SUPPORTING INFORMATION

Antimalarial N^1,N^3-Dialkyldioxonaphthoimidazoliums: Synthesis, biological activity and structure-activity relationships.

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1. Description of methods employed in the synthesis of intermediates/ final compounds in Series A-C.

1.1. General Chemistry

Reagents were purchased from commercial sources and used as received. Reactions were monitored by thin layer chromatography (TLC) using pre-coated aluminium plates (silica gel 60, F254, Merck). Compounds were purified by column chromatography on silica gel 60 (230-400 mesh, Merck). ^{1}H and ^{13}C NMR spectra were recorded at 298 K on a Bruker Ultrashield Avance 400 (AV400) or Avance 500 (AV500) instrument (Bruker, Billerica, MA, USA). Chemical shifts were reported in parts per million (ppm) on the □ scale using residual protio-solvent signals (^{1}H NMR, $CDCl_3$ δ 7.26, DMSO-d_6 δ 2.50, MeOH-d_4 δ 3.31; ^{13}C NMR, $CDCl_3$ δ 77.0, DMSO-d_6 δ 9.5, MeOH-d_4 δ 49.0) as internal references. Nominal mass spectra were captured on an AB Sciex QTrap 2000 mass spectrometer (AB Sciex, Framingham, MA, USA) by electrospray ionization (ESI). Accurate mass information was obtained on a Bruker micrOTOFQII mass spectrometer (Bruker, Billerica, MA, USA) by ESI. Compounds subjected to biological testing were found to be ≥ 95% pure as determined by reverse-phase HPLC on a Shimadzu Nexera SR HPLC system (Shimadzu Scientific Instruments, Columbia, MD, USA) on two mobile phases

1.2. General procedure for the synthesis of 2-chloro-3-(N-substituted amino) naphthalene-1,4-diones **(41a-51a)**

The reported method was followed.[S1] To 2,3-dichloro-1,4-naphthoquinone (1.5 mmol) in 10mL ethanol was added the amine (1.5 mmol) and triethylamine (2.25 mmol) and the reaction mixture stirred at room temperature (25^{o}C) for 24 h. A colored precipitate formed. This was collected by filtration, washed with distilled water and dried to afford the crude product which was recrystallized from ethanol. Yields varied from 65% to 90%.

1.3. General procedure for the synthesis of N-(3-chloro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-N-substituted acetamides **(41b-51b)**

Following the reported method,[S1] two drops of concentrated sulfuric acid were added to a suspension of **41a-51a,** (2.0 mmol) in acetic anhydride (18.0 mmol) and stirred for 1.5h, room temperature. Distilled water (10 mL) was added dropwise to the reaction mixture with stirring after which extraction with ethyl acetate (EtOAc) was carried out. The organic layer was washed with saturated $NaHCO_3$ solution, brine and dried over anhydrous Na_2SO_4. Purification by column chromatography (EtOAc/hexane) gave **41b-51b** as colored oils/ solids in yields varying from 50-80%.

1.4. General procedure for the synthesis of [3-(N-substituted amino)-1,4-dioxo-1,4-dihydronaphthalen-2-yl]-N-substituted acetamides **(4a-35a)**

To a stirred suspension of **41b-51b** (1.0 mmol) in toluene (2mL) was added dropwise equimolar amounts (1.5 mmol) of the amine and trimethylamine as described previously.[S1] The mixture was stirred at 45 ^{0}C for 2-5 h, after which it was concentrated *in vacuo* and purified by column chromatography (MeOH or EtOAc/DCM) to afford the desired product **4a-35a** as colored solids/oils in yields ranging from 20-60%.

1.5. General procedure for the synthesis of N^1 N^3- disubstituted-2-methyl-4,9-dioxo-4,9-dihydro-1H-naphtho[2,3-d] imidazol-3-ium bromides **(4-35)**

Following the reported method,[S1] 48% aqueous hydrobromic acid (10.0 mmol, ~2 mL) was added dropwise to a solution of **4a-35a** (1.0 mmol) in a mixture of 1:1 EtOH/EtOAc and stirred at 40 °C for 4h, followed by stirring for 18 h at room temperature. The reaction mixture was concentrated *in vacuo* and purified by column chromatography (MeOH/DCM) to afford the desired compounds as colored solids in yields ranging from 10-60%.

1.6. General procedure for the synthesis of [3-(N-substituted amino)-1,4-dioxo-1,4-dihydronaphthalen-2-yl]acetamides **(36a-40a)**

52 and **53** were synthesized as reported.[S1] **53** was reacted by the method described for the syntheses of **4a-35a** to give the desired compounds as colored solids in yields ranging from 42% to 59%.

1.7. General procedure for the synthesis of N-substituted-2-methyl-4,9-dioxo-4,9-dihydro-1H-naphtho[2,3-d] imidazol-3-ium bromides **(36-40)**

The method described for **4-35** was employed to give the desired compounds as colored solids in yields ranging from 20-35%.

2. Characterization of Intermediates (4a-35a, 36a-40a, 42a-51a, 42b-51b)

N-[1,4-Dioxo-3-methylamino-1,4-dihydro-naphthalen-2-yl]-*N*-methyl-acetamide (**4a**) [S1]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (dd, *J*= 7.7, 0.8 Hz, 1H), 8.08 (dd, *J*=7.7, 0.9 Hz, 1H), 7.78 (dt, *J*=7.6, 1.3 Hz), 7.66 (dt, *J*=7.6, 1.3 Hz, 1H), 6.24 (br s, 1H), 3.13 (s, 3H), 3.11 (d, *J*= 5.8 Hz, 3H), 1.99 (s, 3H).

***N*-(3-(Ethylamino)-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-N-methylacetamide (5a)**

Brown solid; Yield: 69.4%; mp: 169-169.9 ^{0}C ;^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (dd, *J* = 7.7, 1.1 Hz, 1H), 8.08 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.77 (td, *J* = 7.6, 1.3 Hz, 1H), 7.66 (td, *J* = 7.6, 1.3 Hz, 1H), 5.96 (s, 1H), 3.46 – 3.40 (m, 2H), 3.11 (s, 3H), 1.97 (s, 3H), 1.34 (t, *J* = 7.2 Hz, 3H); Calculated for $C_{15}H_{16}N_2O_3$ 272.1; Found MS (ESI) m/z 273.2 $[M+H]^+$

(*N*-(1,4-Dioxo-3-(propylamino)-1,4-dihydronaphthalen-2-yl)-N-methylacetamide (6a)

Red solid; Yield: 71.4%; mp: 179.3-180.5 ^{0}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 7.7 Hz, 1H), 8.08 (d, *J* = 7.7 Hz, 1H), 7.77 (t, *J* = 8.2 Hz, 1H), 7.71 – 7.62 (m, 1H), 6.04 (s, 1H), 3.35 (d, *J* = 5.7 Hz, 2H), 3.11 (s, 3H), 1.97 (s, 3H), 1.70 (q, *J* = 7.2 Hz, 2H), 1.02 (t, *J* = 7.4 Hz, 3H); Calculated for $C_{16}H_{18}N_2O_3$ 286.1; Found MS (ESI) m/z 287.2 $[M+H]^+$

(*N*-(3-(Isopropylamino)-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-N-methylacetamide (7a)

Red solid; Yield: 33.4%, mp: 178.0-179.5 ^{0}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (dd, *J* = 7.7, 1.0 Hz, 1H), 8.08 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.76 (td, *J* = 7.6, 1.3 Hz, 1H), 7.65 (td, *J* = 7.6, 1.3 Hz, 1H), 6.02 (s, 1H), 4.09 (m, 1H), 3.10 (s, 3H), 1.98 (s, 3H), 1.29 (d, *J* = 6.4 Hz, 3H), 1.24 (d, *J* = 6.4 Hz, 3H); Calculated for $C_{16}H_{18}N_2O_3$ 286.1; Found MS (ESI) m/z 287.1 $[M+H]^+$

(*N*-(3-(Cyclopropylamino)-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-N-methylacetamide (8a)

Red solid; yield: 41.7%; mp: 197.1-197.4 ^{0}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 – 8.00 (m, 2H), 7.67 (m, 2H), 5.84 (br s, 1H), 3.57 – 3.39 (m, 1H), 3.13 (s, 3H), 1.29 (dt, *J* = 22.6, 7.2 Hz, 3H), 0.95 – 0.63 (m, 4H); Calculated for $C_{16}H_{16}N_2O_3$ 284.1; Found MS (ESI) m/z 285.2 $[M+H]^+$

(*N*-(3-(Butylamino)-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-N-methylacetamide (9a)

Red solid; Yield: 80.1%; mp: 187.6-188.8 ^{0}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 – 8.11 (m, 2H), 7.77-7.65 (m, 2H), 6.03 (br s, 1H), 3.41-3.36 (m, 2H), 3.10 (s, 3H), 1.98 (s, 3H), 1.65-1.61 (m, 2H), 1.44-1.39 (dq, *J* = 12.4, 6.1, 4.9 Hz, 2H), 0.98-0.94 (t, *J* = 7.3 Hz, 3H); Calculated for $C_{17}H_{20}N_2O_3$ 300.2; Found MS (ESI) m/z 301.1 $[M+H]^+$

(N-Ethyl-N-(3-(ethylamino)-1,4-dioxo-1,4-dihydronaphthalen-2 yl) acetamide (10a)

Red oil; Yield: 47.8%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16-8.13 (m, 1H), 8.08 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.77 (td, *J* = 7.6, 1.3 Hz, 1H), 7.66 (td, *J* = 7.6, 1.3 Hz, 1H), 5.96 (s, 1H), 3.48-3.36 (m, 2H), 3.13 (m, 2H), 1.98 (s, 3H), 1.32 (t, *J* = 7.2 Hz, 3H), 1.13 (t, *J* = 7.2 Hz, 3H); Calculated for $C_{16}H_{18}N_2O_3$ 286.1; Found MS (ESI) m/z 287.2 $[M+H]^+$

