A Mild and Efficient Synthesis of 4-Quinolones and Quinolone Heterocycles

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Supporting Information-1

Table of contents

General Experimental Methods for compounds 1 – 9.	S2 –S3
Table-1 and Characterization Data (ESI-HRMS and ¹ H/ ¹³ C NMR) for compounds 1 – 9.	S3 – S6
Table-2 and General Experimental Methods for compounds 10 – 12.	S6 –S7
Characterization Data (ESI-HRMS and ¹ H/ ¹³ C NMR) for compounds 10– 12.	S7 – S8
Table-3 and General Experimental Methods for compounds 13 – 16.	S8 – S9
Characterization Data (ESI-HRMS and ¹ H/ ¹³ C NMR) for compounds 13– 16.	S9 – S10
Table-4 and General Experimental Methods for compounds 17 – 26.	S10 –S11
Characterization Data (ESI-HRMS and ¹ H/ ¹³ C NMR) for compounds 17– 26.	S12 – S16

Experimental Section: Unless otherwise noted reactions were carried out under N_2 atmosphere in pre-dried glassware. All solvents and aniline starting materials were purchased from commercial sources and were used as received. 1H NMR (400 & 500 MHz) and ^{13}C NMR (100 & 125 MHz) chemical shifts are referenced to tetramethylsilane. Coupling constants (J) are given in Hz. ESI-HRMS results were collected using a mass spectrometer that was operated at a resolution of 10,000 using an electrospray interface and a liquid carrier of 50% aqueous 10 mM ammonium acetate and 50% acetonitrile. A sample concentration of 50 $\mu g/mL$ was used. 1 μL of sample was injected into the carrier stream.

1. General Procedure for preparation of enamine diester adducts (Table 1, 1a – 9a) and (Table 3, 13a – 16a). To a solution of *o*-anisidine (1g, 8.1 mmol) in MeOH (10 mL) at 5 $^{\circ}C$ was added dimethylacetylenedicarboxylate (DMAD), (1.4g, 9.7 mmol, 1.2 eq). The mixture was aged at rt over 2h. The product precipitated during the aging process. The yellow solid was filtered and washed with MTBE (10 mL) followed by heptane (20 mL). Enamine diester **1a** was isolated as a yellow solid in 93% yield (2g, 7.5 mmol). Crude solid was directly used for the subsequent cyclization reaction. This procedure was used for the preparation of *bis*-enamine adducts (Table 3, 13a–16a), with DMAD (2.5 eq) and for the preparation of heterocyclic adducts 17a, 17c, 18a, 20a, 22a, 23a, and 26a.

2. General Procedure for the preparation of 4-quinolones (1b – 9b), and (13b – 16b). Enamine diester **1a** (1.8g, 6.6 mmol), was added to a RBF that was equipped with a thermocouple and a stirrer. Eaton's reagent (7 mL) was then added to the flask. Reaction mixture was aged at 50 $^{\circ}C$, and progress of reaction was followed by HPLC. HPLC conditions: Zorbax RX-C8 column, 150 x 3 mm, gradient method, ACN:0.1% H_3PO_4 15:85 over 20 min hold 5 min at 80:20 then to 15:85 over 1 min. Flow rate = 1 mL/min, λ = 210 nm. Retention time, **1a** = 18.0 min, **1b** = 12.2 min. When conversion was $\geq 98\%$, reaction mixture was cooled to 5 $^{\circ}C$ and slowly transferred to an excess saturated sodium carbonate solution (10 eq.) that was cooled to 10 $^{\circ}C$. Solid was filtered and washed with water (20 mL) and was dried in a vac. oven at 50 $^{\circ}C$ for 12 h. **1b** was isolated in 97% yield (1.5g, 6.4 mmol) and 98 wt%. This

procedure was used for the preparation of *bis*-quinolones (Table 3, 13b–16b) and heterocyclic quinolones (17b, 17d, 18b, 20b, 22b, 23b, and 26b)

Table 1: Synthesis of 2-Carboxy-4-Quinolones

Entry	Reactant	Product	% Yield
1			98
2			95
3			94
4			85
5			95
6			92
7			90
8			96
9			90

3. Spectral Data for enamine substrates and 4-quinolone products (Table-1)

1a: ^1H NMR (500 MHz, DMSO- d_6): δ ppm 9.66 (s, 1H), 7.06 (m, 1H), 7.03(dd, J = 8.2, 1.8 Hz, 1H), 6.88 (m, 1H), 6.79 (d, J = 8.2, 1.8 Hz, 1H), 5.25 (s, 1H), 3.80 (s, 3H), 3.69 (s, 3H), 3.67 (s, 3H). ^{13}C

NMR (125 MHz, DMSO- d_6): δ ppm 169.0, 163.82, 149.9, 147.7, 128.4, 124.5, 120.6, 119.6, 111.5, 91.1, 55.5, 52.8, 51.1. Yellow solid, m/z : 265.0950 [M^+]. ESI-HRMS Calcd. for $C_{13}H_{15}NO_5$: 266.1028 [$M+H$] $^+$. Found 266.1034.

1b: 1H NMR (400 MHz, D_3CCO_2D): δ ppm 7.86 (d, $J=8.2$ Hz, 1H), 7.38 (t, $J=8.2$ Hz, 1H), 7.25 (d, $J=8.2$ Hz, 1H), 7.19 (s, 1H), 4.07 (s, 3H), 4.06 (s, 3H). ^{13}C NMR (100 MHz, D_3CCO_2D): δ ppm 181.3, 163.5, 149.7, 137.9, 131.6, 127.1, 126.3, 117.7, 112.9, 111.4, 57.1, 54.6. White solid, m/z : 233.0688 [M^+]. ESI-HRMS Calcd. for $C_{12}H_{11}NO_4$; 256.0586 [$M+Na$] $^+$. Found 256.0586

2a: 1H NMR (400 MHz, $CDCl_3$): δ ppm 9.80 (s, 1H), 7.17 (dd, $J= 8.0, 1.0$ Hz, 1H), 7.08(t, $J= 8.0$ Hz, 1H), 6.66 (dd, $J= 8.0, 1.0$ Hz, 1H), 5.61 (s, 1H), 3.78 (s, 3H), 3.74 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 169.6, 164.4, 146.1, 139.4, 133.9, 127.2, 125.3, 124.3, 118.7, 97.6, 523.2, 51.8. Yellow solid, m/z : 303.0065 [M^+]. ESI-HRMS Calcd. for $C_{12}H_{11}Cl_2NO_4$; 325.9963 [$M+Na$] $^+$. Found 325.9957.

