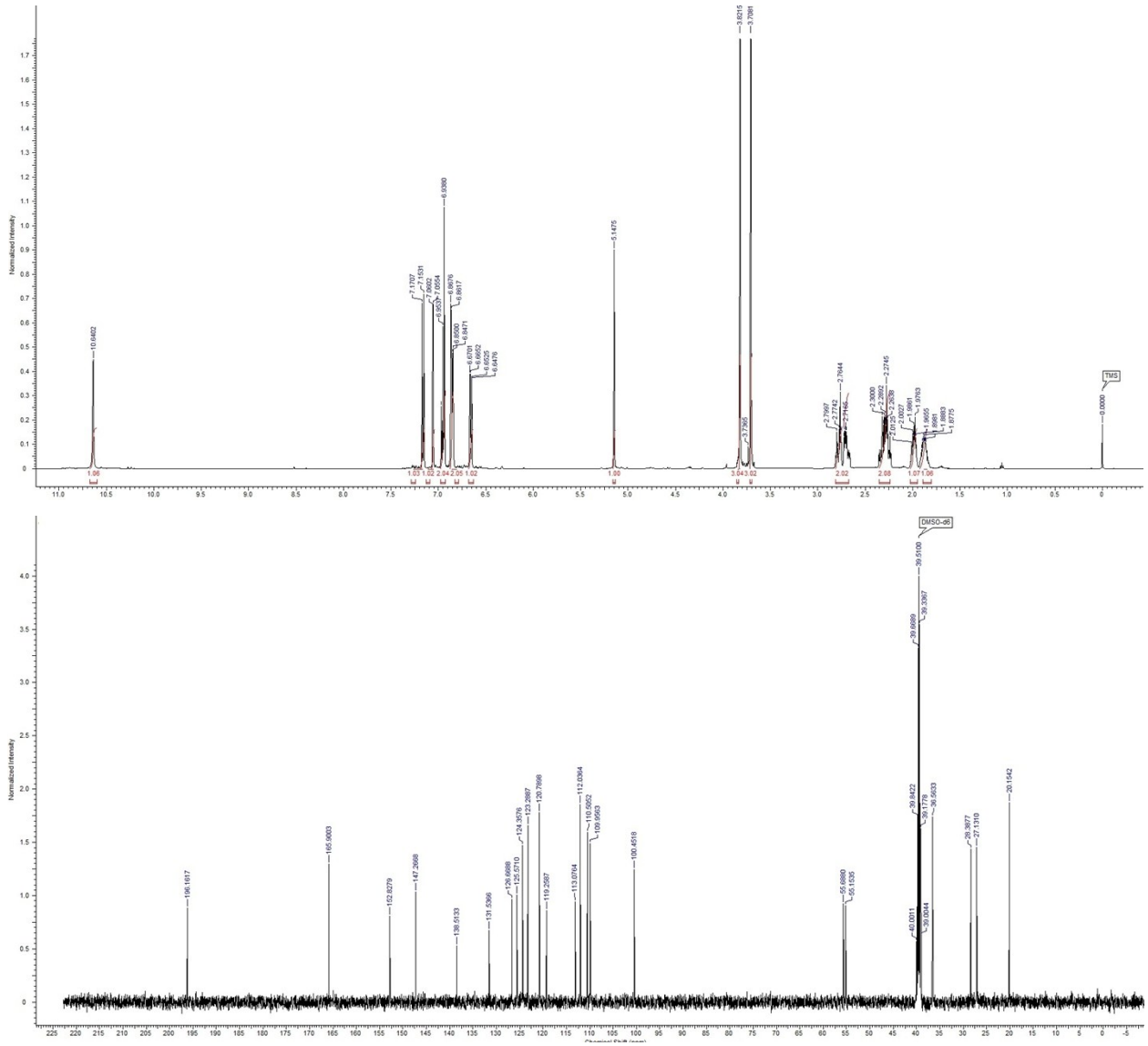
[1]H and [13]C NMR of 9-(5-bromo-1H-indol-3-yl)-5-methoxy-2,3,4,9-tetrahydro-1H-xanthen-1-one (**4b**):



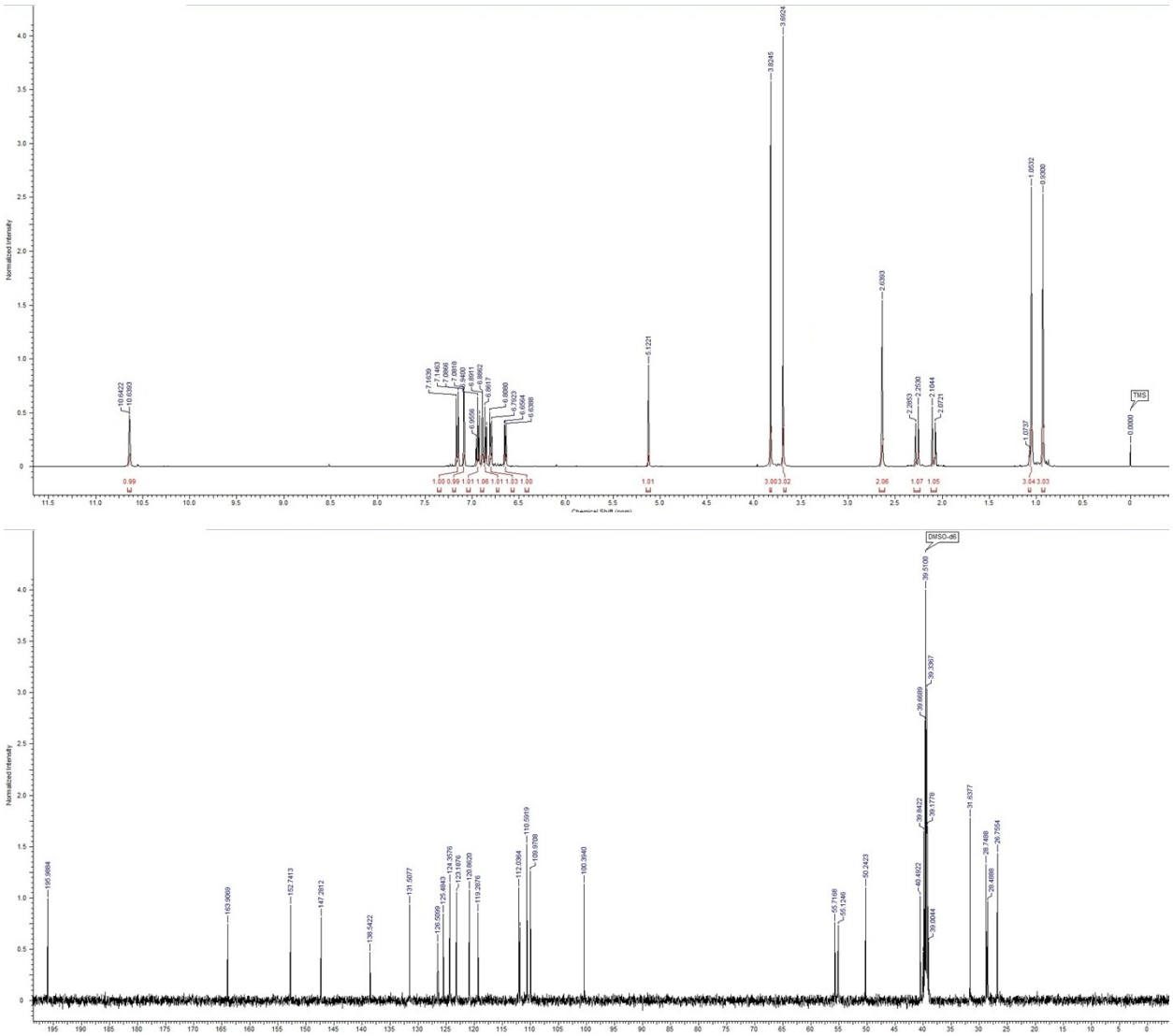
^{1}H and ^{13}C NMR of 9-(5-bromo-1H-indol-3-yl)-5-methoxy-3,3-dimethyl-2,3,4,9-tetrahydro-1H-xanthen-1-one (**4c**):



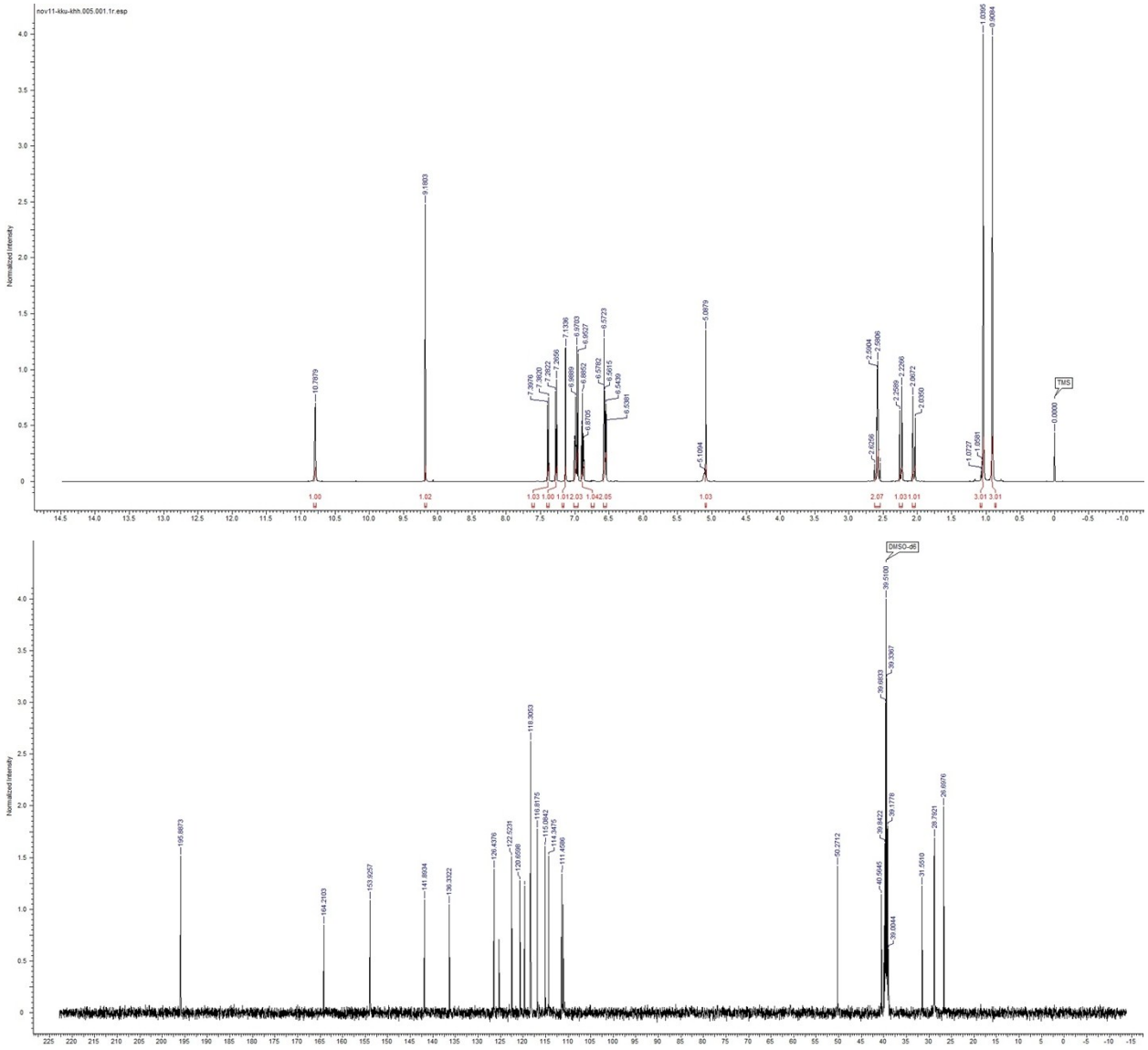
[1]H and [13]C NMR of 5-methoxy-9-(5-methoxy-1H-indol-3-yl)-2,3,4,9-tetrahydro-1H-xanthen-1-one (**4d**):