[N-(3-(Ethylamino)-1,4-dioxo-1,4-dihydronaphthalen-2-yl]-N-propylacetamide (11a)

Red semi-solid; Yield: 24.2%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (dd, 1H, J = 7.7, 1.0 Hz), 8.08 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.76 (td, J = 7.6, 1.3 Hz, 1H), 7.65 (td, *J* = 7.6, 1.3 Hz, 1H), 5.95 (br s, 1H), 3.51-3.33 (m, 2H), 2.96 (m, 2H), 1.98 (s, 3H), 1.75 – 1.64 (m, 3H), 1.33 –

1.23 (m, 2H), 0.86 (t, *J* = 7.4 Hz, 3H); Calculated for $C_{17}H_{20}N_2O_3$ 300.2; Found MS (ESI) m/z 301.2 $[M+H]^+$

[N-(3-(Ethylamino)-1,4-dioxo-1,4-dihydronaphthalen-2-yl]-N-isopropylacetamide (12a)

Red oil; Yield: 26.4%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16-8.08 (m, 2H), 7.80-7.64 (m, 2H), 5.93 (br s, 1H), 4.52-4.42 (m, 1H), 3.54-3.33 (m, 2H), 1.96 (s, 3H), 1.35 – 1.28 (m, 6H), 1.05-1.03 (d, *J* = 7.0 Hz, 3H); Calculated for $C_{17}H_{20}N_2O_3$ 300.2; Found MS (ESI) m/z 301.1 $[M+H]^+$

[N-Cyclopropyl-N-(3-(ethylamino)-1,4-dioxo-1,4-dihydronaphthalen-2-yl] acetamide (13a)

Red oil; Yield: 36.5%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12-8.00 (m, 2H), 7.67 (m, 2H), 5.84 (m, 1H), 3.57 – 3.39 (m, 1H), 3.13 (m, 2H), 1.91 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 3H), 0.95 – 0.63 (m, 4H); Calculated for $C_{17}H_{18}N_2O_3$ 298.1; Found MS (ESI) m/z 299.2 $[M+H]^+$

[N-Butyl-N-(3-(ethylamino)-1,4-dioxo-1,4-dihydronaphthalen-2-yl]acetamide (14a)

Red oil; Yield: 78.4%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15-8.14 (dd, *J* = 7.7, 1.0 Hz, 1H), 8.08-8.07 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.77-7.75 (td, *J* = 7.6, 1.3 Hz, 1H), 7.68-7.64 (td, *J* = 7.6, 1.3 Hz, 1H), 6.02 (s, 1H), 4.00 (m, 1H), 3.45-3.34 (m, 2H), 3.11 (m, 1H), 1.97 (s, 3H), 1.68-1.60 (m, 2H), 1.46-1.40 (m, 2H), 1.13 (t, *J* = 7.2 Hz, 3H), 0.96 (t, *J* = 7.3 Hz, 3H); Calculated for $C_{18}H_{22}N_2O_3$ 314.2; Found MS (ESI) m/z 315.2 $[M+H]^+$

[N-(1,4-Dioxo-3-(propylamino)-1,4-dihydronaphthalen-2-yl]-N-propylacetamide (15a)

Red oil; Yield: 48.6%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16-8.07 (m, 2H), 7.79-7.64 (m, 2H), 6.03 (br s, 1H), 3.86 (m, 1H), 3.45-3.27 (m, 2H), 2.89 (m, 1H), 1.98 (s, 3H), 1.74-1.64 (m, 4H), 1.02 (t, *J* = 7.4 Hz, 3H), 0.87 (t, *J* = 7.4 Hz, 3H); Calculated for $C_{18}H_{22}N_2O_3$ 314.2; Found MS (ESI) m/z 315.1 $[M+H]^+$

N-[3-(Isopropylamino)-1,4-dioxo-1,4-dihydronaphthalen-2-yl]-N-propylacetamide (16a)

Red oil; Yield: 46.0%; ^{1}H NMR (400 MHz, $CDCl_3$)δ 8.14-8.12 (dd, *J* = 7.7, 1.1 Hz, 1H), 8.08-8.06 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.77-7.73 (td, *J* = 7.6, 1.3 Hz, 1H), 7.66-7.62 (td, *J* = 7.6, 1.3 Hz, 1H), 5.96 (br s, 1H), 4.00-3.91 (m, 1H), 2.98 – 2.75 (m, 2H), 1.96 (s, 3H), 1.65 (d,*J* = 5.5 Hz, 2H), 1.31 (d, *J* = 6.4 Hz, 3H), 1.17 (d, *J*= 6.3 Hz, 3H), 0.86 (t, *J* = 7.4 Hz, 3H); Calculated for $C_{18}H_{22}N_2O_3$ 314.2; Found MS (ESI) m/z 315.2 $[M+H]^+$

N-[3-(cyclopropylamino)-1,4-dioxo-1,4-dihydronaphthalen-2-yl]-N-propylacetamide (17a)

Red oil; Yield: 34.1%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14-8.03 (m, 2H), 7.78-7.62 (m, 2H), 6.13 (s, 1H), 4.10-4.03 (m, 1H), 2.91 – 2.83 (m, 2H), 2.01 (s, 3H), 1.74-1.69 (m, 2H),1.00 - 0.80 (m, 5H), 0.73 - 0.56 (m, 2H); Calculated for $C_{18}H_{20}N_2O_3$ 312.2; Found MS (ESI) m/z 313.1 $[M+H]^+$

N-[3-(Butylamino)-1,4-dioxo-1,4-dihydronaphthalen-2-yl]-N-propylacetamide (18a)

Red oil; Yield: 52.3%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 – 8.10 (m, 1H), 8.05 (dd, *J* = 7.7, 0.9 Hz, 1H), 7.74 (td, *J* = 7.6, 1.3 Hz, 1H), 7.63 (td, *J* = 7.6, 1.3 Hz, 1H), 6.03 (s, 1H), 3.85 (m, 1H), 3.43-3.29 (m, 2H), 2.90 (m, 1H), 1.95 (s, 3H), 1.72 – 1.55 (m, 4H), 1.47 – 1.32 (m, 2H), 0.96 – 0.84 (m, 6H); Calculated for $C_{19}H_{24}N_2O_3$ 328.2; Found MS (ESI) m/z 329.3 $[M+H]^+$

[N-Isopropyl-N-(3-(isopropylamino)-1,4-dioxo-1,4-dihydronaphthalen-2-yl]acetamide (19a)

Red oil; Yield: 35.8%; ^{1}H NMR (400 MHz, MeOD) δ 8.09-8.06 (m, 2H), 7.83-7.79 (td, *J* = 9.4, 1.65 Hz, 1H), 7.74-7.70 (td, *J* = 9.55, 1.45 Hz, 1H), 4.46-4.27 (m, 2H), 1.96 (s, 3H), 1.34 (d,

J = 8.05 Hz, 3H), 1.27 (d, *J* = 8 Hz, 3H), 1.24 (d, *J* = 8 Hz, 3H), 1.12 (d, *J* = 8.6 Hz, 3H); Calculated for $C_{18}H_{22}N_2O_3$ 314.2; Found MS (ESI): m/z 313.2 $[M-H]^-$

N-(3-[Cyclopropylamino)-1,4-dioxo-1,4-dihydronaphthalen-2-yl]-N-isopropylacetamide (20a)

Red oil; Yield: 68.9%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 - 8.05 (m, 2H), 7.79 – 7.63 (m, 2H), 6.07 (s br, 1H), 4.52-4.42 (m, 1H), 2.91-2.87 (m, 1H), 1.99 (s, 3H), 1.34-1.32 (d, *J* = 6.3 Hz, 3H), 1.08-1.07 (d, *J* = 7.0 Hz, 3H), 0.98 – 0.83 (m, 2H), 0.72 – 0.55 (m, 2H); Calculated for $C_{18}H_{20}N_2O_3$ 312.2; Found MS (ESI) m/z 313.1 $[M+H]^+$

N-[3-(Butylamino)-1,4-dioxo-1,4-dihydronaphthalen-2-yl]-N-isopropylacetamide (21a)

Red oil; Yield: 66.4%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13-8.05 (m, 2H), 7.77-7.62 (m, 2H), 5.99 (s br, 1H), 4.47-4.39 (m, 1H), 3.48-3.27 (m, 2H), 1.93 (m, 3H), 1.67 – 1.59 (m, 2H), 1.46-1.39 (m, 2H), 1.28-1.27 (d, *J* = 6.3 Hz, 3H), 1.03-1.01 (d, *J* = 7.0 Hz, 3H), 0.96-0.92 (t, *J* = 7.3 Hz, 3H); Calculated for $C_{19}H_{24}N_2O_3$ 328.2; Found MS (ESI) m/z 329.2 $[M+H]^+$

N-Cyclopropyl-N-(3-(cyclopropylamino)-1,4-dioxo-1,4-dihydronaphthalen-2-yl] acetamide (22a)

Red oil; Yield: 35.1%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12-8.00 (m, 2H), 7.75-7.50 (m, 2H), 5.29 (s, 1H), 3.17 (m, 1H), 2.95 (m, 1H), 2.00 (s, 3H), 0.91 – 0.60 (m, 8H); Calculated for $C_{18}H_{18}N_2O_3$ 310.1; Found MS (ESI) m/z 311.4 $[M+H]^+$

N-Butyl-N-(3-(cyclopropylamino)-1,4-dioxo-1,4-dihydronaphthalen-2-yl]acetamide (23a)

Red semi-solid; Yield: 67.5%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14-8.09 (dd, J = 7.7, 1.0 Hz, 1H), 8.05-8.01 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.76-7.74 (td, *J* = 7.6, 1.3 Hz, 1H), 7.64-7.62 (td, *J* = 7.6, 1.3 Hz, 1H), 6.11 (s, 1H), 4.09-4.08 (ddd, *J* = 13.0,10.6, 5.6 Hz, 1H), 2.95 – 2.83 (m, 2H), 2.01 (s, 3H), 1.38 – 1.22 (m, 4H), 0.90-0.83 (t, *J* = 7.2 Hz, 3H), 0.74 – 0.56 (m, 4H); Calculated for $C_{19}H_{22}N_2O_3$ 326.2; Found MS (ESI) m/z 327.4 $[M+H]^+$