2b: 1H NMR (400 MHz, $CDCl_3$): δ ppm 9.33 (s, 1H), 8.19 (d, $J= 8.8$ Hz, 1H), 7.44 (d, $J= 8.8$ Hz, 1H), 6.98 (s, 1H), 4.07 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 178.8, 162.9, 137.9, 137.1, 136.7, 125.8, 125.8, 125.7, 120.9, 112.7, 54.3. Off-white solid, m/z : 270.9803 [M^+]. ESI-HRMS Calcd. for $C_{11}H_7Cl_2NO_3$; 271.9881, [$M+H$] $^+$. Found 271.9878

3a: 1H NMR (500 MHz, $CDCl_3$): δ ppm 9.63 (s, 1H), 6.98 (d, $J= 8.7, 1.6$ Hz, 1H), 6.78 (d, $J= 8.7, 1H$), 6.74 (s, 1H), 5.47 (s, 1H), 3.84 (s, 3H), 3.77 (s, 3H), 3.76 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 169.9, 164.6, 149.3, 147.1, 130.8, 125.7, 123.8, 120.1, 112.0, 94.6, 56.1, 52.9, 51.5. Yellow Solid, m/z : 299.0561 [M^+]. ESI-HRMS Calcd. for $C_{13}H_{14}ClNO_5$; 322.0458 [$M+Na$] $^+$. Found 322.0458.

3b: 1H NMR (500 MHz, CD_3CO_2D): δ ppm 7.43 (d, $J= 8.3$ Hz, 1H), 7.33 (s, 1H), 7.25 (d, $J= 8.3$ Hz, 1H), 4.11 (s, 3H), 4.09 (s, 3H). Note: DMSO at 2.86. ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 179.1, 162.4, 148.5, 138.2, 133.5, 129.4, 124.2, 121.9, 113.5, 112.3, 57.6, 54.9. Off-white solid, m/z : 267.0298 [M^+]. ESI-HRMS Calcd. for $C_{12}H_{10}ClNO_4$: 268.0377 [$M+H$] $^+$, found 268.0308.

4a: No satisfactory NMR data was obtained. Yellow solid, m/z : 265.095 [M^+]. ESI-HRMS Calcd. for $C_{13}H_{15}NO_5$: 288.0848 [$M+Na$] $^+$, found 288.0851.

4b: ^1H NMR (400 MHz, $\text{D}_3\text{CCO}_2\text{D}$): δ ppm 7.86 (d, $J=9.2$ Hz, 1H), 7.72 (d, $J=2.8$ Hz, 1H), 7.42 (dd, $J=9.2, 2.8$ Hz, 1H), 7.23 (s, 1H) 4.05 (s, 3H), 3.93 (s, 3H). ^{13}C NMR (100 MHz, $\text{D}_3\text{CCO}_2\text{D}$): δ ppm 180.2, 164.0, 158.91, 137.98, 135.9, 127.9, 126.6, 122.1, 110.1, 104.5, 56.3, 54.5. Light-yellow solid, m/z : 233.0688 $[\text{M}^+]$. ESI-HRMS Calcd. for $\text{C}_{12}\text{H}_{11}\text{NO}_4$: 234.0766 $[\text{M}+\text{H}]^+$. Found 234.0760.

5a: ^1H NMR (500 MHz, CDCl_3): δ ppm 9.75 (s, 1H), 7.58 (dd, $J=7.8, 1.6$ Hz, 1H), 7.20 (td, $J=7.8, 1.6$ Hz, 1H), 6.95 (td, $J=7.8, 1.6$ Hz, 1H), 6.77 (dd, $J=7.8, 1.6$ Hz, 1H), 5.56 (s, 1H), 3.78 (s, 3H), 3.72 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3): δ ppm 169.6, 164.5, 146.6, 138.9, 133.2, 127.9, 125.1, 121.05, 115.8, 96.1, 52.9, 51.6. Light-yellow solid, m/z : 312.995 $[\text{M}^+]$. ESI-HRMS Calcd. for $\text{C}_{12}\text{H}_{12}\text{BrNO}_4$: 314.0028 $[\text{M}+\text{H}]^+$, found 314.0027

5b: ^1H NMR (400 MHz, CDCl_3): δ ppm 9.39 (brs, 1H), 8.30 (dd, $J=8.0, 1.2$ Hz, 1H), 7.90 (td, $J=8.0, 1.2$ Hz, 1H), 7.26 (td, $J=8.0, 1\text{H}$), 6.99 (d, $J=1.2$ Hz, 1H), 4.07 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ ppm 179.1, 162.9, 126.9, 136.7, 136.3, 127.5, 126.2, 125.2, 112.4, 112.0, 54.2. White solid, m/z : 280.9688 $[\text{M}^+]$. ESI-HRMS Calcd. for $\text{C}_{11}\text{H}_8\text{BrNO}_3$: 303.9579 $[\text{M}+\text{Na}]^+$. Found 303.9577.

6a: ^1H NMR (400 MHz, CDCl_3): δ ppm 9.65 (s, 1H), 7.29 (dd $J=7.6, 1.6$ Hz, 1H), 7.13 (td, $J=7.6, 1.6$ Hz, 1H), 7.08 (td, $J=7.6, 1.6$ Hz, 1H), 6.76 (dd, $J=7.6, 1.6$ Hz, 1H), 5.40 (s, 1H), 3.74 (s, 3H), 3.61 (s, 3H), 3.27 (septet, $J=6.8$ Hz, 1H), 1.28 (d, $J=6.8$ Hz, 6H). ^{13}C NMR (100 MHz, CDCl_3): δ ppm 170.5, 164.8, 149.7, 141.4, 138.0, 126.3, 126.1, 125.7, 122.7, 92.5, 52.6, 51.2, 28.4, 22.9. Yellow oil, m/z : 277.1314 $[\text{M}^+]$. ESI-HRMS Calcd. for $\text{C}_{15}\text{H}_{19}\text{NO}_4$: 278.1392 $[\text{M}+\text{H}]^+$, found 278.1393.