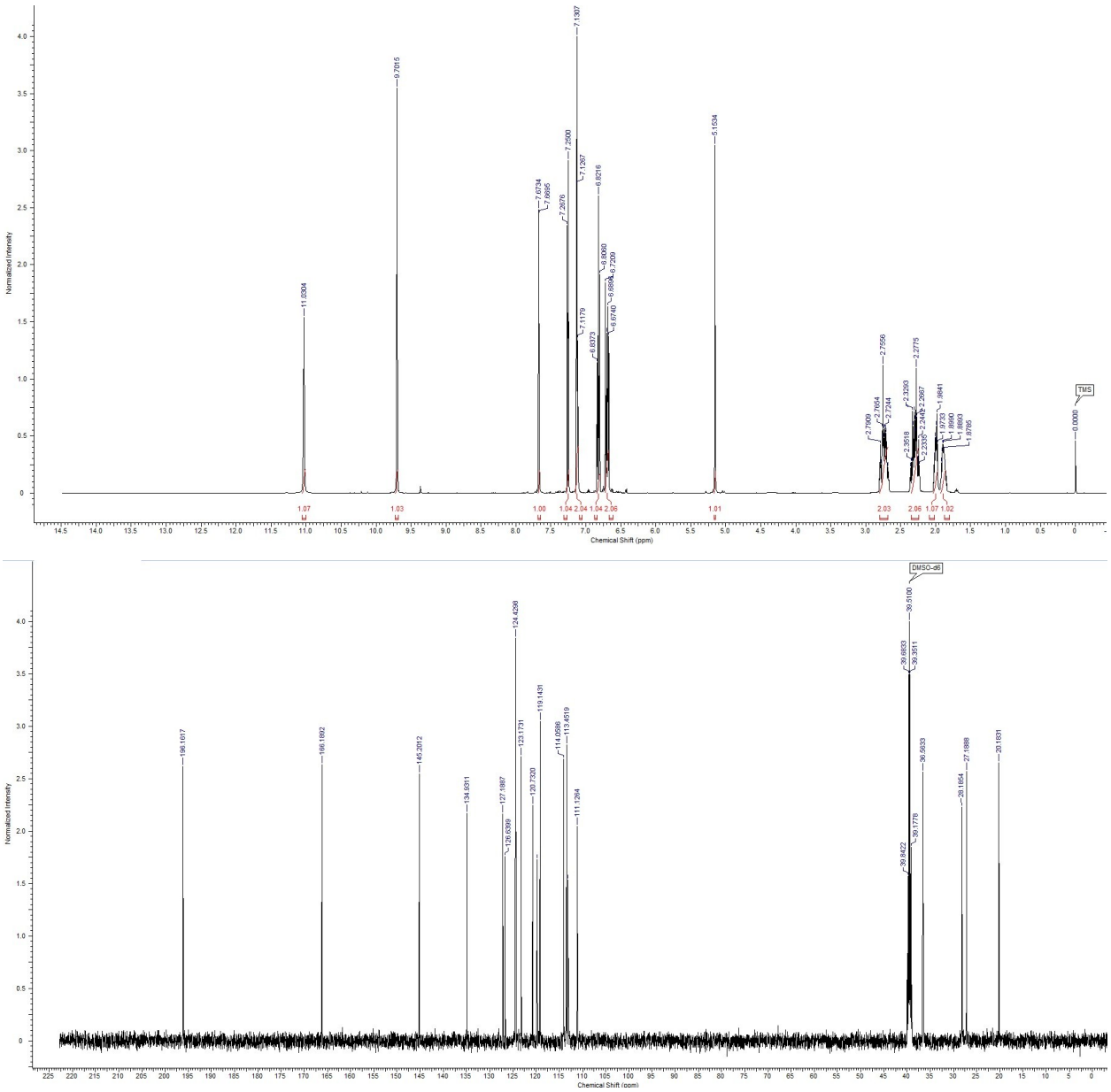
[1]H and [13]C NMR of 5-methoxy-9-(5-methoxy-1H-indol-3-yl)-3,3-dimethyl-2,3,4,9-tetrahydro-1H-xanthen-1-one (**4e**):



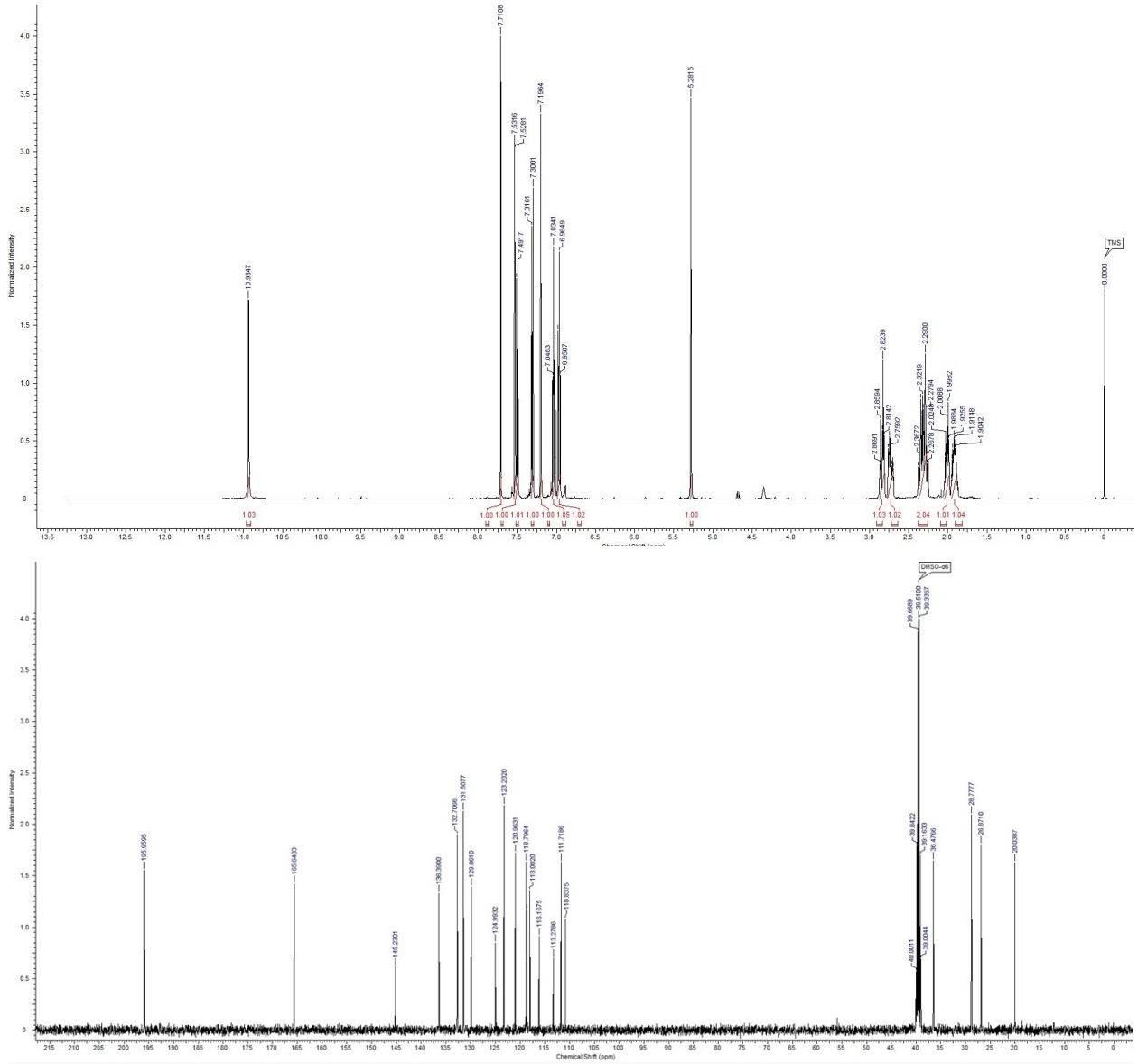
[1]H and [13]C NMR of 7-hydroxy-9-(1H-indol-3-yl)-3,3-dimethyl-2,3,4,9-tetrahydro-1H-xanthen-1-one (**4f**):