N-Butyl-N-[3-(butylamino)-1,4-dioxo-1,4-dihydronaphthalen-2-yl]acetamide (24a)

Red semi-solid; Yield: 65.7%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15-8.14 (d, *J* = 7.7 Hz, 1H), 8.09-8.07 (d, *J* = 7.7 Hz, 1H), 7.79 – 7.73 (m, 1H), 7.68 – 7.62 (m, 1H), 6.01(s, 1H), 3.96-3.94 (m, 1H), 3.46 – 3.32 (m, 2H), 2.93-2.91 (m, 1H), 1.97 (s, 3H), 1.67-1.60 (m, 4H), 1.46 – 1.26 (m, 4H), 0.97 – 0.86 (m, 6H); Calculated for $C_{20}H_{26}N_2O_3$ 342.2; Found MS (ESI) m/z 343.3 $[M+H]^+$

***N*-Isobutyl-N-[3-(methylamino)-1,4-dioxo-1,4-dihydronaphthalen-2-yl]acetamide (25a)**

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (dd, *J* = 7.7, 1.1 Hz, 1H), 8.08 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.77 (td, *J* = 7.6, 1.3 Hz, 1H), 7.66 (td, *J* = 7.6, 1.3 Hz, 1H), 6.22 (s, 1H), 4.03 (dd, *J* = 13.1, 9.8 Hz, 1H), 3.08-3.07 (m, 4H), 2.03 (s, 3H), 1.74-1.69 (m, 1H), 1.08 (d, *J* = 6.5 Hz, 3H), 0.83 (d, *J* = 6.7 Hz, 3H); Calculated for $C_{17}H_{20}N_2O_3$ 300.2; Found MS (ESI) m/z 301.2 $[M+H]^+$

N-[3-(Ethylamino)-1,4-dioxo-1,4-dihydronaphthalen-2-yl]-N-isobutylacetamide (26a)

Red oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (d, J = 7.75 Hz, 1H), 8.05 (d, *J* = 7.7 Hz, 1H), 7.72-7.69 (t, *J* = 6.85 Hz, 1H), 7.62-7.59 (t, J = 7.45 Hz, 1H), 6.09 (br s, 1H), 3.37-3.31 (quint, *J* = 7.1 Hz, 2H), 3.12-3.07 (m, 2H), 1.93 (s, 3H), 1.71-1.66 (m, 1H), 1.29-1.26 (t, *J* = 7.35 Hz, 3H), 0.93 (d, J = 6.3 Hz, 3H) 0.91 (d, *J* = 7.2 Hz, 3H); Calculated for $C_{18}H_{22}N_2O_3$ 314.2; Found MS (ESI) m/z 315.1 $[M+H]^+$

N-[1,4-Dioxo-3-(propylamino)-1,4-dihydronaphthalen-2-yl]-N-isobutylacetamide (27a)

Red oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (dd, *J* = 7.7, 1.1 Hz, 1H), 8.07 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.78 – 7.74 (m, 1H), 7.67-7.63 (m, 1H), 6.02 (s, 1H), 3.99 (dd, *J* = 13.2, 9.9 Hz, 1H), 3.50 – 3.14 (m, 3H), 2.01 (s, 3H), 1.68-1.66 (m, 3H), 1.07 – 0.99 (m, 6H), 0.82 (d, *J* = 6.7 Hz, 3H); Calculated for $C_{19}H_{24}N_2O_3$ 328.2; Found MS (ESI) m/z 329.2 $[M+H]^+$

N-Isobutyl-N-[3-(isopropylamino)-1,4-dioxo-1,4-dihydronaphthalen-2-yl]acetamide (28a)

Red semi-solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (dd, *J* = 7.7, 1.0 Hz, 1H), 8.07 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.75 (td, *J* = 7.6, 1.3 Hz, 1H), 7.64 (td, *J* = 7.6, 1.3 Hz, 1H), 5.94 (br s, 1H), 3.98-3.94(m, 2H), 2.65-2.55 (m, 1H), 2.02 (s, 3H), 1.68-1.63 (m, 1H) , 1.31 (d, *J* = 6.4 Hz, 3H), 1.15 (d, *J* = 6.3 Hz, 3H), 1.04 (d, *J* = 6.6 Hz, 3H), 0.81 (d, *J* = 6.7 Hz, 3H); Calculated for $C_{19}H_{24}N_2O_3$ 328.2; Found MS (ESI) m/z 329.2 $[M+H]^+$

N-[3-(Cyclopropylamino)-1,4-dioxo-1,4-dihydronaphthalen-2-yl]-N-isobutylacetamide (29a)

Red semi-solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (dd, *J* = 7.7, 1.0 Hz, 1H), 8.06 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.76 (td, *J* = 7.6, 1.3 Hz, 1H), 7.65 (td, *J* = 7.6, 1.3 Hz, 1H), 6.09 (s, 1H), 4.15-4.10 (m, 1H), 2.72 – 2.67 (m, 2H), 2.07 (s, 3H), 1.68-1.66 (m, 1H), 1.08 (d, *J* = 6.5 Hz, 3H), 0.98-0.82 (m, 4H), 0.75-0.44 (m, 3H), Calculated for $C_{19}H_{22}N_2O_3$ 326.2; Found MS (ESI) m/z 327.2 $[M+H]^+$

N-Butyl-N-{3-[(2-methylpropyl)amino]-1,4-dioxo-1,4-dihydronaphthalen-2-yl}acetamide (30a)

Red semi-solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (d, J = 7.6 Hz, 1H), 8.06 (d, *J* = 7.5 Hz, 1H), 7.74 (t, *J* = 7.45 Hz, 1H), 7.63 (t, *J* = 7.6 Hz, 1H), 6.12 (s, 1H), 4.01-3.96 (m, 1H), 3.30-3.25 (m, 2H), 2.01 (s, 3H), 1.65-1.65 (m, 4H), 1.45-1.39 (m, 2H), 1.06 (d, *J* = 6.8 Hz, 3H), 0.96 (t, *J* = 6.8 Hz, 3H), 0.83 (t, *J* = 7.25, 3H); Calculated for $C_{20}H_{26}N_2O_3$ 342.2; Found MS (ESI) m/z 343.0 $[M+H]^+$

N-(2-Methylpropyl)-N-{3-[(2-methylpropyl)amino]-1,4-dioxo-1,4-dihydronaphthalen-2-yl }acetamide (31a)

Red semi-solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, J = 7.5 Hz, 1H), 8.04 (d, *J* = 7.3 Hz, 1H), 7.74-7.41 (td, *J* = 7.6, 1 Hz, 1H), 7.63-7.60 (td, J = 7.6, 1.05 Hz, 1H), 6.10 (s, 1H), 3.96-3.92 (t, J = 10.1 Hz, 1H), 3.19-3.10 (m, 1H), 3.09 (m, 1H), 2.60-2.58 (m, 1H), 1.96 (s, 3H), 1.86-1.78 (m, 1H), 1.67-1.60 (m, 1H), 1.02 (d, *J* = 6.55 Hz, 3H), 0.98 (d, *J* = 6.75 Hz, 3H), 0.95 (d, *J* = 6.6 Hz, 3H), 0.79 (d, *J* = 6.75 Hz, 3H); Calculated for $C_{20}H_{26}N_2O_3$ 342.2; Found MS (ESI) m/z 343.2 $[M+H]^+$

N-Hexyl-N-{3-[(2-methylpropyl)amino]-1,4-dioxo-1,4-dihydronaphthalen-2-yl}acetamide (32a)

Red semi-solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10-8.08 (dd, *J* = 8.25, 0.7 Hz, 1H), 8.03-8.02 (dd, *J* = 7.55, 0.75 Hz, 1H), 7.73-7.70 (td, J = 7.55, 0.95 Hz, 1H), 7.62-7.59 (td, J = 7.6, 1.05 Hz, 1H), 6.11 (s, 1H), 3.91-3.85 (m, 1H), 3.20-3.12 (m, 2H), 2.01 (s, 3H), 1.65-1.60 (m, 4H) 1.38-1.28 (m, 6H), 0.97 (d, *J* = 6.85 Hz, 3H), 0.95 (d, *J* = 6.85 Hz, 3H), 0.76 (t, *J* = 6.8 Hz, 3H); Calculated for $C_{22}H_{30}N_2O_3$ 370.2; Found MS (ESI) m/z 371.1 $[M+H]^+$

N-{3-[(2-Methylpropyl)amino]-1,4-dioxo-1,4-dihydronaphthalen-2-yl}-N-octylacetamide (33a)

Red liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (d, *J* = 7.85 Hz, 1H), 8.05 (d, *J* = 7.35 Hz, 1H), 7.73 (t, *J* = 7.5 Hz, 1H), 7.63 (t, *J* = 7.55 Hz, 1H), 6.11 (s, 1H), 3.92-3.86 (m, 1H), 3.20-3.18 (m, 2H), 2.90-2.87 (m, 1H), 1.93 (s, 3H), 1.87-1.79 (sept, *J* = 6.6 Hz, 1H), 1.63-1.60 (m, 1H), 1.37-1.18 (m, 11H), 0.99 (d, *J* = 6.9 Hz, 3H), 0.97 (d, *J* = 6.95 Hz, 3H), 0.79 (t, *J* = 6.7 Hz, 3H); Calculated for $C_{24}H_{34}N_2O_3$ 398.3; Found MS (ESI) m/z 399.1 $[M+H]^+$

N-Decyl-N-{3-[(2-methylpropyl)amino]-1,4-dioxo-1,4-dihydronaphthalen-2-yl}acetamide (34a)