6b: ^1H NMR (400 MHz, CDCl_3): δ ppm 9.09 (s, 1H), 8.23 (d, $J=7.8$ Hz, 1H), 7.59 (d, $J=7.8$ Hz, 1H), 7.35 (t, $J=7.8$ Hz, 1H), 6.95 (d, $J=1.6$ Hz, 1H), 4.05 (s, 3H), 3.28 (septet, $J=6.8$ Hz, 1H), 1.42 (d, $J=6.8$ Hz, 6H). ^{13}C NMR (100 MHz, CDCl_3): δ ppm 180.2, 163.9, 136.6, 135.8, 135.8, 129.3, 126.9, 124.5, 124.3, 111.3, 54.0, 27.8, 22.9. Light-yellow solid, m/z : 245.1052 $[\text{M}^+]$. ESI-HRMS Calcd. for $\text{C}_{14}\text{H}_{15}\text{NO}_3$: 268.0950 $[\text{M}+\text{Na}]^+$, found 268.0944.

7a: ^1H NMR (400 MHz, CDCl_3): δ ppm 9.72 (s, 1H), 7.94 (m, 2H), 6.85 (m, 2H), 5.53 (s, 1H), 3.87 (s, 3H), 3.74 (s, 3H), 3.72 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ ppm 169.6, 166.7, 164.6, 146.5, 144.6,

131.3, 131.0, 125.3, 120.5, 119.3, 96.9, 53.1, 52.1, 51.6. Yellow solid, m/z : 293.0899 $[M^+]$. ESI-HRMS Calcd. for $C_{14}H_{15}NO_6$: 294.0978 $[M+H]^+$, found 294.09

7b: 1H NMR (400 MHz, CF_3CO_2D): δ ppm 9.34 (m, 1H), 8.78 (m, 1H), 8.43 (m, 1H), 8.05 (m, 1H) 4.26 (m, 3H), 4.17 (m, 3H). ^{13}C NMR (100 MHz, CF_3CO_2D): δ ppm 175.8, 170.0, 162.9, 144.9, 144.1, 138.9, 133.3, 129.6, 123.5, 123.2, 109.3, 57.6, 55.9. White solid, m/z : 261.0637 $[M^+]$. ESI-HRMS Calcd. for $C_{13}H_{11}NO_5$: 262.0715 $[M+H]^+$, found 262.0721.

8a: 1H NMR (400 MHz, $CDCl_3$): δ ppm 9.78 (s, 1H), 7.39 (dd, J = 8.0, 1.6 Hz, 1H), 7.15 (td, J = 8.0, 1.6 Hz, 1H), 7.01 (td, J = 8.0, 1.6 Hz, 1H), 6.78 (dd, J = 8.0, 1.6 Hz, 1H), 5.55 (s, 1H), 3.77 (s, 3H), 3.72 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 169.7, 164.6, 146.7, 137.6, 130.1, 127.3, 125.7, 124.7, 121.0, 96.1, 53.0, 51.6. Yellow solid, m/z : 269.0455 $[M^+]$. ESI-HRMS Calcd. for $C_{12}H_{12}ClNO_4$: 270.0533 $[M+H]^+$, found 270.0530.

8b: 1H NMR (400 MHz, $CDCl_3$): δ ppm 9.13 (very br s, 1H), 8.22 (dd, J = 8.0, 1.2 Hz, 1H), 7.72 (dd, J = 7.8, 1.2 Hz, 1H), 7.31 (t, J =8.0 Hz, 1H), 6.93(s, 1H), 4.07 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 178.9, 162.9, 136.4, 135.9, 132.7, 127.4, 125.3, 124.5, 122.5, 112.1, 54.1. White solid, m/z : 237.0193 $[M^+]$. ESI-HRMS Calcd. for $C_{11}H_8ClNO_3$: 260.0090 $[M+Na]^+$, found 260.0084.

9a: No satisfactory NMR and ESI-HRMS data was obtained

9b: 1H NMR (400 MHz, CD_3OD): δ ppm 8.09 (d, J = 2.0 Hz, 1H), 7.81 (d, J = 8.8 Hz, 1H), 7.70 (dd, J = 8.8, 2.0 Hz, 1H), 6.98 (s, 1H), 4.04 (s, 3H), 2.69 (m, 1H), 1.91 (m, 4H), 1.79 (m, 1H), 1.58–1.43 (om, 4H), 1.33 (m, 1H). Note; DMSO at 2.70. ^{13}C NMR (100 MHz, CD_3OD): δ ppm 180.8, 163.7, 147.1, 140.2, 140.1, 134.8, 126.9, 122.8, 120.7, 110.6, 54.3, 45.8, 35.7, 28.0, 27.3. Light-yellow solid, m/z : 285.1365 $[M^+]$. ESI-HRMS Calcd. for $C_{17}H_{19}NO_3$: 308.1263 $[M+Na]^+$, found 308.1259.

4. General Procedure for preparation of enamine diester adducts. (Table 2, 10a – 12a):

To a solution of *o*-chloroaniline (2g, 16.3 mmol) in toluene (10 mL) was added dimethyl methoxymethylenemalonate (3.4 g, 19.6 mmol, 1.2 eq). The mixture was aged at reflux (110 °C) over 6 h. Reaction mixture was cooled to rt and MTBE (20 mL) was added. Product is filtered and cake washed with heptane. After overnight drying in vac oven at 50 °C, 4.0g of **10a** (15.1 mmol, 93%) was

collected in 96 wt%. Crude solid was directly used for the subsequent cyclization reaction. This procedure was applied to the preparation of *bis*-enamine adducts (Table 3, 13a – 16a) and heterocyclic enamines; 19a, 21a, 24a, and 25a.

Table 2: Synthesis of 3-Carboxy-4-Quinolones

Entry	Reactant	Product	% Yield
10			96
11			90
12			94

5. General Procedure for the preparation of 4-quinolones (10b – 12b).

Enamine **10 a** (1.g, 3.8 mmol), was added to a RBF that was equipped with a thermocouple and a stirrer, Eaton's reagent (4 mL) was then added to the flask. Reaction mixture was aged at 90 °C, and progress of reaction was followed by HPLC. When conversion was ≥ 98 %, reaction mixture was cooled to 5 °C and slowly transferred to an excess saturated sodium carbonate solution (10 eq) that was cooled to 10 °C. The solid was filtered, washed with water (10 mL) and was dried in a vac. oven at 50 °C over 12 h. 0.9g of **10b** (3.7 mmol, 97%) was collected in 98 wt % purity. The same cyclization protocol was applied to the preparation of heterocyclic quinolones; 19b, 21b, 24b, and 25b.