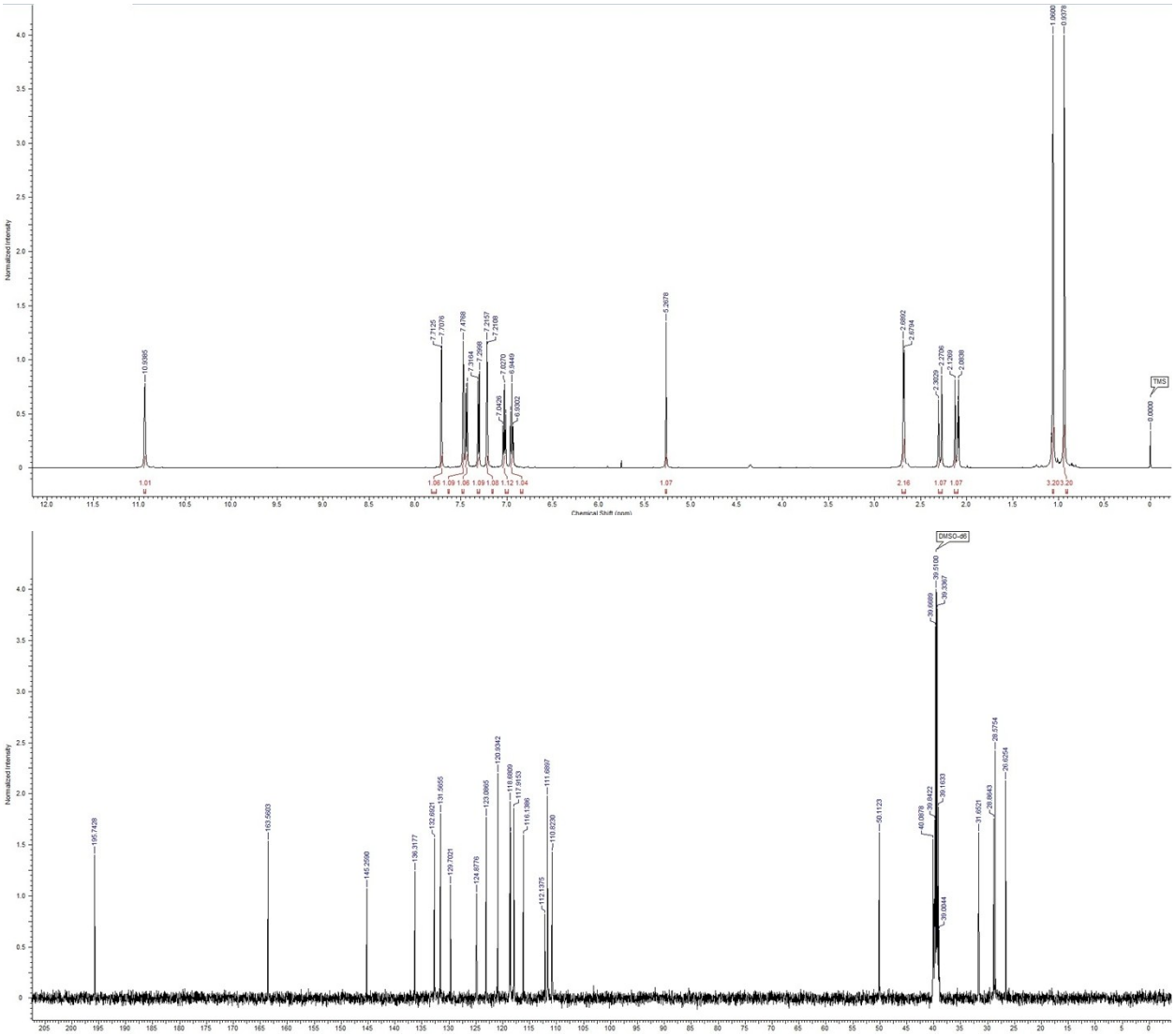
[1]H and [13]C NMR of 9-(5-bromo-1H-indol-3-yl)-5-hydroxy-2,3,4,9-tetrahydro-1H-xanthen-1-one (**4g**):



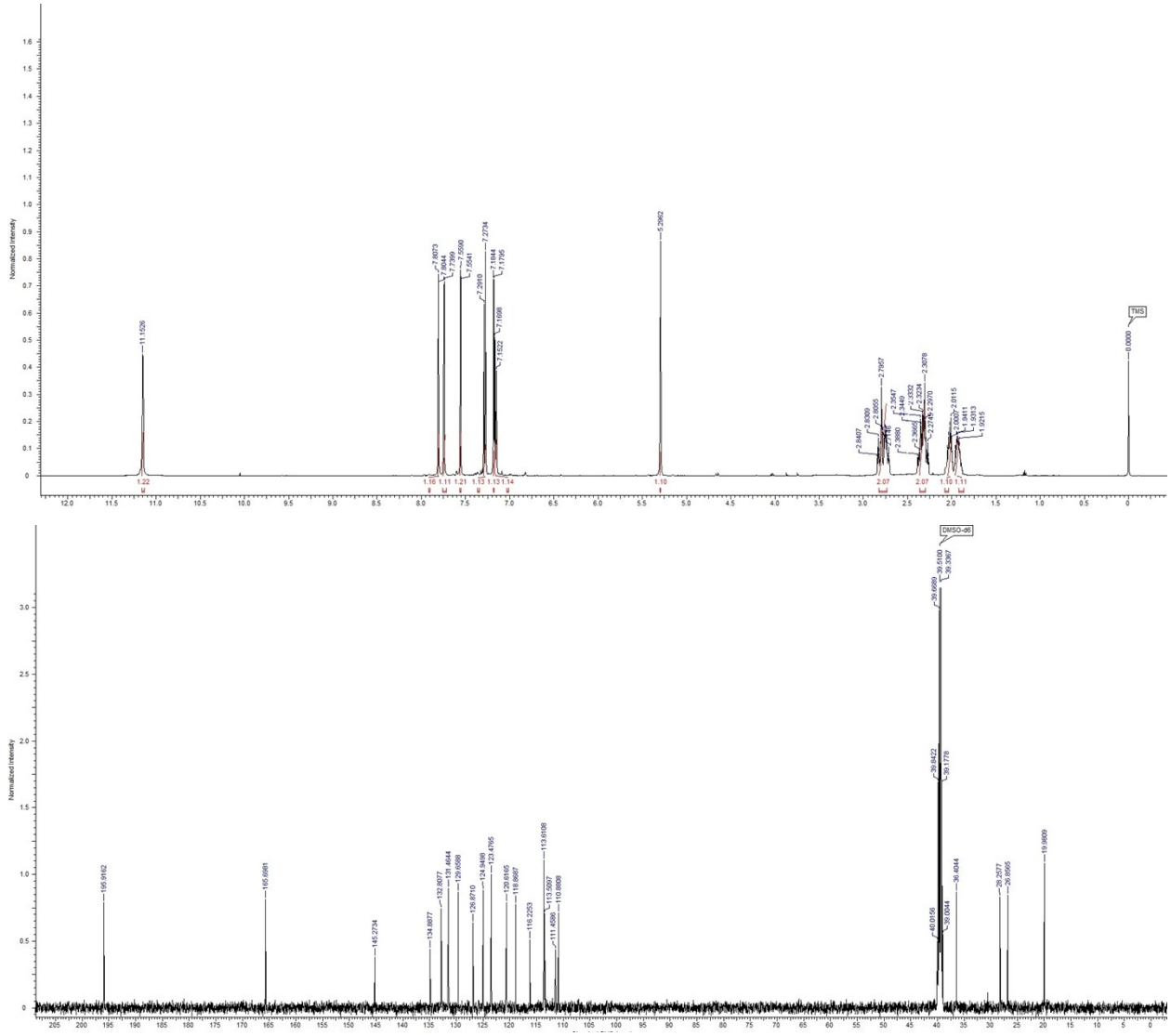
[1]H and [13]C NMR of 5,7-dibromo-9-(1H-indol-3-yl)-2,3,4,9-tetrahydro-1H-xanthen-1-one (**4h**):



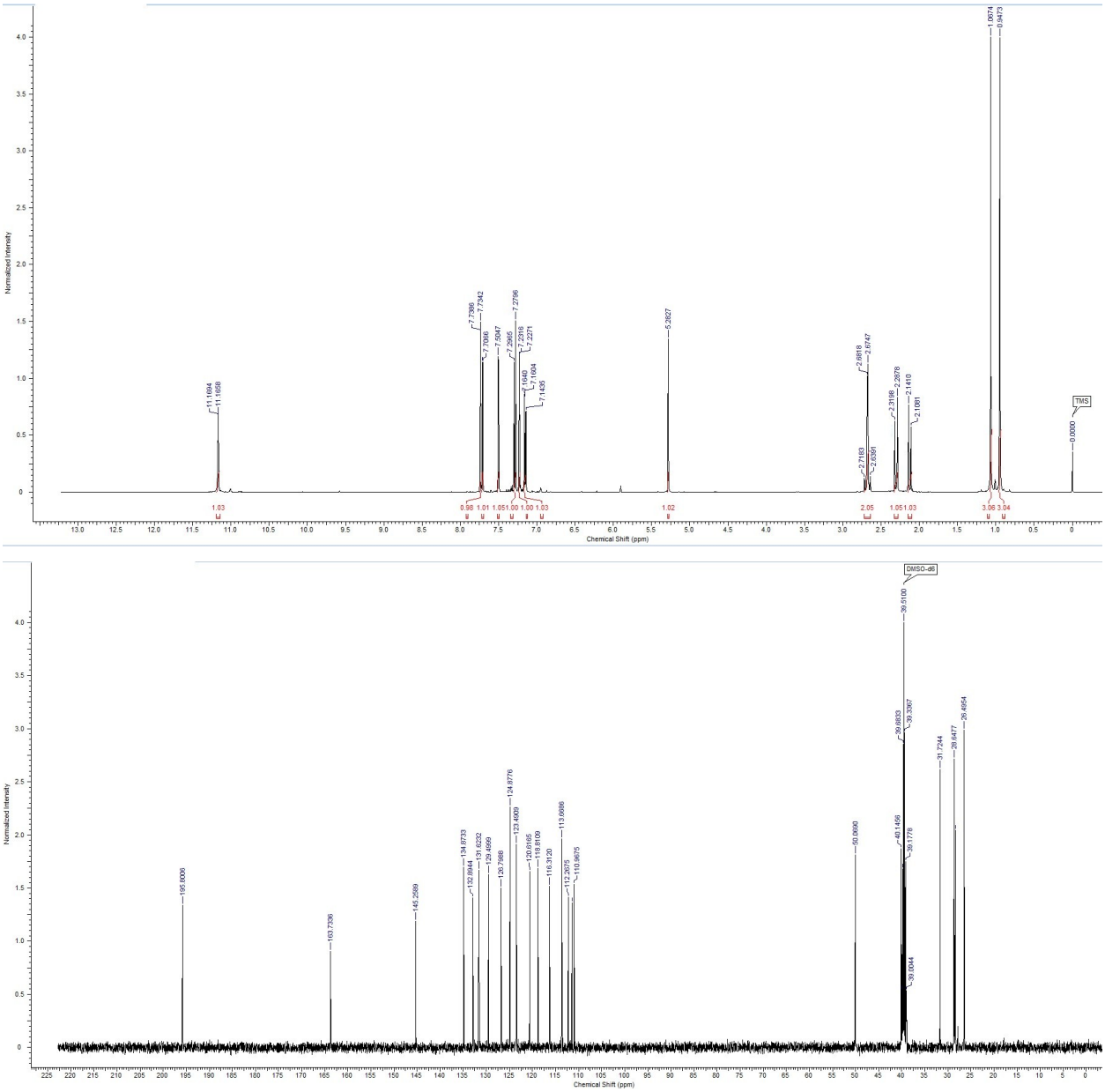
[1]H and [13]C NMR of 5,7-dibromo-9-(1H-indol-3-yl)-3,3-dimethyl-2,3,4,9-tetrahydro-1H-xanthen-1-one (**4i**):