Red liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (d, J = 7.65 Hz, 1H), 8.05 (d, J = 7.55 Hz, 1H), 7.73 (t, J = 7.5 Hz, 1H), 7.63 (t, J = 7.6 Hz, 1H), 6.11 (s, 1H), 3.92-3.86 (m, 1H), 3.27-3.18 (m, 2H), 2.90-2.88 (m, 1H), 1.93 (s, 3H), 1.87-1.79 (sept, J = 6.5 Hz, 1H), 1.64-1.63 (m, 1H), 1.37-1.17 (m, 15H), 0.99 (d, J = 7.35 Hz, 3H), 0.97 (d, J = 7.05 Hz, 3H), 0.81 (t, J = 5.65 Hz, 3H); Calculated for $C_{26}H_{38}N_2O_3$ 426.3; Found MS (ESI) m/z 427.1 $[M+H]^+$

N-dodecyl-N-{3-[(2-methylpropyl)amino]-1,4-dioxo-1,4-dihydronaphthalen-2-yl}acetamide (35a)

Red liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, J = 7.65 Hz, 1H), 8.04 (d, J = 7.55 Hz, 1H), 7.72 (t, J = 7.55 Hz, 1H), 7.62 (t, J = 7.55 Hz, 1H), 6.11 (s, 1H), 3.91-3.85 (m, 1H), 3.21-3.15 (m, 2H), 2.90-2.86 (m, 1H), 1.92 (s, 3H), 1.87-1.79 (sept, J = 6.65 Hz, 1H), 1.66-1.59 (m, 1H), 1.27-1.15 (m, 19H), 0.98 (d, J = 6.85 Hz, 3H) 0.95 (d, J = 6.75 Hz, 3H), 0.80 (t, J = 6.8 Hz, 3H); Calculated for $C_{28}H_{42}N_2O_3$ 454.3; Found MS (ESI) m/z 455.1 $[M+H]^+$

[N-(3-(Methylamino)-1,4-dioxo-1,4-dihydronaphthalen-2-yl] acetamide (36a)

Red solid; Yield: 41.9%; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.99 (s, 1H), 7.97 (d, *J* = 7.5 Hz, 1H), 7.95 (d, J = 7.55 Hz, 1H), 7.83-7.80 (dt, J = 7.55, 0.95 Hz, 1H), 7.73-7.70 (dt, J = 7.55, 0.95 Hz, 1H), 7.26 (m, 1H), 2.97 (d, J = 5.45 Hz, 3H), 2.00 (s, 3H);
Calculated for $C_{13}H_{12}N_2O_3$ 244.1; Found MS (ESI) m/z 244.9 $[M+H]^+$

N-[3-(Ethylamino)-1,4-dioxo-1,4-dihydronaphthalen-2-yl] acetamide (37a)

Red solid; Yield: 43.8%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (d, J = 7.55 Hz, 1H), 8.01 (d, *J* = 7.6 Hz, 1H), 7.69-7.66 (t, J = 7.45 Hz, 1H), 7.60-7.57 (t, *J* = 7.5 Hz, 1H), 7.35 (br s, 1H), 6.07 (br s, 1H), 3.50-3.46 (q, *J* = 6.95 Hz, 2H), 2.23 (s, 3H), 1.27-1.24 (t, *J* = 7.25 Hz, 3H).
Calculated for $C_{14}H_{14}N_2O_3$ 258.1; Found MS (ESI) m/z 259.0 $[M+H]^+$

***N*-[1,4-Dioxo-3-(propylamino)-1,4-dihydronaphthalen-2-yl]acetamide (38a)**

Red oil; Yield: 53.8%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (dd, *J* = 9.2, 5.4 Hz, 1H) 8.04 (dd, *J* = 13.8, 7.5 Hz, 1H), 7.70 (t, *J* = 7.3 Hz, 1H) 7.60 (t, *J* = 7.5 Hz, 1H), 3.41 (t, *J* = 6.8 Hz, 2H), 2.23 (s, 3H), 1.64 (q, *J* = 7.3 Hz, 2H), 0.97 (t, *J* = 7.4 Hz, 3H); Calculated for $C_{15}H_{16}N_2O_3$ 272.1; Found MS (ESI) m/z 273.2 $[M+H]^+$

N-[3-(Isopropylamino)-1,4-dioxo-1,4-dihydronaphthalen-2-yl]acetamide ($C_{15}H_{16}N_2O_3$) **(39a)**

Red solid; Yield: 49.1%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (d, J = 7.5 Hz, 1H), 8.01 (d, *J* = 7.55 Hz, 1H), 7.69-7.66 (t, *J* = 7.3 Hz, 1H), 7.60-7.57 (t, *J* = 7.4 Hz, 1H), 7.44 (br s, 1H), 6.06 (br s, 1H), 3.96 (m, 1H), 2.24 (s, 3H), 1.23 (d, *J* = 6.3 Hz, 6H); Calculated for $C_{15}H_{16}N_2O_3$ 272.1; Found MS (ESI) m/z 273.0 $[M+H]^+$

N-[3-(Butylamino)-1,4-dioxo-1,4-dihydronaphthalen-2-yl]acetamide (40a)

Red solid; Yield: 58.7%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, J = 7.6 Hz, 1H), 8.01 (d, *J* = 7.55 Hz, 1H), 7.69-7.66 (t, J = 7.2 Hz, 1H), 7.60-7.57 (t, *J* = 7.5 Hz, 1H), 7.38 (s, 1H), 6.15 (br s, 1H), 3.43 (t, *J* = 7.1 Hz, 2H), 2.23 (s, 3H), 1.61-1.55 (quint, *J* = 7.2 Hz, 2H), 1.42-1.35

(sept, *J* = 7.35 Hz, 2H), 0.95-0.92 (t, *J* = 7.4 Hz, 3H); Calculated for $C_{16}H_{18}N_2O_3$ 286.1; Found MS (ESI) m/z 287.0 $[M+H]^+$

2-Chloro-3-(methylamino)naphthalene-1,4-dione (41a)

Red solid; Yield: 84.10%; mp: 111.3-112.9 ^{0}C;^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d,*J* = 7.7 Hz, 1H), 8.02 (d, *J* = 7.3 Hz, 1H), 7.72 (td, *J* = 7.4, 0.6 Hz, 1H), 7.64 – 7.58 (m, 1H), 6.09 (br s, 1H), 3.42 (s, 3H); Calculated for $C_{11}H_8ClNO_2$ 221.0, Found MS (ESI): m/z 222.4 $[M+H]^+$.

2-Chloro-3-(ethylamino)naphthalene-1,4-dione (42a)

Red solid; Yield: 77.8%; mp: 115.7-116.9 ^{0}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (dd, *J* = 7.7, 1.0 Hz, 1H), 8.03 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.72 (td, *J* = 7.6, 1.3 Hz, 1H), 7.62 (td, *J* = 7.6, 1.3 Hz, 1H), 6.00 (br s, 1H), 3.95 – 3.86 (m, 2H), 1.34 (t, *J* = 7.2 Hz, 3H); Calculated for $C_{12}H_{10}ClNO_2$ 235.0; Found MS (ESI): m/z 236.3 $[M+H]^+$

(2-Chloro-3-(propylamino) naphthalene-1,4-dione (43a)

Red solid; Yield: 87.4%; mp: 123.1-124.5 ^{0}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (dd, *J* = 7.7, 1.2 Hz, 1H), 8.03 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.72 (td, *J* = 7.6, 1.3 Hz, 1H), 7.62 (td, *J* = 7.6, 1.3 Hz, 1H), 6.08 (s, 1H), 3.85 – 3.78 (m, 2H), 1.72 (q, *J* = 7.3 Hz, 2H), 1.02 (t, *J* = 7.4 Hz, 3H); Calculated for $C_{13}H_{12}ClNO_2$ 249.1; Found MS (ESI): m/z 250.7 $[M+H]^+$

(2-Chloro-3-(isopropylamino) naphthalene-1,4-dione (44a)

Red solid; Yield: 86.7%; mp 122.8-123.1 ^{0}C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.97-7.96 (dd, J = 4.1, 1.2 Hz, 1H), 7.95-7.94 (dd, J = 4.2, 1.4 Hz, 1H), 7.83-7.79 (dt, J = 9.4, 1.6 Hz, 1H), 7.74-7.70 (dt, J = 9.4, 1.6 Hz, 1H), 6.71 (d, J = 11.1 Hz, 1H), 4.74-4.66 (m, 1H), 1.27 (d, J = 8 Hz, 6H); Calculated for $C_{13}H_{12}ClNO_2$ 249.1; Found MS (ESI): m/z 250.4 $[M+H]^+$

(2-Chloro-3-(cyclopropylamino) naphthalene-1,4-dione (45a)

Red solid; Yield: 88.1%; mp: 123.4-123.7 ^{0}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15-8.14 (dd, *J* = 7.7, 0.9 Hz, 1H), 8.02-8.01 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.74-7.70 (td, *J* = 7.6, 1.4 Hz, 1H), 7.64-7.60 (td, *J* = 7.6, 1.3 Hz, 1H), 6.12 (s, 1H), 3.33-3.27 (m, 1H), 0.97 – 0.92 (m, 2H), 0.78 – 0.73 (m, 2H). Calculated for $C_{13}H_{10}ClNO_2$ 247.0; Found MS (ESI): m/z 248.3 $[M+H]^+$

(2-(Butylamino)-3-chloronaphthalene-1,4-dione (46a)

Red solid; Yield: 80.1%; mp: 125.3-125.6 ^{0}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (dd, J = 7.7, 0.9 Hz, 1H), 8.02 (dd, *J* = 7.7, 0.9 Hz, 1H), 7.74 (td, J = 7.5, 1.3 Hz, 1H), 7.64 (td, *J* = 7.5, 1.3 Hz, 1H), 6.05 (br s, 1H), 3.85 (t, *J* = 7.0 Hz, 2H), 1.72 (m, 2H), 1.49 (m, 2H), 1.00 (t, *J* = 7.3 Hz, 3H). Calculated for $C_{14}H_{14}ClNO_2$ 263.1; Found MS (ESI): m/z 264.6 $[M+H]^+$

2-Chloro-3-(isobutylamino)naphthalene-1,4-dione (47a)