6. Spectral Data for enamine substrates and 4-quinolone products (Table- 2)

10a: ^1H NMR (400 MHz, CD_3CN): δ ppm 11.28 (d, $J=12.8$ Hz, 1H), 8.55 (d, $J=12.8$ Hz, 1H), 7.47 (ddd, $J=9.4, 8.0, 1.2$ Hz, 1H), 7.37 (m, 1H), 7.13 (td, $J=7.8, 1.8$ Hz, 1H), 3.79 (s, 3H), 3.73 (s, 3H). ^{13}C NMR (100 MHz, CD_3CN): δ ppm 169.8, 166.3, 152.0, 137.3, 131.1, 129.6, 126.3, 124.0, 117.3, 95.7, 52.2, 51.9. White solid, m/z : 269.0455 [M^+]. ESI-HRMS Calcd. for $\text{C}_{12}\text{H}_{12}\text{ClNO}_4$: 292.0353 [$\text{M}+\text{Na}$] $^+$, found 292.0356.

10b: ^1H NMR (400 MHz, $\text{F}_3\text{CCO}_2\text{D}$): δ ppm 9.37 (s, 1H), 8.60 (d, $J=7.6$ Hz, 1H), 8.26 (d, $J=7.6$ Hz, 1H), 7.91 (t, $J=7.6$ Hz, 1H), 4.18 (s, 3H). ^{13}C NMR (100 MHz, $\text{F}_3\text{CCO}_2\text{D}$): δ ppm 176.4, 169.9, 148.4, 139.8, 138.4, 132.7, 127.6, 126.11, 123.8, 107.81, 56.1. Brown solid, m/z : 237.0193 [M^+]. ESI-HRMS Calcd. for $\text{C}_{11}\text{H}_8\text{ClNO}_3$: 238.0271 [$\text{M}+\text{H}$] $^+$, found 238.0268.

11a: ^1H NMR (400 MHz, CDCl_3): δ ppm 10.97 (d, $J=14.0$ Hz, 1H), 8.41 (d, $J=14.0$ Hz, 1H), 7.05 (m, 2H), 6.87 (m, 2H), 3.82 (s, 3H), 3.77 (s, 3H), 3.74 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ ppm 169.6, 166.2, 157.4, 153.0, 132.7, 119.0, 115.1, 91.9, 55.7, 51.5, 51.4. White solid, m/z : 265.0950 [M^+]. ESI-HRMS Calcd. for $\text{C}_{13}\text{H}_{15}\text{NO}_5$: 288.0848 [$\text{M}+\text{Na}$] $^+$, found 288.0850.

11b: ^1H NMR (400 MHz, $\text{CF}_3\text{CO}_2\text{D}$): δ ppm 9.11 (s, 1H), 8.02 (d, $J=9.2$ Hz, 1H), 7.89 (s, 1H), 7.82 (d, $J=9.2$ Hz, 1H), 4.17 (s, 3H), 4.06 (s, 3H). ^{13}C NMR (100 MHz, $\text{CF}_3\text{CO}_2\text{D}$): δ ppm 174.2, 170.5, 144.4, 137.2, 132.6, 124.3, 123.9, 106.9, 104.8, 57.7, 55.8. White solid, m/z : 233.0688 [M^+]. ESI-HRMS Calcd. for $\text{C}_{12}\text{H}_{11}\text{NO}_4$: 234.0766 [$\text{M}+\text{H}$] $^+$, found 234.0762.

12a: ^1H NMR (400 MHz, CDCl_3): δ ppm 10.98 (d, $J=13.2$ Hz, 1H), 8.38 (d, $J=13.2$ Hz, 1H), 6.66 (m, 2H), 6.57 (tt, $J=8.8, 2.2$ Hz, 1H), 3.83 (s, 3H), 3.77 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ ppm 169.1 (dd, $J_{\text{CF}}=241.9, 15.2$ Hz), 151.2 141.7 (t, $J_{\text{CF}}=12.4$ Hz), 100.58 (m), 100.2 (t, $J_{\text{CF}}=25.2$ Hz), 95.1, 51.9, 51.8. Off-white solid, m/z : 271.0656 [M^+]. ESI-HRMS Calcd. for $\text{C}_{12}\text{H}_{11}\text{F}_2\text{NO}_4$: 272.0734 [$\text{M}+\text{H}$] $^+$, found 272.0737.

12b: ^1H NMR (400 MHz, $\text{CF}_3\text{CO}_2\text{D}$): δ ppm 9.25 (s, 1H), 7.60 (dd, $J=8.0, 2.0$ Hz, 1H), 7.31 (td, $J=8.8, 2.0$ Hz, 1H), 4.13 (3, 3H). ^{13}C NMR (100 MHz, $\text{CF}_3\text{CO}_2\text{D}$): δ ppm 176.3 (d, $J_{\text{CF}}=2.9$ Hz), 170.7 (dd, $J_{\text{CF}}=266.8, 13.3$ Hz), 170.2, 164.5 (dd, $J_{\text{CF}}=275.7, 15.0$ Hz), 149.3, 144.2 (dd, $J_{\text{CF}}=15.1, 4.5$ Hz), 110.8 (dd, $J_{\text{CF}}=13.6, 2.0$ Hz), 109.2 (dd, $J_{\text{CF}}=27.9, 23.6$ Hz), 107.3, 104.7 (dd, $J_{\text{CF}}=26.3, 4.9$ Hz), 56.0. White solid, m/z : 239.0394 [M^+]. ESI-HRMS Calcd. for $\text{C}_{11}\text{H}_7\text{F}_2\text{NO}_3$: 240.0472 [$\text{M}+\text{H}$] $^+$, found 240.0473.

7. General Procedure for preparation of bis-enamine tetra ester adducts (Table 3, 13a – 16a).

Refer to procedure 1.