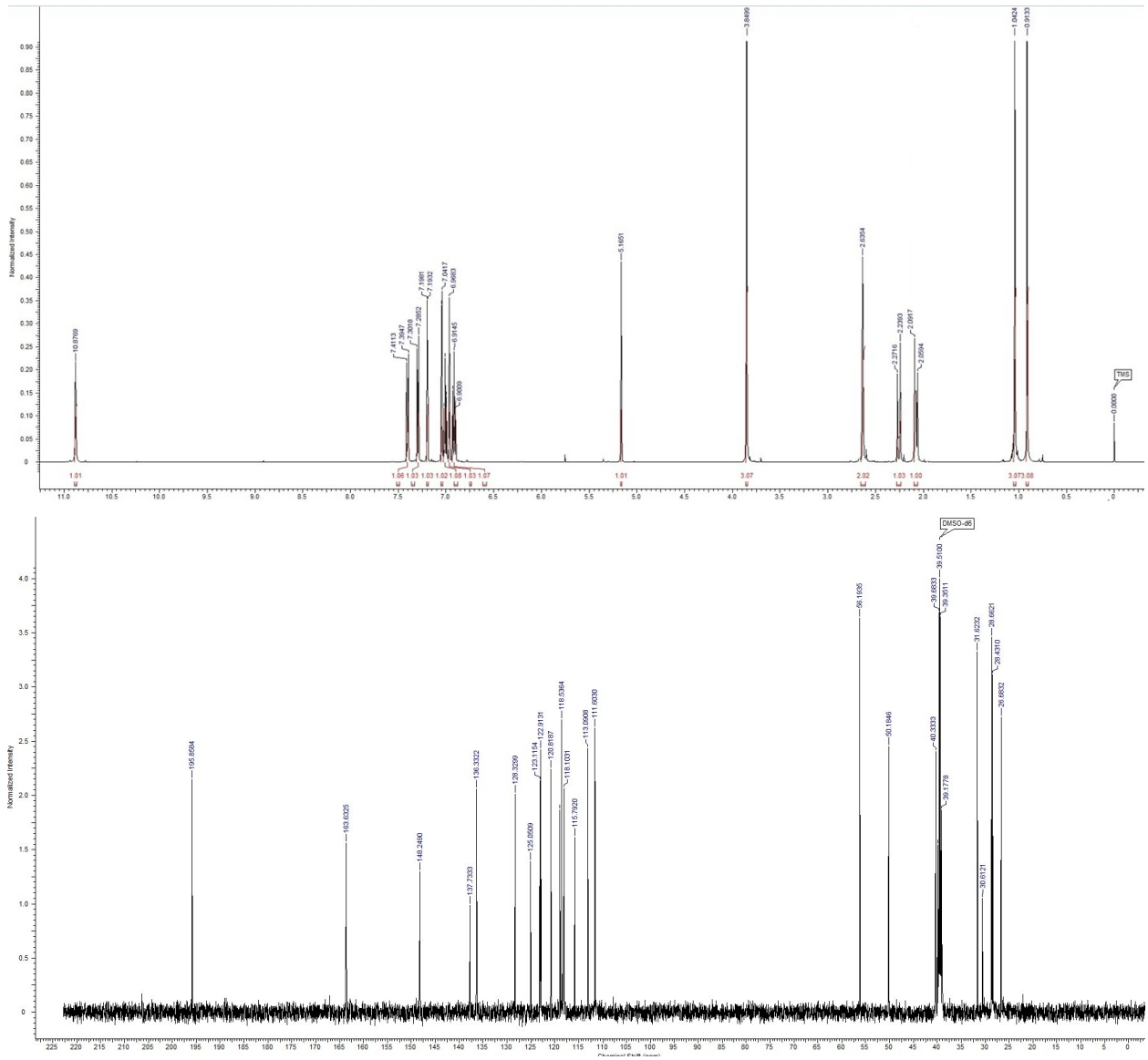
[1]H and [13]C NMR of 5,7-dibromo-9-(5-bromo-1H-indol-3-yl)-2,3,4,9-tetrahydro-1H-xanthen-1-one (**4j**):



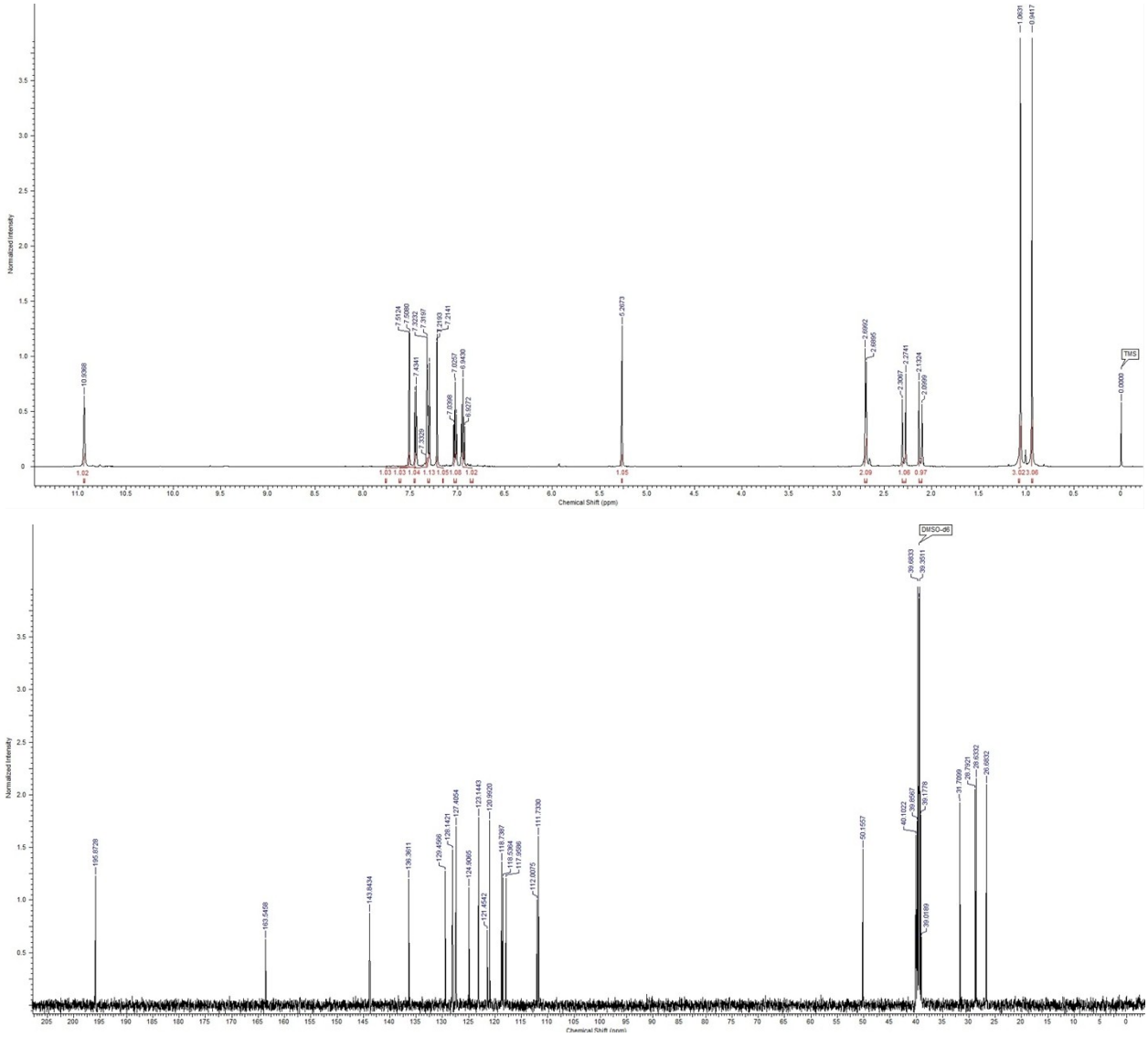
[1]H and [13]C NMR of 5,7-dibromo-9-(5-bromo-1H-indol-3-yl)-3,3-dimethyl-2,3,4,9-tetrahydro-1H-xanthen-1-one (**4k**):