Red solid; Yield: 87.8%; mp: 142.1-143.8 ^{0}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (dd, *J* = 7.7, 1.0 Hz, 1H), 8.03 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.72 (td, *J* = 7.6, 1.3 Hz, 1H), 7.62 (td, *J* = 7.6, 1.3 Hz, 1H), 6.15 (br s, 1H), 3.67 – 3.66 (m, 2H), 1.95 (m, 1H), 1.01 (d, *J* = 6.7 Hz, 6H). Calculated for $C_{14}H_{14}ClNO_2$ 263.1; Found MS (ESI): m/z 264.1 $[M+H]^+$

2-Chloro-3-(hexylamino)naphthalene-1,4-dione (48a)

Red solid; Yield: 90.1%; mp: 171.3-1173.6 ^{0}C; ^{1}H NMR (400 MHz, $CDCl_3$): 8.15-8.13 (dd, *J* = 7.7, 0.92 Hz, 1H), 8.03-8.01 (dd, *J* = 7.64, 0.92 Hz, 1H) 7.74-7.69 (td, *J* = 7.52, 1.32 Hz, 1H), 7.63-7.59 (td, *J* = 7.56, 1.28 Hz, 1H), 6.07 (br s, 1H), 3.86-3.81 (q, *J* = 7.08 Hz, 2H), 1.72-1.64 (quint, *J* = 7.04 Hz, 2H), 1.44-1.29 (m, 6H), 0.92-0.88 (t, *J* = 6.92 Hz, 3H). Calculated for $C_{16}H_{18}ClNO_2$ 291.1; Found MS (ESI): m/z 292.1 $[M+H]^+$

2-Chloro-3-(octylamino)naphthalene-1,4-dione (49a)

Red solid; Yield: 90.1%; mp: 171.3-173.6 ^{0}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (dd, J = 7.7, 0.8 Hz, 1H), 8.03 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.72 (td, *J* = 7.6, 1.3 Hz, 1H), 7.62 (td, J = 7.6, 1.3 Hz, 1H), 6.06 (br s, 1H), 3.84 (t, *J* = 6.9 Hz, 2H), 1.67 (m, 2H), 1.35 (m, 10H), 0.88 (m, 3H). Calculated for $C_{18}H_{22}ClNO_2$ 319.1; Found MS (ESI): m/z 320.1 $[M+H]^+$

2-Chloro-3-(decylamino)naphthalene-1,4-dione (50a)

Red solid; Yield: 89.4%; mp: 160.3-162.6 ^{0}C; ^{1}H NMR (500 MHz, $CDCl_3$): 8.13 (d, *J* = 7.6 Hz, 1H), 8.00 (d, *J* = 7.85 Hz, 1H) 7.71-7.68 (td, *J* = 7.6, 1.05 Hz, 1H), 7.61-7.58 (td, *J* = 7.6, 1.05 Hz, 1H), 6.07 (bs, 1H), 3.84-3.80 (q, *J* = 6.8 Hz, 2H), 1.69-1.64 (quint, *J* = 7.1 Hz, 2H), 1.41-1.25 (m, 14H), 0.87-0.85 (t, *J* = 6.75 Hz, 3H). Calculated for $C_{20}H_{26}ClNO_2$ 347.2; Found MS (ESI): m/z 348.2 $[M+H]^+$

2-Chloro-3-(dodecylamino)naphthalene-1,4-dione (51a)

Red solid; Yield: 94.4%; mp: 191.3-193.6 ^{0}C; ^{1}H NMR (500 MHz, $CDCl_3$): 8.07 (d, *J* = 7.6 Hz, 1H), 7.95 (d, *J* = 7.55 Hz, 1H) 7.67-7.64 (td, *J* = 7.55, 0.95 Hz, 1H), 7.56-7.53 (td, *J* = 7.55, 1 Hz, 1H), 6.04 (bs, 1H), 3.80-3.76 (q, J = 6.85 Hz, 2H), 1.67-1.61 (quint, *J* = 7.25 Hz, 2H), 1.36-1.21 (m, 18H), 0.85-0.82 (t, *J* = 6.65 Hz, 3H). Calculated for $C_{22}H_{30}ClNO_2$ 375.2; Found MS (ESI): m/z 376.3 $[M+H]^+$

***N*-(3-Chloro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-N-methylacetamide (41b)**

Yellow solid; Yield: 71.4%; mp: 125.0-126.9 ^{0}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 – 8.13 (m, 2H), 7.82 (s, 2H), 3.18 (s, 3H), 2.12 (m, 3H); Calculated for $C_{13}H_{10}ClNO_3$ 263.0; Found MS (ESI): m/z 264.5 $[M+H]^+$

***N*-(3-Chloro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-N-ethylacetamide (42b)**

Yellow oil; Yield: 64.1%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 – 8.12 (m, 2H), 7.81 (s, 2H), 3.70 (m, 2H), 2.03 (s, 3H), 1.26 – 1.13 (m, 3H). Calculated for $C_{14}H_{12}ClNO_3$ 277.1; Found MS (ESI): m/z 278.4 $[M+H]^+$

***N*-(3-Chloro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-N-propylacetamide (43b)**

Yellow oil; Yield: 78.4%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20-8.16 (m, 2H), 7.81 (s, 2H), 3.61-3.52 (m, 2H), 2.02 (s, 3H), 1.63-1.48 (m, 2H), 0.93 – 0.81 (m, 3H).

***N*-(3-Chloro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-N-isopropylacetamide (44b)**

Yellow oil; Yield: 67.5%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 – 8.13 (m, 2H), 7.88 – 7.79 (m, 2H), 4.50-4.42 (m, 1H), 1.84 (s, 3H), 1.24 – 1.19 (m, 6H). Calculated for $C_{15}H_{14}ClNO_3$ 291.1; Found MS (ESI): m/z 291.1 $[M]^-$

***N*-(3-Chloro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-N-cyclopropylacetamide (45b)**

Yellow oil; Yield: 84.4%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 – 8.12 (m, 2H), 7.78 (s, 2H), 3.22 (s, 1H), 2.43 (s, 3H), 2.22 (s, 1H), 0.91-0.69 (m, 4H). Calculated for $C_{15}H_{12}ClNO_3$ 289.1; Found MS (ESI): m/z 290.5 $[M+H]^+$

***N*-Butyl-N-(3-chloro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)acetamide (46b)**

Yellow oil; Yield: 81.7%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 – 8.07 (m, 2H), 7.82 – 7.72 (m, 2H), 3.64 – 3.60 (m, 2H), 2.15 (s, 3H), 1.58-1.51 (m, 2H), 1.38 – 1.22 (m, 2H), 0.89-0.85 (t, *J* = 7.1 Hz, 3H). Calculated for $C_{16}H_{16}ClNO_3$ 305.1; Found MS (ESI): m/z 306.4 $[M+H]^+$

***N*-(3-Chloro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-N-isobutylacetamide (47b)**

Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.1 (m, 2H), 7.8 (m, 2H), 3.53-3.40 (m, 2H), 1.89 (s, 3H), 1.66 (m, 1H), 0.90 (d, *J* = 6.25, 3H), 0.86 (d, *J* = 6 Hz, 3H).

***N*-(3-Chloro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-N-hexylacetamide (48b)**

Dark yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 9.7 Hz, 2H), 7.81 (s, 2H), 3.62-3.58 (m, 2H), 2.20 (s,3H), 1.53 – 1.23 (m, 8H), 0.8 (t, *J* = 6.5 Hz, 3H). Calculated for $C_{18}H_{20}ClNO_3$ 333.1; Found MS (ESI): m/z 334.2 $[M+H]^+$

***N*-(3-Chloro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-N-octylacetamide (49b)**

Dark yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (m, 2H), 7.83 (m, 2H), 3.63-3.60 (m, 2H), 1.92 (s, 3H), 1.57-1.47 (m, 2H), 1.24-1.22 (m, 10H), 0.90 (t, *J* = 6.65 Hz, 3H). MS (ESI) Calculated for $C_{20}H_{24}ClNO_3$ 361.1; Found m/z 362.2 $[M+H]^+$

***N*-(3-Chloro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-N-decylacetamide (50b)**

Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (m, 2H), 7.83 (m, 2H), 3.63-3.60 (m, 2H), 1.92 (s, 3H), 1.54-1.47 (m, 2H), 1.26-1.21 (m, 14H), 0.85 (t, *J* = 6.8 Hz, 3H).Calculated for $C_{22}H_{28}ClNO_3$ 389.2; Found MS (ESI) m/z 390.2 $[M+H]^+$

***N*-(3-Chloro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-N-dodecylacetamide (51b)**

Yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22 (m, 2H), 7.83 (m, 2H), 3.63-3.60 (m, 2H), 1.92 (s, 3H), 1.54-1.50 (m, 2H), 1.26-1.21 (m, 18H), 0.86 (t, *J* = 6.85 Hz, 3H). Calculated for $C_{24}H_{32}ClNO_3$ 417.2; Found MS (ESI) m/z 418.2 $[M+H]^+$

3. Characterization of Final Compounds (4-40)

3.1. Series A (4-24)

1,2,3-Trimethyl-4,9-dioxo-4,9-dihydro-1H-naphtho[2,3-d]imidazol-3-ium bromide [S1] (4)

Beige solid, 21.9%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16-8.14 (dd, *J* = 7.7, 1.2 Hz, 1H), 8.09-8.06 (m, 1H), 7.79-7.75 (td, *J* =7.4, 1.2 Hz, 1H), 7.68-7.64 (td, *J* =7.6, 1.5 Hz, 1H), 3.13-3.10 (m, 6H), 1.98 (s, 3H). Calculated for $C_{14}H_{13}N_2O_2$ 241.1; Found MS (ESI): m/z 241.1 $[M-Br]^+$

3-Ethyl-1,2-dimethyl-4,9-dioxo-4,9-dihydro-1H-naphtho[2,3-d]imidazol-3-ium bromide (5)