8. General Procedure for preparation of bis-quinolones (13b – 16b). Refer to procedure 2.

Table 3: Bis-Cyclization of Diamine Derivatives

Entry	Reactant	Product	% Yield
13	13a	13b	80
14	14a	14b	90
15	15a	15b	85
16	16a	16b	92

9. Spectral Data for bis-enamine substrates and bis-quinolone products (Table-3):

13a: ^1H NMR (400 MHz, CDCl_3): δ ppm 9.61 (s, 2H), 6.83 (s, 4H), 5.38 (s, 2H), 3.73 (s, 6H), 3.68 (s, 6H). ^{13}C NMR (100 MHz, CDCl_3): δ ppm 170.1, 164.9, 148.2, 137.1, 121.9, 93.7, 52.9, 51.4. Yellow solid, m/z : 392.122 [M^+]. ESI-HRMS Calcd. for $\text{C}_{18}\text{H}_{20}\text{N}_2\text{O}_8$: 393.1298 [$\text{M}+\text{H}$] $^+$, found 393.1295

13b: ^1H NMR (400 MHz, $\text{D}_3\text{CCO}_2\text{D}$): δ ppm 8.51 (s, 2H), 7.55 (s, 2H), 4.09 (s, 6H). Note: DMSO at 2.84. ^{13}C NMR (100 MHz, $\text{D}_3\text{CCO}_2\text{D}$): δ ppm 177.6, 162.6, 144.3, 141.5, 130.43, 121.1, 114.7, 54.6. Yellow solid, m/z : 328.0695 [M^+]. ESI-HRMS Calcd. for $\text{C}_{16}\text{H}_{12}\text{N}_2\text{O}_6$: 329.0774 [$\text{M}+\text{H}$] $^+$, found 329.0774.

14a: ^1H NMR (400 MHz, CDCl_3): δ ppm 7.49 (m, 4H), 6.95 (m, 4H), 5.43 (s, 2H), 3.76 (s, 6H), 3.74 (s, 6H). ^{13}C NMR (100 MHz, CDCl_3): δ ppm 170.1, 165.1, 147.9, 139.6, 136.3, 127.6, 121.09, 9.17, 53.1, 51.5. Yellow solid, m/z : 468.1533 $[\text{M}^+]$. ESI-HRMS Calcd. for $\text{C}_{24}\text{H}_{24}\text{N}_2\text{O}_8$: 469.1611 $[\text{M}+\text{H}]^+$, found 469.1611.

14b: ^1H NMR (500 MHz, $\text{CF}_3\text{CO}_2\text{D}$): δ ppm 9.04 (s, 2H), 8.67 (m, 2H), 8.61 (m, 2H), 8.13 (s, 2H), 4.35 (s, 6H). ^{13}C NMR (125 MHz, $\text{CF}_3\text{CO}_2\text{D}$): δ ppm 174.6, 163.1, 143.6, 142.7, 141.9, 138.6, 124.9, 124.0, 124.0, 108.9, 57.4. Yellow solid: m/z : 404.1008 $[\text{M}^+]$. ESI-HRMS Calcd. for $\text{C}_{22}\text{H}_{16}\text{N}_2\text{O}_6$: 405.1087 $[\text{M}+\text{H}]^+$, found 405.1088.

15a: ^1H NMR (400 MHz, CDCl_3): δ ppm 10.13 (s, 2H), 7.65 (d, $J=7.8$ Hz, 2H), 7.35 (t, $J=7.8$ Hz, 2H), 6.93 (d, $J=7.8$ Hz, 2H), 5.49 (s, 2H), 3.68 (s, 6H), 3.55 (s, 6H). ^{13}C NMR (100 MHz, CDCl_3): δ ppm 169.7, 165.1, 148.1, 137.2, 136.3, 126.6, 125.9, 123.5, 121.8, 93.9, 52.8, 51.2. Yellow solid, no satisfactory ESI-HRMS data was obtained.

15b: ^1H NMR (400 MHz, $\text{CF}_3\text{CO}_2\text{D}$): δ ppm 8.77 (d, $J=8.8$ Hz, 2H), 8.31 (d, $J=8.8$ Hz, 2H), 8.15 (s, 2H), 4.39 (s, 6H). Note: DMSO at 3.20. ^{13}C NMR (100 MHz, $\text{CF}_3\text{CO}_2\text{D}$): δ ppm 168.9, 166.70, 146.8, 146.3, 142.3, 132.2, 126.8, 123.4, 118.7, 56.6. Note: DMSO at 40.96. Brown solid, m/z : 378.0852 $[\text{M}^+]$. ESI-HRMS Calcd. for $\text{C}_{20}\text{H}_{14}\text{N}_2\text{O}_6$: 379.0930 $[\text{M}+\text{H}]^+$, found 379.0929.

16a: ^1H NMR (400 MHz, CDCl_3): δ ppm 10.08 (br s, 2 H), 7.95 (d, $J=8.4$ Hz, 2 H), 7.43 (t, $J=8.0$ Hz, 2 H), 6.97 (d, $J=7.6$ Hz, 2 H), 5.56 (s, 2 H), 3.79 (s, 6 H), 3.61 (s, 6 H). ^{13}C NMR (100 MHz, CDCl_3): δ ppm 170.5, 164.9, 149.3, 137.3, 128.9, 126.1, 119.4, 118.8, 94.7, 52.9, 51.6. Yellow solid, m/z : 442.1376 $[\text{M}^+]$. ESI-HRMS Calcd. for $\text{C}_{22}\text{H}_{22}\text{N}_2\text{O}_8$: 443.1454 $[\text{M}+\text{H}]^+$, found 443.1454.

16b: ^1H NMR (400 MHz, $\text{CF}_3\text{CO}_2\text{D}$): δ ppm 9.32 (d, $J=8.8$ Hz, 2H), 8.97 (d, $J=8.8$ Hz, 2H), 8.34 (s, 2H), 4.32 (s, 6H). ^{13}C NMR (100 MHz, $\text{CF}_3\text{CO}_2\text{D}$): δ ppm 175.0, 162.2, 143.9, 139.4, 128.5, 125.4, 125.0, 124.5, 111.5, 57.4. Light-brown solid, m/z : 378.0852 $[\text{M}^+]$. ESI-HRMS Calcd. for $\text{C}_{20}\text{H}_{14}\text{N}_2\text{O}_6$: 379.0930 $[\text{M}+\text{H}]^+$, found 379.0925.