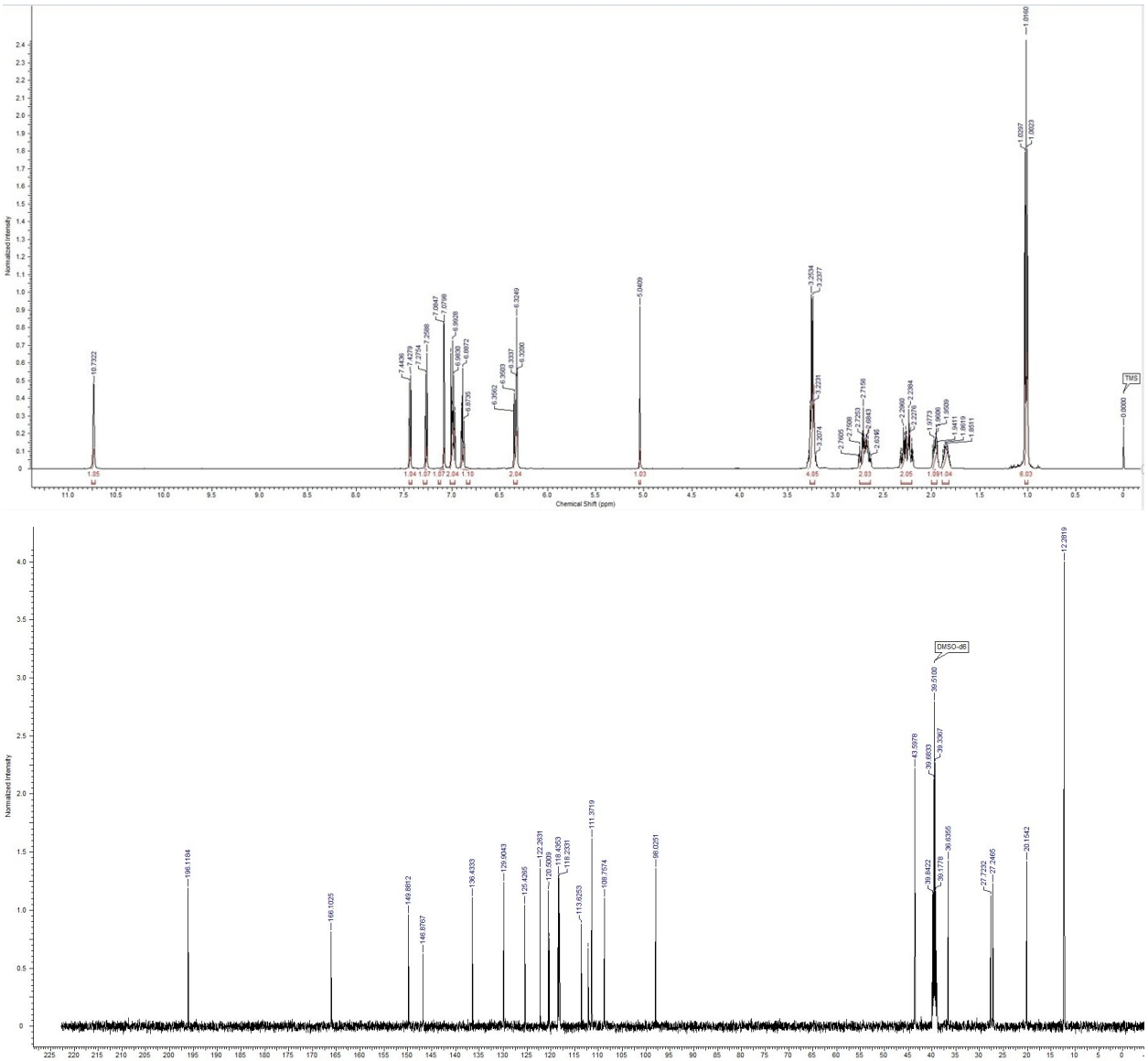
^{1}H and ^{13}C NMR of 7-bromo-9-(1H-indol-3-yl)-5-methoxy-3,3-dimethyl-2,3,4,9-tetrahydro-1H-xanthen-1-one (**4l**):



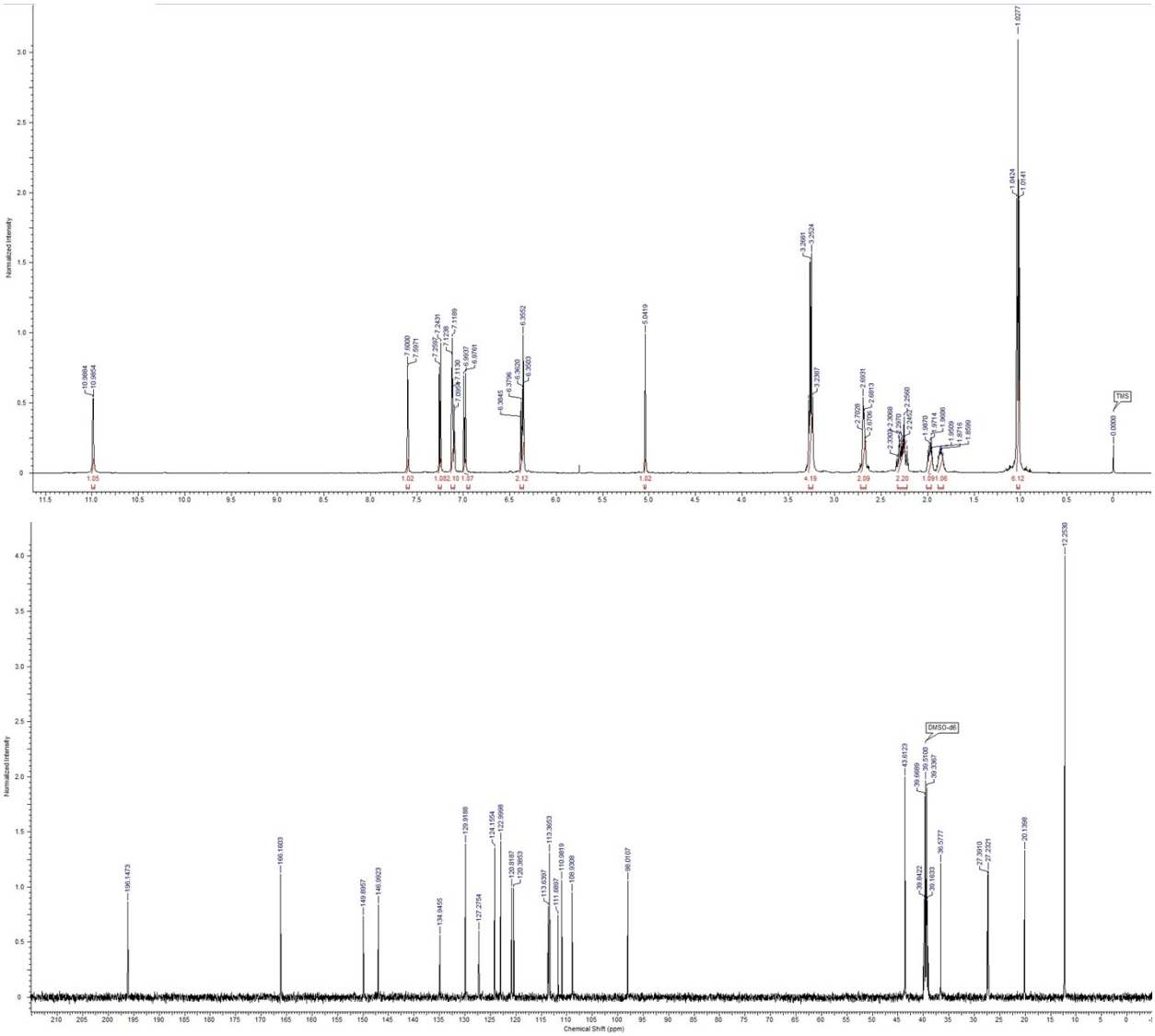
[1]H and [13]C NMR of 5,7-dichloro-9-(1H-indol-3-yl)-3,3-dimethyl-2,3,4,9-tetrahydro-1H-xanthen-1-one (**4m**):



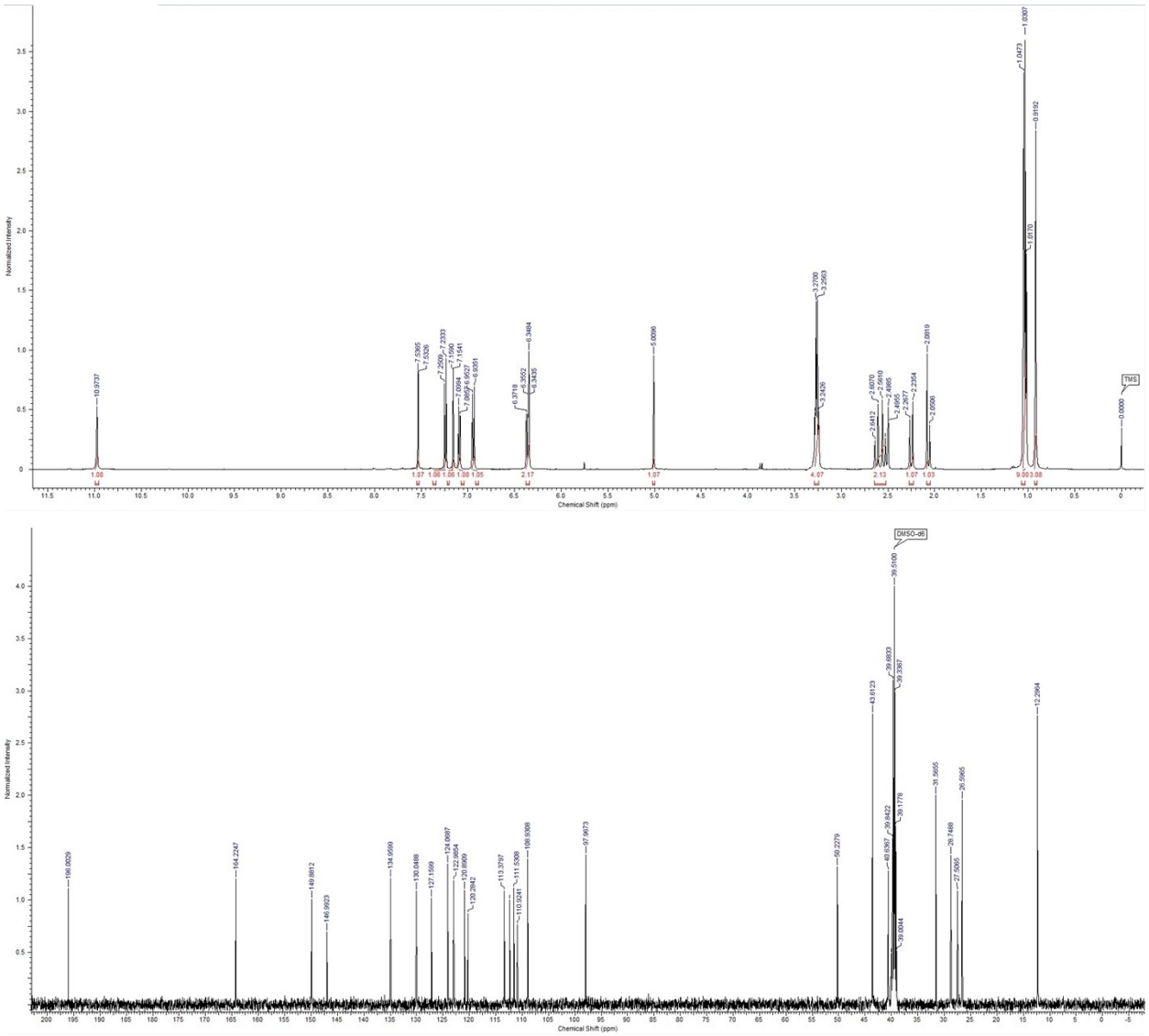
[1]H and [13]C NMR of 6-(diethylamino)-9-(1H-indol-3-yl)-2,3,4,9-tetrahydro-1H-xanthen-1-one (**4n**):