Light yellow solid; Yield: 24.1%; mp: 234.7-234.9 °C; ^{1}H NMR (400 MHz, DMSO) δ 8.21-8.18 (m, 2H), 8.02 – 7.99 (m, 2H), 4.68 (q, *J* = 7.2 Hz, 2H), 4.15 (s, 3H), 2.9 (s, 3H), 1.41 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ 175.0, 174.6, 152.5, 135.2, 131.6, 131.5, 130.4, 129.5, 126.8, 45.7, 42.7, 34.0, 14.3, 9.7, 8.6; Calculated for $C_{15}H_{15}N_2O_2$ 255.1; Found MS (ESI): m/z 255.2 $[M-Br]^+$

1,2-Dimethyl-4,9-dioxo-3-propyl-4,9-dihydro-1H-naphtho[2,3-d]imidazol-3-ium bromide (6)

Yellow solid; Yield: 26.1%; mp: 236.5-236.8 °C; : ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15-8.07 (m, 2H), 7.79-7.75 (m, 1H), 7.67-7.64 (m,1H), 3.35 (t, J = 7.1 Hz, 2H), 3.11 (s, 3H), 1.97 (s, 3H), 1.70 (m, 2H), 1.02 (t, J = 7.4 Hz, 3H); ^{13}C NMR (400 MHz, DMSO) δ 175.6, 175.2, 153.1, 135.8, 135.7, 132.2, 132.0, 131.0, 127.4, 127.3, 48.8, 34.6, 22.8, 11.0, 10.5.
Calculated for $C_{16}H_{17}N_2O_2$ 269.1; Found MS (ESI): m/z 267.2 $[M-Br-2H]^+$

3-Isopropyl-1,2-dimethyl-4,9-dioxo-4,9-dihydro-1H-naphtho[2,3-d]imidazol-3-ium bromide (7)

Yellow solid; Yield: 22.9%; mp: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15-8.07 (m, 2H), 7.76 (td, *J*= 7.6, 1.3Hz, 1H), 7.65 (td, *J* = 7.6, 1.3 Hz, 1H), 4.13-4.04 (m, 1H), 3.10 (s, 3H), 1.98 (s, 3H), 1.30-1.23 (m, 6H) ^{13}C NMR (400 MHz, DMSO) δ 175.8, 175.4, 152.7, 135.8, 135.5, 132.3, 131.5, 130.6, 127.7, 127.1, 53.2, 34.3, 20.0, 11.7; Calculated for $C_{16}H_{17}N_2O_2$ 269.1; Found MS (ESI): m/z 269.2 $[M-Br]^+$

3-Cyclopropyl-1,2-dimethyl-4,9-dioxo-4,9-dihydro-1H-naphtho[2,3-d]imidazol-3-ium bromide (8)

Yellow solid; Yield: 23.2%; mp: 246.7-246.9 °C; ^{1}H NMR (400 MHz, DMSO) δ 8.22 – 8.17 (m, 2H), 8.03 – 7.97 (m, 2H), 4.13 (s, 3H), 3.73 – 3.68 (m, 1H), 2.90 (s, 3H), 1.39 – 1.34 (m, 2H), 1.20 – 1.16 (m, 2H); ^{13}C NMR (400 MHz, DMSO) δ 175.6, 173.8, 155.7, 135.8, 135.4, 132.4, 132.7, 131.7, 130.3, 127.4, 127.2 34.5, 29.8, 12.2, 9.4; Calculated for $C_{16}H_{15}N_2O_2$ 267.1; Found MS (ESI): m/z 267.2 $[M-Br]^+$

3-Butyl-1,2-dimethyl-4,9-dioxo-4,9-dihydro-1H-naphtho[2,3-d]imidazol-3-ium bromide (9)

Yellow solid; Yield: 24.7%; mp: 206.4-206.8 °C; ^{1}H NMR (400 MHz, DMSO) δ 8.17-8.15 (dt, 2H, *J* = 6.0, 3.2 Hz), 7.96-7.95 (dd, 2H, *J* = 5.7, 3.3 Hz), 4.57-4.54 (m, 2H), 4.09 (s, 3H), 2.77 (s, 3H), 1.78-1.70 (m, 2H), 1.41-1.35 (m, 2H), 0.92 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (400 MHz, DMSO) δ 175.6, 175.2, 152.8, 135.7, 135.6, 132.0, 131.0, 130.9, 129.9, 127.3, 127.2, 47.4, 34.4, 31.1, 19.4, 13.9, 10.2; Calculated for $C_{17}H_{19}N_2O_2$ 283.1; Found MS (ESI): m/z 283.1 $[M-Br]^+$

1,3-Diethyl-2-methyl-4,9-dioxo-4,9-dihydro-1H-naphtho[2,3-d]imidazol-3-ium bromide (10)

Yellow solid; Yield: 19.4%; mp: 209.7-211.9 °C; ^{1}H NMR (400 MHz, DMSO) δ 8.20 (dd, *J* = 5.4, 3.4 Hz, 2H), 8.00 (dd, *J* = 5.5, 3.3 Hz, 2H), 4.66 (q, *J* = 7.1 Hz, 4H), 2.92 (s, 3H), 1.42 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (101 MHz, DMSO) δ 174.8, 173.4, 154.4, 135.2, 134.9, 132.0, 131.8, 131.3, 129.3, 126.9, 126.7, 42.7, 29.3, 14.0, 11.3, 8.9; Calculated for $C_{16}H_{17}N_2O_2$ 269.1; Found MS (ESI): m/z 269.3 $[M\text{-}Br]^+$

3-Ethyl-2-methyl-4,9-dioxo-1-propyl-4,9-dihydro-1H-naphtho[2,3-d]imidazol-3-ium bromide (11)

Yellow solid; Yield: 21.9%; mp: 210.4-210.7 °C; ^{1}H NMR (400 MHz, DMSO) δ 8.20-8.00 (m, 4H), 4.66-4.60 (m, 4H), 2.93 (br s, 3H), 1.86-1.81 (q, J = 7.4 Hz, 2H), 1.44-1.41 (t, J = 7.2 Hz, 3H), 1.00-0.96 (t, J = 7.4 Hz, 3H), ^{13}C NMR (400 MHz, DMSO-d_6) δ 175.1, 175.1, 152.0, 135.6, 131.9, 130.4, 127.2, 127.2, 48.75, 43.1, 31.0, 22.5, 14.3, 10.9, 9.6. Calculated for $C_{17}H_{19}N_2O_2$ 283.1; Found MS (ESI): m/z 283.1 $[M\text{-}Br]^+$

3-Ethyl-1-isopropyl-2-methyl-4,9-dioxo-4,9-dihydro-1H-naphtho[2,3-d]imidazol-3-ium bromide (12)

Yellow solid; Yield: 25.7%; mp: 253.2-253.6 °C; ^{1}H NMR (400 MHz, DMSO) δ 8.21-8.19 (m, 2H), 8.01-7.99 (m, 2H), 5.42-5.40(m, 1H), 4.70-4.68 (m, 2H), 2.97 (s, 3H), 1.64 (d, *J* = 6.9 Hz, 6H), 1.42 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (400 MHz, DMSO) δ 175.4, 174.7, 152.1, 135.8, 135.6, 132.3, 131.6, 131.3, 127.7, 127.1, 53.2, 43.2, 20.1, 14.6, 11.6; Calculated for $C_{17}H_{19}N_2O_2$ 283.1; Found MS (ESI): m/z 283.2 $[M\text{-}Br]^+$

3-Cyclopropyl-1-ethyl-2-methyl-4,9-dioxo-4,9-dihydro-1H-naphtho[2,3-d]imidazol-3-ium bromide (13)

Yellow solid; Yield: 22.4%; mp: 218.3-218.5 °C; ^{1}H NMR (400 MHz, DMSO) δ 8.21-8.18 (m, 2H), 8.02 – 7.98 (m, 2H), 4.64 (q, *J* = 7.2 Hz, 2H), 3.67 (dt, *J* = 7.1, 3.4 Hz, 1H), 2.93 (s, 3H), 1.42 (t, *J* = 7.2 Hz, 3H), 1.36 (d, *J* = 6.2 Hz, 2H), 1.23-1.18 (m, 2H); ^{13}C NMR (101 MHz, DMSO) δ 175.1, 174.6, 152.6, 135.2, 135.2, 131.6, 131.5, 130.5, 129.6, 126.9, 126.8, 48.3, 34.1, 22.3, 10.5, 9.9; Calculated for $C_{17}H_{17}N_2O_2$ 281.1; Found MS (ESI): m/z 281.2 $[M\text{-}Br]^+$

1-Butyl-3-ethyl-2-methyl-4,9-dioxo-4,9-dihydro-1H-naphtho[2,3-d]imidazol-3-ium bromide (14)

Yellow solid; Yield: 15.4%; mp:198.4-199.7 °C; ^{1}H NMR (400 MHz, DMSO) δ 8.20 (dd, *J* = 5.6, 3.4 Hz, 2H), 8.00 (dd, *J* = 5.7, 3.3 Hz, 2H), 4.64 (m, 4H), 2.92 (s, 3H), 1.80 – 1.76 (m, 2H), 1.44-1.40 (m, 5H), 0.95 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, DMSO) δ 174.7, 174.7, 151.7, 135.2, 131.6, 130.0, 126.8, 126.9, 46.9, 42.8, 30.8, 19.0, 14.1, 13.5, 9.5; Calculated for $C_{18}H_{21}N_2O_2$ 297.2; Found MS (ESI): m/z 297.2 $[M\text{-}Br]^+$

2-Methyl-4,9-dioxo-1,3-dipropyl-4,9-dihydro-1H-naphtho[2,3-d]imidazol-3-ium bromide (15)