10. General Procedure for preparation of heterocyclic enamine adducts (Table 4, 17c, 17a – 26a).

Refer to procedures 1 and 4.

11. General Procedure for preparation of heterocyclic quinolones (Table 4, 17d, 17b – 26b).

Refer to procedures 2 and 5.

Table 4: Synthesis of Heterocyclic Quinolones

Entry	Reactant	Product	% Yield
17	<p>17a, x = H 17c, x = Br</p>	<p>17b, x = H 17d, x = Br</p>	17b, 93 17d, 90
18	<p>18a</p>	<p>18b</p>	88
19	<p>19a</p>	<p>19b</p>	88
20	<p>20a</p>	<p>20b</p>	85
21	<p>21a</p>	<p>21b</p>	88
22	<p>22a</p>	<p>22b</p>	90
23	<p>23a</p>	<p>23b</p>	80
24	<p>24a</p>	<p>24b</p>	80
25	<p>25a</p>	<p>25b</p>	60
26	<p>26a</p>	<p>26b</p>	75

12. Spectral Data for heterocyclic enamines and heterocyclic quinolones (Table-4):

17a: ^1H NMR (400 MHz, CDCl_3): δ ppm 7.18 (m, 1H), 7.10 (m, 1H), 6.94 (td, $J=7.8, 1.0$ Hz, 1H), 6.83 (d, $J=7.8$ Hz, 1H), 5.04 (s, 1H), 4.01 (s, 3H), 3.86 (t, $J=8.4$ Hz, 2H), 3.70 (s, 3H), 3.17 (t, $J=8.4$ Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3): δ ppm 167.8, 165.6, 147.3, 142.6, 132.4, 127.9, 125.7, 123.1, 111.4, 91.6, 53.3, 51.3, 51.3, 27.4. White solid, m/z : 261.1001 [M^+]. ESI-HRMS Calcd. for $\text{C}_{14}\text{H}_{15}\text{NO}_4$: 262.1079 [$\text{M}+\text{H}$] $^+$, found 262.1079.

17b: ^1H NMR (400 MHz, DMSO-d_6): δ ppm 7.75 (m, 1H), 7.61 (m, 1H), 7.34 (t, $J=7.6$ Hz, 1H), 6.66 (s, 1H), 4.80 (t, $J=7.8$ Hz, 2H), 3.93 (s, 3H), 3.48 (t, $J=7.6$ Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ ppm 176.6, 162.4, 144.8, 137.6, 134.5, 127.0, 125.2, 124.1, 120.8, 112.9, 53.2, 52.5, 27.6. Light-yellow solid, m/z : 229.0739 [M^+]. ESI-HRMS Calcd. for $\text{C}_{13}\text{H}_{11}\text{NO}_3$: 230.0817 [$\text{M}+\text{H}$] $^+$, found 230.0816.

17c: ^1H NMR (400 MHz, CDCl_3): δ ppm 7.29 (m, 1H), 7.20 (m, 1H), 6.67 (d, $J=8.8$ Hz, 1H), 5.05 (s, 1H), 3.99 (s, 3H), 3.87 (t, $J=8.4$ Hz, 2H), 3.70 (s, 3H), 3.16 (t, $J=8.4$ Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3): δ ppm 167.6, 165.3, 146.9, 141.9, 134.7, 130.7, 128.8, 115.4, 112.6, 92.7, 53.4, 51.47, 51.4, 27.2. Light-yellow solid, m/z : 339.0106 [M^+]. ESI-HRMS Calcd. for $\text{C}_{14}\text{H}_{14}\text{BrNO}_4$: 340.0184 [$\text{M}+\text{H}$] $^+$, found 340.0181.

17d: ^1H NMR (500 MHz, $\text{D}_3\text{CCO}_2\text{D}$): δ ppm 8.12 (s, 1H), 7.69 (s, 1H), 7.26 (s, 1H), 4.98 (t, $J=7.6$ Hz, 2H), 4.02 (s, 3H), 3.57 (t, $J=7.6$ Hz, 2H). Note: DMSO at 2.84. ^{13}C NMR (125 MHz, $\text{D}_3\text{CCO}_2\text{D}$): δ ppm 178.7, 163.2, 145.2, 139.6, 138.6, 131.9, 125.7, 125.1, 121.1, 114.8, 55.1, 54.1, 28.5. Off-white solid, m/z : 306.9844 [M^+]. ESI-HRMS Calcd. for $\text{C}_{13}\text{H}_{10}\text{BrNO}_3$: 329.9742 [$\text{M}+\text{Na}$] $^+$, found 329.9736.

18a: No satisfactory NMR data obtained. Yellow solid, m/z : 292.0518 [M^+]. ESI-HRMS Calcd for $\text{C}_{13}\text{H}_{12}\text{N}_2\text{O}_4\text{S}$: 315.0415 [$\text{M}+\text{Na}$] $^+$, found 315.0418.

18b: ^1H NMR (500 MHz, DMSO-d_6): δ ppm 12.64 (brs, 1H), 9.44 (s, 1H), 8.41 (d, $J=8.8$ Hz, 1H), 8.14 (d, $J=8.8$ Hz, 1H), 6.88 (s, 1H), 3.99 (s, 3H). Note: MeOH at 3.16. ^{13}C NMR (500 MHz, DMSO-d_6): δ ppm 175.5, 162.5, 157.7, 150.18, 138.3, 137.3, 128.3, 127.7, 120.5, 111.5, 110.3, 53.6. Note: MeOH at

48.59. Off-white solid, m/z: 260.0256 [M^+]. ESI-HRMS Calcd. for $C_{12}H_8N_2O_3S$: 261.0334 [$M+H$] $^+$, found 261.0330.

19a: 1H NMR (500 MHz, D_3CCO_2D): δ ppm 9.26 (s, 1H), 8.63 (s, 1H), 8.14 (d, $J=8.7$ Hz, 1H), 7.92 (d, $J=2.4$ Hz, 1H), 7.48 (dd, $J=8.7, 2.4$ Hz, 1H), 3.81 (s, 3H), 3.79 (s, 3H). ^{13}C NMR (100 MHz, D_3CCO_2D): δ ppm 170.2, 168.2, 157.6, 153.8, 150.3, 138.6, 136.2, 124.7, 118.6, 111.27, 94.2, 52.43, 52.1. Off-white solid, m/z: 292.0518 [M^+]. ESI-HRMS Calcd. for $C_{13}H_{12}N_2O_4S$: 315.0415 [$M+Na$] $^+$, found 315.0419.