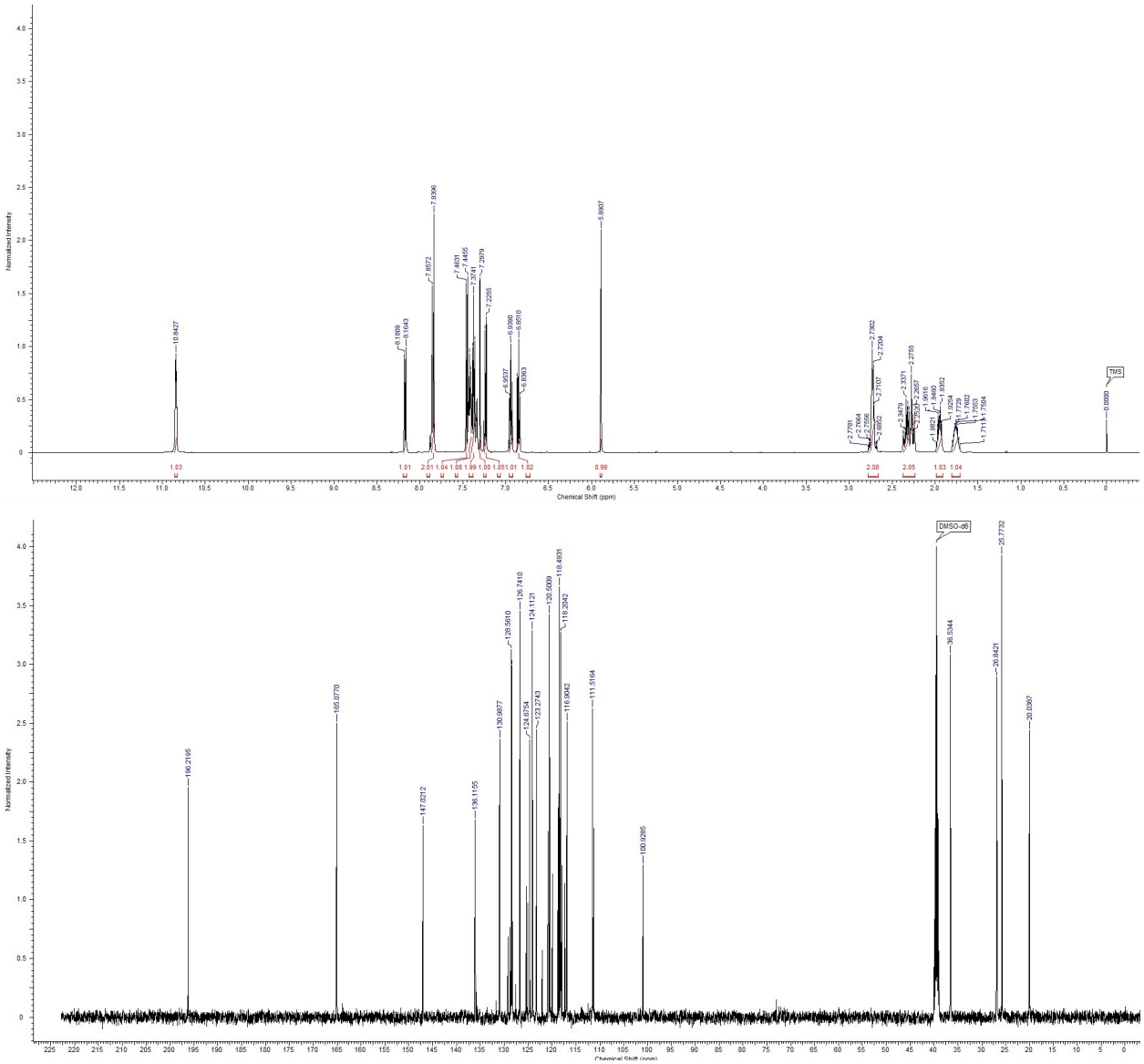
[1]H and [13]C NMR of 9-(5-bromo-1H-indol-3-yl)-6-(diethylamino)-2,3,4,9-tetrahydro-1H-xanthen-1-one (**4o**):



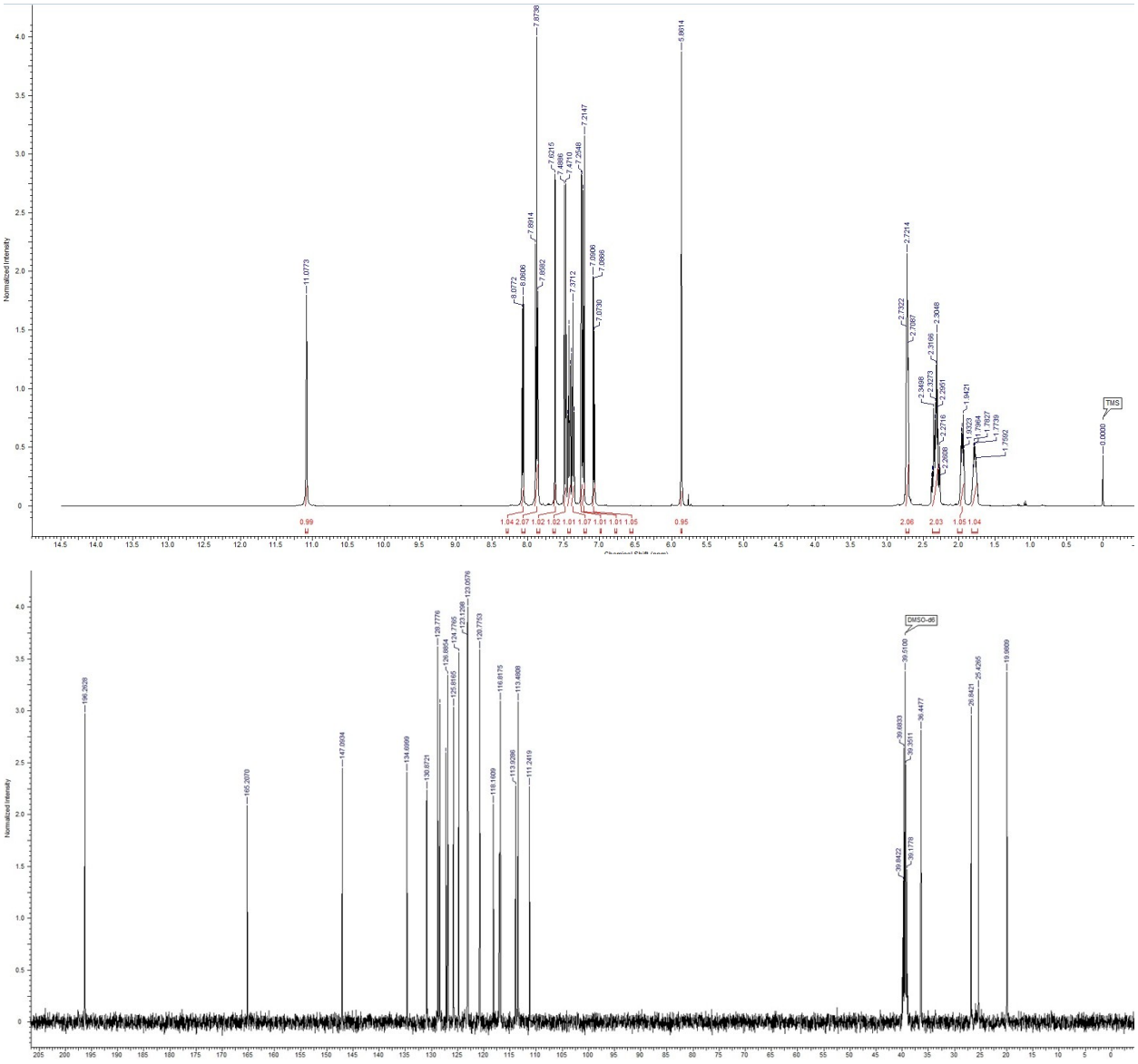
^{1}H and ^{13}C NMR of bromo-1H-indol-3-yl)-6-(diethylamino)-3,3-dimethyl-2,3,4,9-tetrahydro-1H-xanthen-1-one (**4p**):