Yellow solid; Yield: 20.7%; mp: 213.1-213.3 °C; ^{1}H NMR (400 MHz, DMSO) δ 8.21 -8.19 (m, 2H), 8.01-7.99 (m, 2H), 4.59 (t, *J* = 6.9 Hz, 4H), 2.92 (s, 3H), 1.84 (dd, *J* = 14.9, 7.4 Hz, 4H), 0.97 (t, *J* = 7.4 Hz, 6H); ^{13}C NMR (400 MHz, DMSO) δ 175.5, 174.7, 152.2, 135.8, 135.6, 132.3, 131.6, 131.4, 127.7, 127.1, 53.3, 48.8, 22.7, 20.1, 11.8, 11.1; Calculated for $C_{18}H_{21}N_2O_2$ 297.2; Found MS (ESI): m/z 297.1 $[M\text{-}Br]^+$

3-Isopropyl-2-methyl-4,9-dioxo-1-propyl-4,9-dihydro-1H-naphtho[2,3-d]imidazol-3-ium bromide (16)

Yellow solid; Yield: 28.5%; mp: 214.8-215.2 °C; ^{1}H NMR (400 MHz, DMSO) δ 8.23 – 8.16 (m, 2H), 8.03 – 7.97 (m, 2H), 5.44-5.40 (m, 1H), 4.64 – 4.57 (m, 2H), 2.98 (s, 3H), 1.85-1.79 (m, 2H), 1.64 (d, *J* = 6.9 Hz, 6H), 1.00 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (400 MHz, DMSO) δ 175.0, 174.2, 151.7, 135.3, 135.1, 131.8, 131.1, 130.9, 127.2, 126.6, 52.8, 48.2, 22.2, 19.5, 11.2, 10.6; Calculated for $C_{18}H_{21}N_2O_2$ 297.2; Found MS (ESI): m/z 297.2 $[M\text{-}Br]^+$

3-Cyclopropyl-2-methyl-4,9-dioxo-1-propyl-4,9-dihydro-1H-naphtho[2,3-d]imidazol-3-ium bromide (17)

Yellow solid; Yield:19.6%; mp; ^{1}H NMR (400 MHz, DMSO) δ 8.20-8.18 (m, 2H) 8.01-7.99 (m, 2H) 4.59-4.55 (m, 2H) 3.81-3.63 (m, 1H), 2.94 (s, 3H), 1.83 (q, J = 7.3 Hz, 2H), 1.37-1.33 (m, 2H) 1.24-1.21 (m, 2H), 0.99 (t, J = 7.4 Hz, 3H); ^{13}C NMR (400 MHz, DMSO) δ 175.4, 174.0, 155.1, 135.8, 135.4, 132.6, 132.4, 131.8, 130.0, 127.4, 127.2, 62.5, 48.8, 29.9, 26.0, 22.6, 12.1, 11.1, 9.4; Calculated for $C_{18}H_{19}N_2O_2$ 295.1; Found MS (ESI): m/z 295.2 $[M\text{-}Br]^+$

3-Butyl-2-methyl-4,9-dioxo-1-propyl-4,9-dihydro-1H-naphtho[2,3-d]imidazol-3-ium bromide (18)

Yellow solid; Yield: 29.9%; mp: 214.4-214.7 °C; ^{1}H NMR (400 MHz, DMSO) δ 8.20-8.19 (m, 2H), 8.01-8.00 (m, 2H), 4.64-4.57 (m, 4H), 2.93 (s, 3H), 1.87-1.75 (m, 4H), 1.44 – 1.39 (m, 2H), 1.00 – 0.93 (m, 6H); ^{13}C NMR (400 MHz, DMSO-d_6) δ175.1, 175.1, 152.1, 135.5, 131.9, 130.4, 127.2, 48.8, 47.4, 30.9, 22.5, 19.4, 13.8, 10.9. 10.1; Calculated for $C_{19}H_{23}N_2O_2$ 311.2; Found MS (ESI): m/z 311.2 $[M\text{-}Br]^+$

1,3-Diisopropyl-2-methyl-4,9-dioxo-4,9-dihydro-1H-naphtho[2,3-d]imidazol-3-ium bromide (19)

Yellow solid; Yield: 26.4%; mp: 266.2-266.5 °C; ^{1}H NMR (400 MHz, DMSO) δ 8.19 (m, 2H), 7.99 (m, 2H), 5.55 (br s, 1H), 3.02 (s, 3H), 2.13-2.03 (m, 1H), 1.64 (d, *J* = 6.9 Hz, 12H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 175.1, 175.1, 152.2, 135.7, 132.2, 131.8,127.5, 53.1, 31.2, 20.1, 13.3; Calculated for $C_{18}H_{21}N_2O_2$ 297.2; Found MS (ESI): m/z 297.1 $[M\text{-}Br]^+$. HRMS (ESI) calculated for $C_{18}H_{21}N_2O_2$ 297.1598. Found 297.1602.

3-Cyclopropyl-1-isopropyl-2-methyl-4,9-dioxo-4,9-dihydro-1H-naphtho[2,3-d]imidazol-3-ium bromide (20)

Yellow solid; Yield: 28.7%; mp: decomposed; ^{1}H NMR (400 MHz, DMSO) δ 8.22-8.16 (m, 2H), 8.01-7.97 (m, 2H), 5.38 (s br, 1H), 3.68-3.62 (m, 1H), 2.99 (s, 3H), 1.63 (d, J = 6.9 Hz, 6H), 1.40-1.34 (m, 2H), 1.23 – 1.19 (m, 2H); ^{13}C NMR (400 MHz, DMSO) δ 174.8, 174.2, 155.0, 140.2, 135.6, 135.5, 132.1, 131.9, 127.6, 127.2, 53.3, 30.0, 20.0, 13.6, 9.7; Calculated for $C_{18}H_{19}N_2O_2$ 295.1; Found MS (ESI): m/z 295.2 $[M\text{-}Br]^+$

3-Butyl-1-isopropyl-2-methyl-4,9-dioxo-4,9-dihydro-1H-naphtho[2,3-d]imidazol-3-ium bromide (21)

Yellow solid; Yield: 21.4%;^{1}H NMR (400 MHz, DMSO) δ 8.22-8.17 (m, 2H), 8.01-7.99 (m, 2H), 5.42-5.40 (m, 1H), 4.65-4.61 (m, 2H), 2.98 (s, 3H), 1.81-1.74 (m, 2H), 1.64 (d, *J* = 6.9 Hz, 6H), 1.47 – 1.41 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (400 MHz, DMSO) δ 175.5, 174.7, 152.2, 135.8, 135.7, 132.3, 131.6, 131.4, 127.7, 127.2, 53.3, 47.3, 31.2, 20.1, 19.6, 14.0, 11.7; Calculated for $C_{19}H_{23}N_2O_2$ 311.2; Found MS (ESI): m/z 311.2 $[M\text{-}Br]^+$

1,3-Dicyclopropyl-2-methyl-4,9-dioxo-4,9-dihydro-1H-naphtho[2,3-d]imidazol-3-ium bromide (22)

Yellow solid; Yield: 21.4; mp: 323.7-324.9 °C; ^{1}H NMR (400 MHz, DMSO) δ 8.19 (dd, *J* = 5.7, 3.3 Hz, 2H), 7.99 (dd, *J* = 5.7, 3.3 Hz, 2H), 3.66 (tt, *J* = 7.3, 3.9 Hz, 2H), 2.94 (s, 3H), 1.38 – 1.34 (m, 4H), 1.22 – 1.20 (m, 4H); ^{13}C NMR (101 MHz, DMSO) δ 173.5, 157.2, 135.0, 131.6, 131.4, 126.7, 29.4, 13.4, 8.9; Calculated for $C_{18}H_{17}N_2O_2$ 293.1; Found MS (ESI): m/z 293.2 $[M-Br]^+$

1-Butyl-3-cyclopropyl-2-methyl-4,9-dioxo-4,9-dihydro-1H-naphtho[2,3-d]imidazol-3-ium bromide (23)

Yellow solid; Yield: 24.7%; mp: 259.7-259.9 °C; ^{1}H NMR (400 MHz, DMSO) δ 8.21-8.18 (m, 2H), 8.01-7.98 (m, 2H), 4.61-4.58 (m, 2H), 3.68 (tt, *J* = 7.3, 3.8 Hz, 1H), 2.93 (s, 3H), 1.81-1.74 (m, 2H), 1.46-1.35 (m, 4H), 1.24-1.20 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (400 MHz, DMSO) δ 174.8, 173.4, 154.5, 135.3, 135.0, 132.1, 131.9, 131.3, 129.4, 126.9, 126.7, 46.9, 30.7, 29.4, 19.1, 13.5, 11.5, 8.9; Calculated for $C_{19}H_{21}N_2O_2$ 309.2; Found MS (ESI): m/z 309.3 $[M-Br]^+$

1,3-Dibutyl-2-methyl-4,9-dioxo-4,9-dihydro-1H-naphtho[2,3-d]imidazol-3-ium bromide (24)

Yellow solid; Yield: 17.9%; mp: 251.6-252.8 °C; ^{1}H NMR (400 MHz, DMSO δ 8.21-8.19 (m, 2H), 8.01-7.99 (m, 2H), 4.63-4.61 (m, 4H), 2.93 (s, 3H), 1.82-1.75 (m, 4H), 1.45-1.39 (m, 4H), 0.95 (t, *J* = 7.4 Hz, 6H); ^{13}C NMR (101 MHz, DMSO) δ 174.9, 173.4, 154.5, 135.3, 135.0, 132.1, 131.87, 131.3, 129.4, 127.0, 126.7, 46.9, 30.67, 29.4, 19.1, 13.5, 11.5, 8.9; Calculated for $C_{20}H_{25}N_2O_2$ 325.2; Found MS (ESI): m/z 325.2 $[M-Br]^+$

3.2. Series B (36-40)

1,2-Dimethyl-1H-naphtho[2,3-d]imidazole-4,9-dione (36)

Dark yellow solid. Yield: 30%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.09 – 8.05 (m, 2H), 7.85 (dd, *J* = 5.7, 3.3 Hz, 2H), 3.96 (s, 3H), 2.50 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 178.7, 176.2.7, 154.4, 142.5, 134.4, 134.2, 133.2, 133.1, 132.87, 126.7, 126.5, 32.6, 13.4; Calculated for $C_{13}H_{10}N_2O_2$ 226.1; Found MS (ESI) m/z 226.4 $[M]^+$