19b: 1H NMR (500 MHz, CF_3CO_2D): δ ppm 10.44 (s, 1H), 9.50 (s, 1H), 8.93 (d, $J=9.3$ Hz, 1H), 8.55 (d, $J=9.3$ Hz, 1H), 4.16 (s, 3H). ^{13}C NMR (500 MHz, CF_3CO_2D): δ ppm 173.6, 169.9, 166.6, 148.9, 144.7, 142.8, 130.1, 130.0, 125.6, 118.6, 110.2, 56.7. Brown solid, m/z: 260.0256 [M^+]. ESI-HRMS Calcd. for $C_{12}H_8N_2O_3S$: 261.0334 [$M+H$] $^+$, found 261.0331.

20a: 1H NMR (400 MHz, $CDCl_3$): δ ppm 11.24 (s, 1H), 7.33 (d, $J=5.4$ Hz, 1H), 6.49 (d, $J=5.4$ Hz, 1H), 5.49 (s, 1H), 3.91 (s, 3H), 3.82 (s, 3H), 3.78 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 168.3, 165.0, 163.9, 145.7, 144.7, 130.8, 119.6, 109.8, 97.4, 53.2, 52.2, 51.8. Yellow solid, m/z: 299.0464 [M^+]. ESI-HRMS Calcd. for $C_{12}H_{13}NO_6S$: 322.0361 [$M+Na$] $^+$, found 322.0360.

20b: 1H NMR (400 MHz, $DMSO-d_6$): δ ppm 10.28 (br s, 1H), 8.79 (s, 1H), 6.46 (d, $J=1.6$ Hz, 1H), 3.99 (s, 3H), 3.94 (s, 3H). ^{13}C NMR (100 MHz, $DMSO-d_6$): δ ppm 175.0, 162.7, 162.3, 143.1, 138.4, 134.1, 132.1, 109.1, 109.5, 53.9, 52.4. Light-yellow solid, m/z: 267.0201 [M^+]. ESI-HRMS Calcd. for $C_{11}H_9NO_5S$: 268.0280 [$M+H$] $^+$, found 268.0282.

21a: 1H NMR (400 MHz, $CDCl_3$): δ ppm 12.39 (d, $J=13.7$ Hz, 1H), 8.43 (d, $J=13.7$ Hz, 1H), 7.51 (d, $J=5.6$ Hz, 1H), 7.17 (d, $J=5.6$ Hz, 1H), 3.93 (s, 3H), 3.90 (s, 3H), 3.78 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 167.7, 166.1, 163.6, 150.8, 145.4, 132.7, 116.7, 111.5, 95.4, 52.5, 52.1, 51.8. White solid, m/z: 299.0464 [M^+]. ESI-HRMS Calcd. for $C_{12}H_{13}NO_6S$: 322.0361 [$M+Na$] $^+$, found 322.0355.

21b: 1H NMR (400 MHz, D_3CCO_2D): δ ppm 8.81 (s, 1H), 8.73 (s, 1H), 3.98 (s, 3H), 3.86 (s, 3H). ^{13}C NMR (100 MHz, D_3CCO_2D): δ ppm 174.3, 167.2, 163.9, 149.5, 143.46, 135.6, 134.7, 113.4, 110.2,

53.1, 52.5. Yellow solid, m/z: 267.0201 [M^+]. ESI-HRMS Calcd. for $C_{11}H_9NO_5S$: 290.0099 [$M+Na$] $^+$, found 290.0096.

22a: 1H NMR (400 MHz, $CDCl_3$): δ ppm 10.03 (s, 1H), 8.26 (d, J = 8.3 Hz, 1H), 8.16 (d, J = 8.3 Hz, 1H), 7.67 -7.61 (om, 3H), 6.80 (d, J = 8.0 Hz, 1H), 5.59 (s, 1H), 3.80 (s, 3H), 3.62 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 170.5, 164.7, 149.1, 136.9, 132.7, 129.5, 129.3, 128.1, 127.5, 127.5, 122.8, 119.4, 118.7, 95.2, 53.0, 51.6. Yellow solid, m/z: 363.0106 [M^+]. ESI-HRMS Calcd. for $C_{16}H_{14}BrNO_4$: 364.0184 [$M+H$] $^+$, found 364.0181

22b: 1H NMR (500 MHz, $DMSO-d_6$): δ ppm 9.14 (dd, J = 8.0, 1.6 Hz, 1H), 8.38 (s, 1H), 8.06 (m, 1H), 7.70 (ddd, J = 8.3, 6.8, 1.6 Hz, 1H), 7.64 (ddd, J = 8.0, 6.8, 1.2 Hz, 1H), 6.80 (s, 1H), 3.85 (s, 3H). Note: MeOH at 3.18 (s). ^{13}C NMR (125 MHz, $DMSO-d_6$): δ ppm 173.5, 168.1, 147.7, 146.5, 133.8, 131.5, 127.9, 126.58, 126.0, 126.0, 125.4, 125.1, 115.0, 111.5, 51.7. Note: acetone at 30.67. Grey solid, m/z: 330.9844 [M^+]. ESI-HRMS Calcd. for $C_{15}H_{10}BrNO_3$: 331.9922 [$M+H$] $^+$, found 331.9926.

23a: 1H NMR (400 MHz, $CDCl_3$): δ ppm 10.02 (s, 1H), 8.95 (dd, J = 4.0, 1.6 Hz, 1H), 8.48 (dd, J = 8.4, 0.8 Hz, 1H), 7.92 (d, J =8.4 Hz, 1H), 7.58 (t, J = 7.8 Hz, 1H), 7.46 (dd, J = 8.4, 4.0 Hz, 1H), 6.99 (dd, J = 7.8, 0.8 Hz, 1H), 5.59 (s, 1H), 3.78 (s, 3H), 3.58 (s, 3H). Note: acetone at 2.16. ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 170.4, 164.6, 151.0, 149.3, 149.0, 136.9, 130.9, 129.0, 126.9, 123.6, 121.5, 118.9, 95.2, 52.9, 51.6. Note: acetone at 31.07. Yellow solid, m/z: 286.0954 [M^+]. ESI-HRMS Calcd. for $C_{15}H_{14}N_2O_4$: 287.1032 [$M+H$] $^+$, found 287.1038.