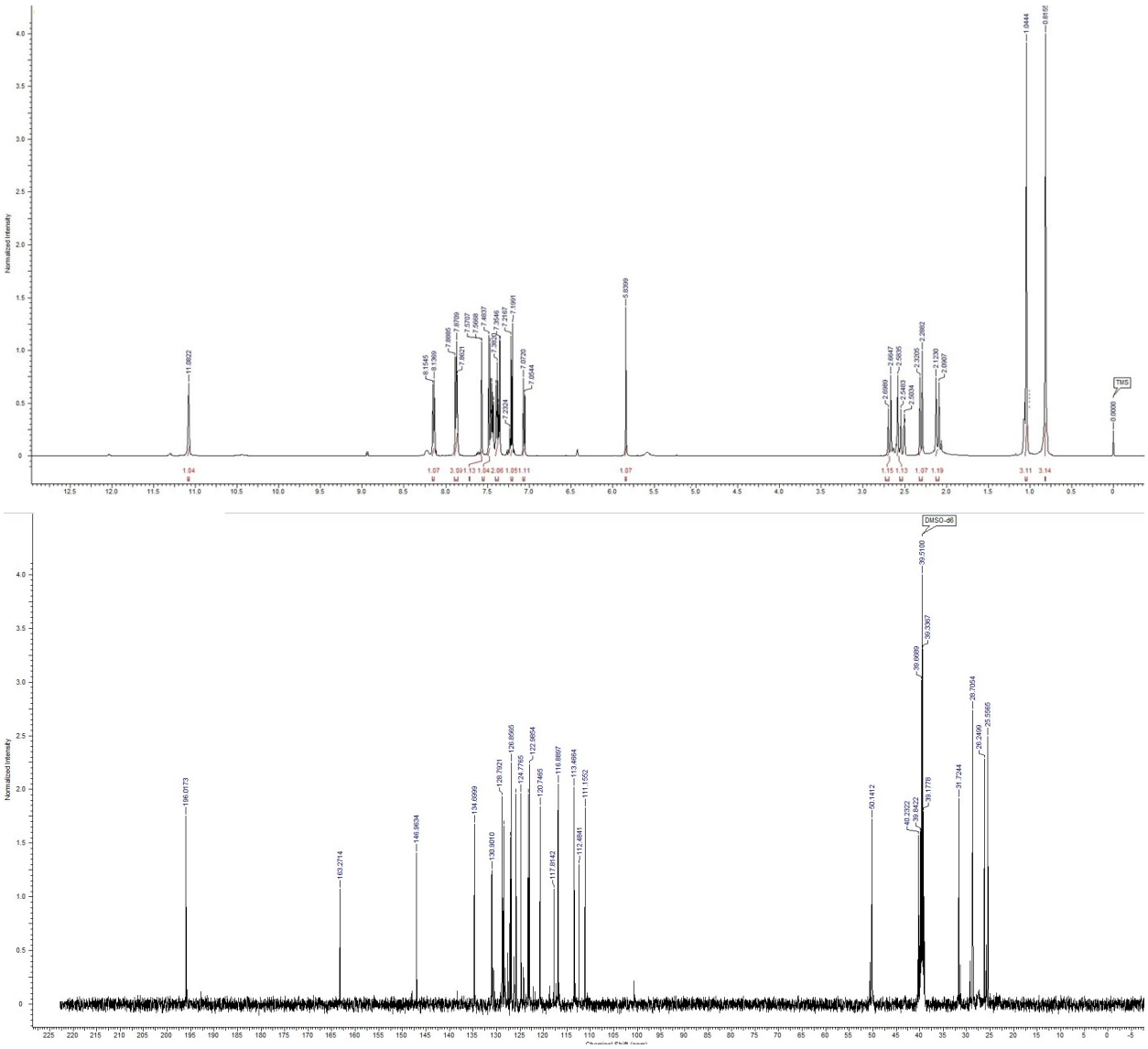
[1]H and [13]C NMR of 12-(1H-indol-3-yl)-9,10-dihydro-8H-benzo[a]xanthen-11(12H)-one (**4q**):



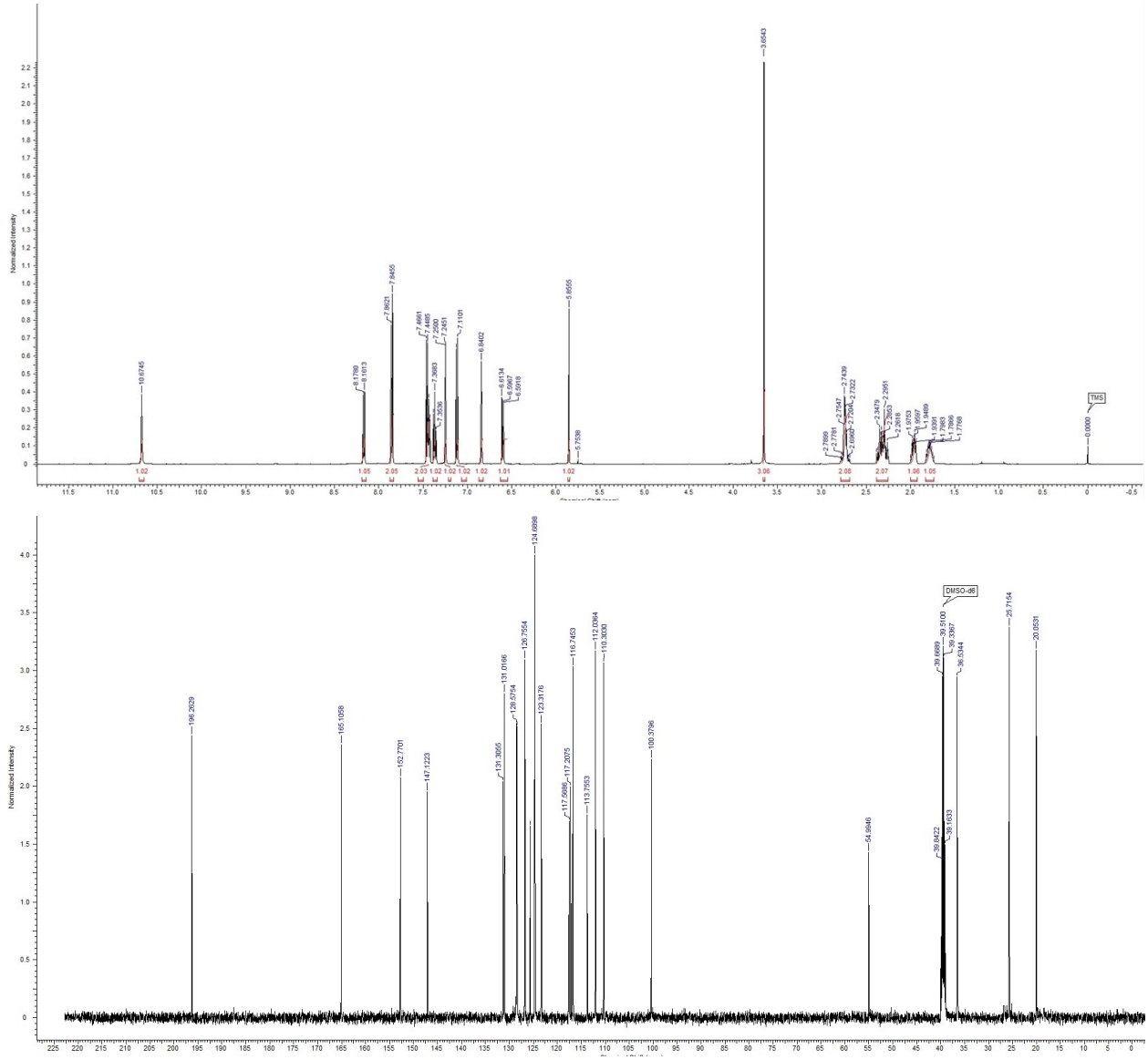
[1]H and [13]C NMR of 12-(5-bromo-1H-indol-3-yl)-9,10-dihydro-8H-benzo[a]xanthen-11(12H)-one (**4r**):



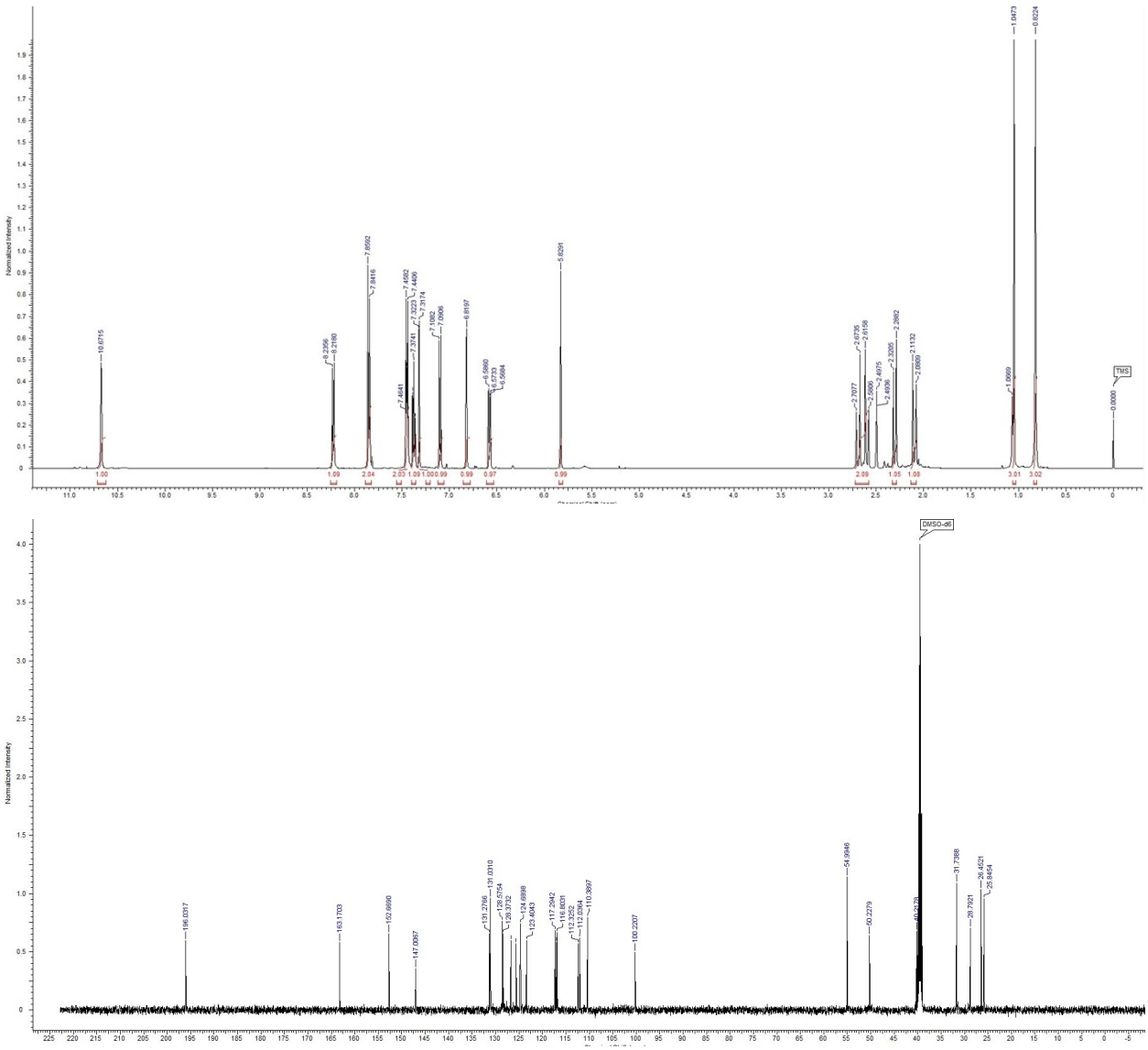
[1]H and [13]C NMR of 12-(5-bromo-1H-indol-3-yl)-9,9-dimethyl-9,10-dihydro-8H-benzo[a]xanthen-11(12H)-one (**4s**):