23b: 1H NMR (500 MHz, D_3CCO_2D): δ ppm 9.46 (d, J = 8.0 Hz, 1H), 9.21 (dd, J =4.4 Hz, 1.2 Hz, 1H), 8.54 (d, J = 9.1 Hz, 1H), 8.10 (d, J = 8.7 Hz, 1H), 7.89 (dd, J =8.7 Hz, 4.4 Hz, 1H) 7.56 (s, 1H), 4.09 (s, 3H). ^{13}C NMR (125 MHz, D_3CCO_2D): δ ppm 175.2, 164.8, 151.7, 148.7, 142.0, 140.7, 135.4, 127.5, 125.5, 123.4, 123.0, 122.8, 112.9, 54.4. Off-white solid, m/z: 254.0691 [M^+]. ESI-HRMS Calcd. for $C_{14}H_{10}N_2O_3$: 277.0589 [$M+Na$] $^+$, found 277.0586.

24a: 1H NMR (400 MHz, $CDCl_3$): δ ppm 11.79 (d, J = 12.8 Hz, 1H), 8.94 (d, J = 4.4, 1.6 Hz, 1H), 8.62 (dd, J = 12.8 Hz, 1H), 8.33 (dd, J = 8.4 Hz, 1H), 7.93 (d, J = 8.4, 1H), 7.68 (t, J =8.0 Hz, 1H), 7.47 (dd, J = 8.4, 4.4 Hz, 1H), 7.38 (d, J = 8.0 Hz, 1H), 3.89 (s, 3H), 3.78 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ

ppm 169.9, 165.7, 153.6, 151.2, 148.8, 135.5, 129.4, 129.3, 127.0, 121.7, 120.7, 113.6, 94.6, 51.9, 51.7.

Yellow solid, m/z : 286.0954 [M^+]. ESI-HRMS Calcd. for $C_{15}H_{14}N_2O_4$: 309.0851 [$M+Na$] $^+$, found 309.0852.

24b: 1H NMR (400 MHz, CF_3CO_2D): δ ppm 10.26 (d, J = 7.6 Hz, 1H), 9.66 (s, 1H), 9.52 (s, 1H), 9.12 (d, J = 8.4 Hz, 1H), 8.68 (d, J = 8.4 Hz, 1H), 8.54 (m, 1H), 4.22 (s, 3H). ^{13}C NMR (100 MHz, CF_3CO_2D): δ ppm 175.4, 169.4, 149.9, 149.4, 145.9, 143.8, 140.1, 132.2, 127.49, 124.4, 123.4, 122.7, 111.5, 56.5. Light- brown solid, m/z : 254.0691 [M^+]. ESI-HRMS Calcd. for $C_{14}H_{10}N_2O_3$: 255.0770 [$M+H$] $^+$, found 255.0766.

25a: 1H NMR (400 MHz, $CDCl_3$): δ ppm 10.72 (d, J = 14.0, 1H), 8.24 (d, J = 14.0 Hz, 1H), 6.78 (d, J =2.2 Hz, 1H), 6.70 (d, J = 2.2 Hz, 1H), 3.89 (s, 3H), 3.82 (s, 6H), 3.74 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 169.6, 166.1, 161.2, 154.6, 125.4, 121.9, 118.69, 107.2, 91.2, 51.5, 51.4, 51.47, 37.0. Off-white solid, m/z : 296.1008 [M^+]. ESI-HRMS Calcd. for $C_{13}H_{16}N_2O_6$: 319.0906 [$M+Na$] $^+$, found 319.0911.

25b: 1H NMR (500 MHz, CF_3CO_2D): δ ppm 9.04 (s, 1H), 7.54 (s, 1H), 4.60 (s, 3H), 4.19 (s, 3H), 4.15 (s, 3H). ^{13}C NMR (125 MHz, CF_3CO_2D): δ ppm 171.2, 165.7, 164.2, 142.9, 139.3, 138.5, 125.2, 107.6, 106.6, 55.9, 55.7, 37.5. Brown solid, m/z : 264.0746 [M^+]. ESI-HRMS Calcd. for $C_{12}H_{12}N_2O_5$: 265.0824 [$M+H$] $^+$, found 265.0824.

26a: 1H NMR (400 MHz, $CDCl_3$): δ ppm 9.71 (s, 1H), 7.69 (m, 2H), 6.88, (m, 2H), 6.81 (t, J = 6.0 Hz, 1H), 5.53 (s, 1H), 3.76 (s, 3H), 3.74(s, 3H), 3.72 (q, J = 6.0 Hz, 2H), 2.72 (t, J =6.0, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 176.4, 169.5, 166.9, 164.4, 146.4, 143.3, 128.9, 128.1, 119.5, 96.3, 52.9, 51.4, 35.2, 33.6. Yellow solid, m/z : 350.1114 [M^+]. ESI-HRMS Calcd. for $C_{16}H_{18}N_2O_7$: 351.1192 [$M+H$] $^+$, found 351.1199.

26b: 1H NMR (400 MHz, D_3CCO_2D): δ ppm 8.83 (d, J = 2.0 Hz, 1H), 8.31 (dd, J =8.8 Hz, 2.0, 1H), 7.94 (d, J = 8.8 Hz, 1H), 7.21 (s, 1H), 4.06 (s, 3H), 3.77 (t, J =6.8 HZ, 2H), 3.71 (s, 3H), 2.78 (t, J =6.8 Hz, 2H). ^{13}C NMR (100 MHz, D_3CCO_2D): δ ppm 181.5, 174.4, 168.5, 163.6, 142.7, 139.8, 133.9, 131.1,

125.6, 125.6, 120.9, 112.0, 54.6, 52.6, 37.1, 34.3. Note: DMSO at 39.54. Grey solid, m/z: 332.1008 [M⁺]. ESI-HRMS Calcd. for C₁₆H₁₆N₂O₆: 333.1087 [M+H]⁺, found 333.1097.