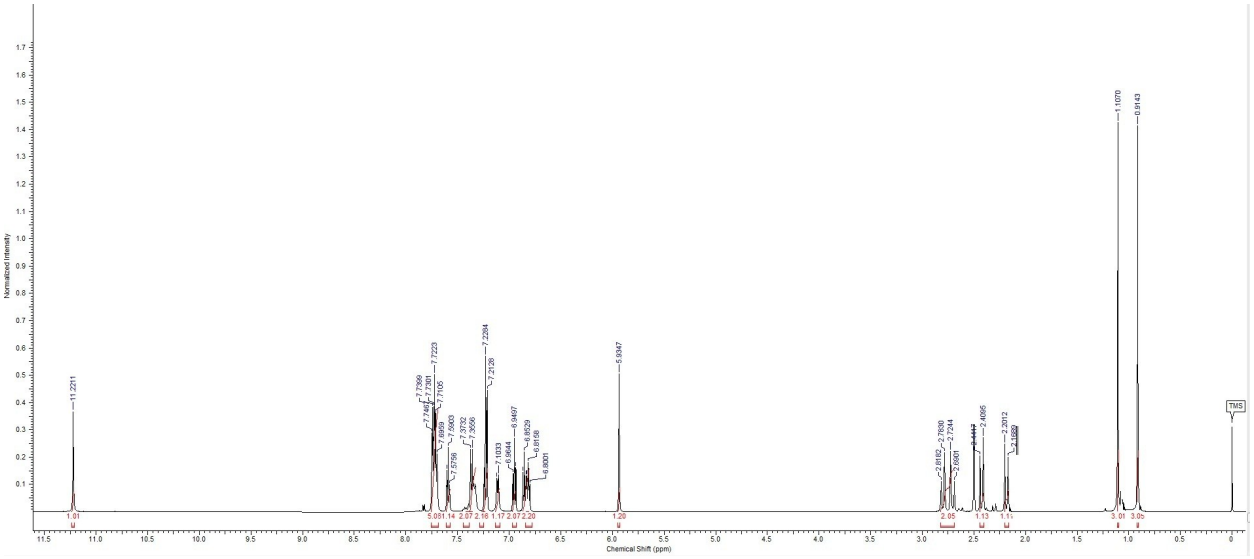
^{1}H and ^{13}C NMR of 12-(5-methoxy-1H-indol-3-yl)-9,10-dihydro-8H-benzo[a]xanthen-11(12H)-one (**4t**):

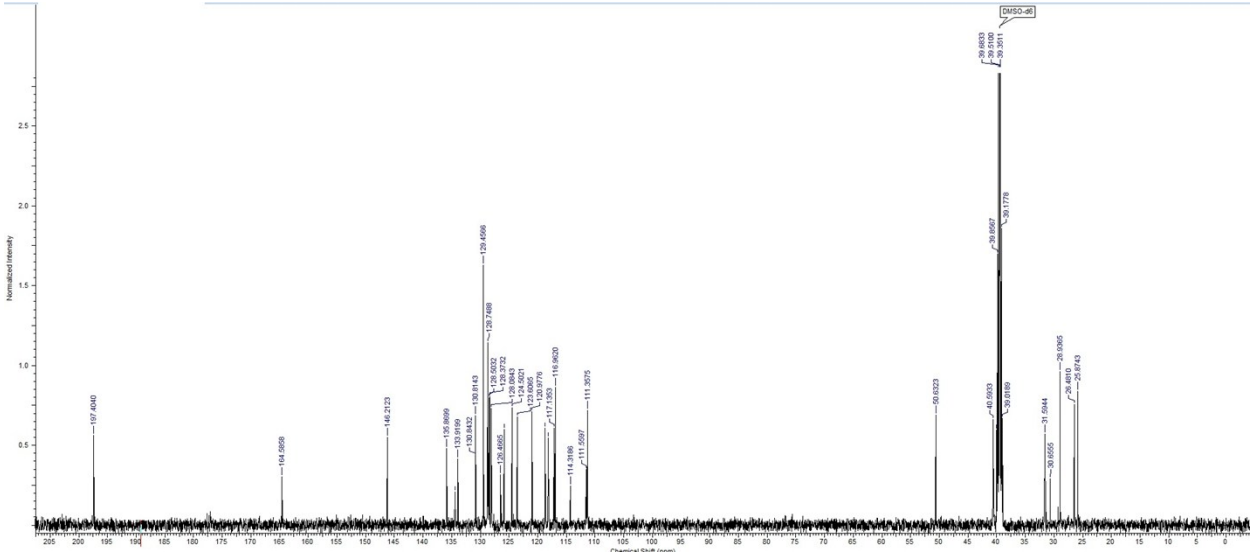


[1]H and [13]C NMR of 12-(5-methoxy-1H-indol-3-yl)-9,9-dimethyl-9,10-dihydro-8H-benzo[a]xanthen-11(12H)-one (**4u**):

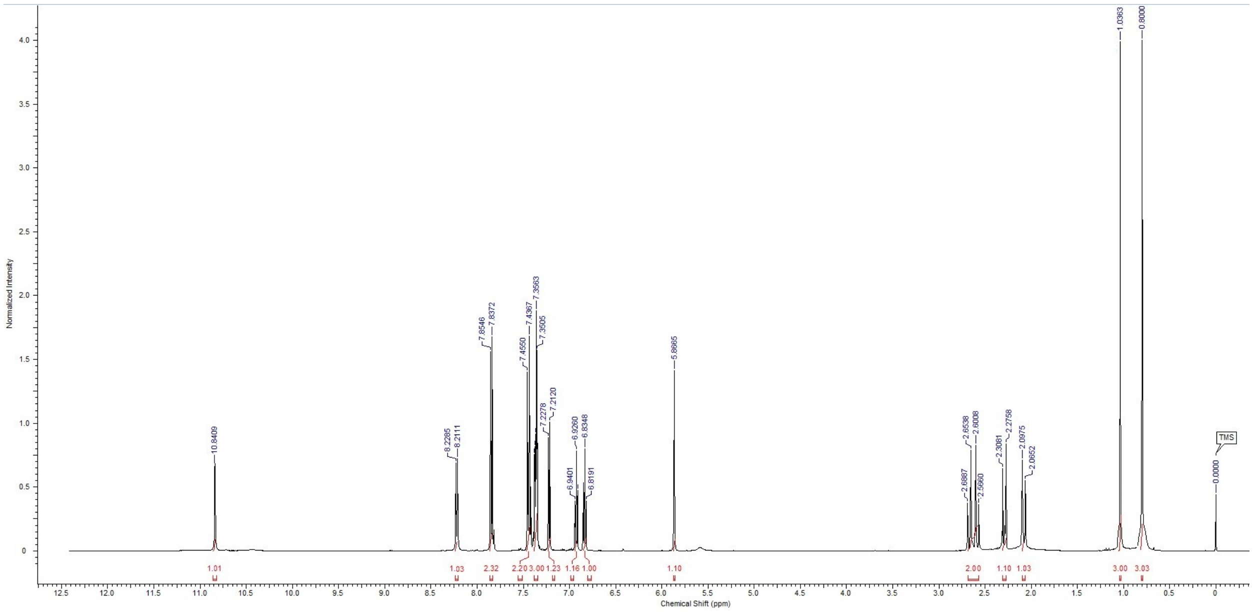


[1]H and [13]C NMR of 12-(2-phenyl-1H-indol-3-yl)-9,10-dihydro-8H-benzo[a]xanthen-11(12H)-one (**4v**):





[1]H and [13]C NMR of 12-(1H-indol-3-yl)-9,9-dimethyl-9,10-dihydro-8H-benzo[a]xanthen-11(12H)-one (**4w**):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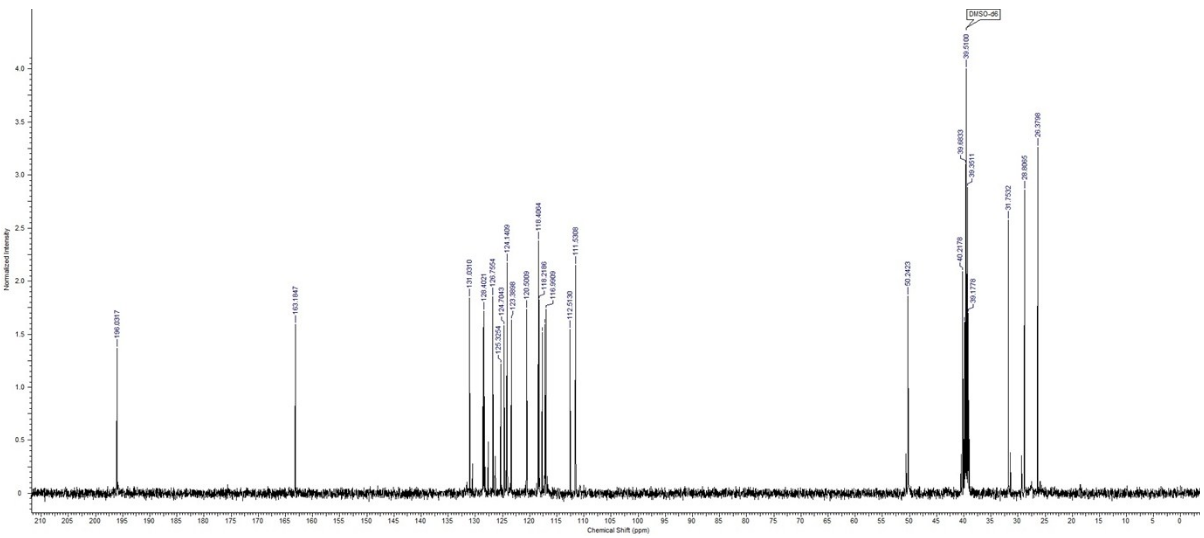
8.2285
8.2111
7.8546
7.8372
7.4550
7.4367
7.3563
7.3505
7.2278
7.2120
6.9401
6.9260
6.8348
6.8191
5.8665
2.6887
2.6538
2.6008
2.5660
2.3081
2.2758
2.0975
2.0652
1.0363
0.8000
TMS
0.0000
1.01
1.03
2.32
2.20
3.00
1.23
1.16
1.00
1.10
2.00
1.10
1.03
3.00
3.03
Chemical Shift (ppm)


Normalized Intensity
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163.1847
131.0310
128.4021
126.7554
125.3254
124.7043
124.1409
123.3898
120.5009
118.4064
118.2186
116.9909
112.5130
111.5308
50.2423
DMSO-d6
40.2178
39.6833
39.5100
39.3511
39.1778
31.7532
28.8065
26.3798
Chemical Shift (ppm)