1-Ethyl-2-methyl-1H-naphtho[2,3-d]imidazole-4,9-dione (37)

Dark yellow solid; Yield: 25%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.07 – 8.04 (m, 2H), 7.84 – 7.82 (m, 2H), 4.39 (q, *J* = 7.2 Hz, 2H), 2.52 (s, 3H), 1.34 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 178.7, 175.8, 153.5, 142.8, 134.3, 134.2, 133.1, 132.8, 132.4, 126. 7, 126.5, 40.8, 15.5, 13.2 Calculated for $C_{14}H_{12}N_2O_2$ 240.1; Found MS (ESI) m/z 240.4 $[M]^+$

2-Methyl-1-propyl-1H-naphtho[2,3-d]imidazole-4,9-dione (38)

Dark yellow solid; Yield: 30%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.07 – 8.05 (m, 2H), 7.84 – 7.82 (m, 2H), 4.35 – 4.31 (m, 2H), 2.52 (s, 3H), 1.76 (q, *J* = 7.4 Hz, 2H), 0.91 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 178.7, 175.8, 153.8, 142.9, 134.3, 134.2, 133.2, 132.8, 132.6, , 126.6, 126.5, 46.9, 23.3, , 13.4, 11.2; Calculated for $C_{15}H_{14}N_2O_2$ 254.1; Found MS (ESI) m/z 254.2 $[M]^+$

1-Isopropyl-2-methyl-1H-naphtho[2,3-d]imidazole-4,9-dione (39)

Yellow solid; Yield: 20 %; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.10 – 8.08 (m, 1H), 8.06 – 8.04 (m, 1H), 7.86 – 7.83 (m, 2H), 5.09 (s, 1H), 2.61 (s, 3H), 1.56 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 178.4, 175.1, 153.4, 142.0, 134.7, 134.5, 133.4, 132.6, 132.1, 127.2, 126.5, 50.3, 20.7, 15.0, 6.36; Calculated for $C_{15}H_{14}N_2O_2$ 254.1; Found MS (ESI) m/z 254.1 $[M]^+$

1-Butyl-2-methyl-1H-naphtho[2,3-d]imidazole-4,9-dione (40)

Yellow solid; Yield: 35%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.05-8.02 (dt, *J* = 5.9, 3.1 Hz, 2H), 7.82-7.80 (dd, *J* = 5.7, 3.3 Hz, 2H), 4.35 – 4.32 (m, 2H), 2.50 (s, 3H), 1.73 – 1.66 (m, 2H), 1.37 – 1.31 (m, 2H), 0.91 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 178.8, 176.0 152.8 143.0, 133.5, 133.3,133.0, 132.6, 132.0, 126.8, 126.3, 45.5, 32.2, 19.8, 13.5, 13.2 Calculated for $C_{16}H_{16}N_2O_2$ 268.1; Found MS (ESI) m/z 268.1 $[M]^+$

3.3. Series C (25-35)

1-Isobutyl-2,3-dimethyl-4,9-dioxo-4,9-dihydro-1H-naphtho[2,3-d]imidazol-3-ium bromide (25)

Yellow solid; Yield: 38.4%; mp: 210.7-212.9 °C; ^{1}H NMR (400 MHz, MeOD) δ 8.32-8.29 (m, 2H), 7.99-7.96 (m, 2H), 4.58 (d, *J* = 7.6 Hz, 2H), 4.29 (s, 3H), 2.91 (s, 3H), 2.32-2.25 (m, 1H), 1.10 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (101 MHz, MeOD) δ 176.4, 176.1, 154.0, 136.2, 136.2, 133.4, 133.3, 132.4, 131.4, 128.2, 128.1, 55.3, 35.1, 30.7, 19.8; Calculated for $C_{17}H_{19}N_2O_2$ 283.1; Found MS (ESI): m/z 282.1 $[M\text{-}H\text{-}Br]^+$

3-Ethyl-1-isobutyl-2-methyl-4,9-dioxo-4,9-dihydro-1H-naphtho[2,3-d]imidazol-3-ium bromide (26)

Yellow solid; Yield: 60.4%; mp: 213.7-215.9 °C; ^{1}H NMR (400 MHz, MeOD) δ 8.32 – 8.29 (m, 2H), 7.98-7.96 (m, 2H), 4.80 (t, *J* = 7.3 Hz, 2H), 4.57 (d, *J* = 7.6 Hz, 2H), 2.94 (s, 3H), 2.33-2.26 (m, 1H), 1.57 (t, *J* = 7.3 Hz, 3H), 1.09 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (101 MHz, MeOD) δ 176.2, 176.1, 153.3, 136.2, 133.4, 133.3, 131.9, 131.9, 128.2, 128.1, 55.3, 44.7, 30.6, 19.9, 14.7, 10.8, 10.6; Calculated for $C_{18}H_{21}N_2O_2$ 297.2; Found MS (ESI): m/z 296.2 $[M\text{-}H\text{-}Br]^+$

1-Isobutyl-2-methyl-4,9-dioxo-3-propyl-4,9-dihydro-1H-naphtho[2,3-d]imidazol-3-ium bromide (27)

Yellow solid; Yield: 47.4%; mp: 218.7-220.7 °C; ^{1}H NMR (400 MHz, MeOD) δ 8.32-8.29 (m, 2H), 7.99-7.96 (m, 2H), 4.72-4.68 (m, 2H), 4.58 (d, *J* = 7.6 Hz, 2H), 2.95 (s, 3H), 2.34-2.27 (m, 1H), 1.99-1.94 (m, 2H 2H), 1.14-1.09 (m, 9H); ^{13}C NMR (101 MHz, MeOD) δ 176.2, 176.1, 153.3, 136.2, 133.3, 133.3, 132.0, 131.9, 128.2, 128.2, 55.4, 50.5, 49.0, 48.4, 30.6, 23.8, 19.9, 11.1; Calculated for $C_{19}H_{23}N_2O_2$ 311.2; Found MS (ESI): m/z 310.1 $[M\text{-}H\text{-}Br]^+$

1-Isobutyl-3-isopropyl-2-methyl-4,9-dioxo-4,9-dihydro-1H-naphtho[2,3-d]imidazol-3-ium bromide (28)

Yellow solid; Yield: 62.3 %; mp: 227.2-229.5 °C; ^{1}H NMR (400 MHz, MeOD) δ 8.33 – 8.30 (m, 1H), 8.29-8.28 (m, 1H), 7.99-7.96 (m, 2H), 5.58 (s, 1H), 4.62 (d, *J* = 7.5 Hz, 2H), 3.01 (s, 3H), 2.33-2.26 (m, 1H), 1.79 (d, *J* = 7.0 Hz, 6H), 1.11 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (101 MHz, MeOD) δ 176.4, 175.6, 153.1, 136.3, 136.0, 133.5, 132.9, 132.7, 128.5, 128.0, 55.2, 30.5, 20.3, 19.9, 12.6; Calculated for $C_{19}H_{23}N_2O_2$ 311.2; Found MS (ESI): m/z 310.2 $[M\text{-}H\text{-}Br]^+$

3-Cyclopropyl-1-isobutyl-2-methyl-4,9-dioxo-4,9-dihydro-1H-naphtho[2,3-d]imidazol-3-ium bromide (29)

Yellow solid; Yield: 57.0 %; mp: 220.1-222.9 °C; ^{1}H NMR (400 MHz, MeOD) δ 8.31-8.28 (m 2H), 7.98 – 7.95 (m, 2H), 4.56 (d, *J* = 7.5 Hz, 2H), 3.74 (dt, *J* = 7.2, 3.5 Hz, 1H), 3.00 (s, 3H), 2.30 (m, 1H), 1.53 (dt, *J* = 7.2, 1.5 Hz, 2H), 1.32 (dd, *J* = 3.9, 1.6 Hz, 2H), 1.10 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.3, 174.8, 156.0, 136.2, 135.9, 133.9, 133.5, 133.1, 131.5, 128.2, 128.1, 55.3, 31.0, 30.5, 19.9, 12.7, 10.2; Calculated for $C_{19}H_{21}N_2O_2$ 309.2; Found MS (ESI): m/z 308.1 $[M-H-Br]^+$

3-Butyl-1-isobutyl-2-methyl-4,9-dioxo-4,9-dihydro-1H-naphtho[2,3-d]imidazol-3-ium bromide (30)

Yellow solid; Yield: 41.4%; mp: 229.4-231.2 °C; ^{1}H NMR (400 MHz, MeOD) δ 8.33-8.29 (m, 2H), 7.99-7.97 (m, 2H), 4.76- 4.72 (m, 2H), 4.59 (d, *J* = 7.6 Hz, 2H), 2.96 (s, 3H), 2.35-2.28 (m, 1H), 1.96 – 1.90 (m, 2H), 1.61 – 1.55 (m, 2H), 1.11 (m, 9H); ^{13}C NMR (101 MHz, MeOD) δ 176.2, 176.1, 153.3, 136.2, 133.4, 133.3, 132.0, 131.9, 128.2, 128.2, 55.3, 32.3, 30.6, 20.8, 19.9, 13.9, 11.0, 10.8; Calculated for $C_{20}H_{25}N_2O_2$ 325.2; Found MS (ESI): m/z 324.1 $[M-H-Br]^+$

1,3-Diisobutyl-2-methyl-4,9-dioxo-4,9-dihydro-1H-naphtho[2,3-d]imidazol-3-ium bromide (31)

Yellow solid; Yield: 57.6 %; mp: 230.6.7-232.4 °C; ^{1}H NMR (400 MHz, MeOD) δ 8.31 -8.29 (m, 2H), 7.98-7.96 (m, 2H), 4.59 (d, *J* = 7.6 Hz, 4H), 2.94 (s, 3H), 2.35-2.28 (m, 2H), 1.09 (d, *J* = 6.7 Hz, 12H); ^{13}C NMR (101 MHz, MeOD) δ 176.2, 153.5, 136.2, 133.3, 132.1, 128.2, 55.4, 30.6, 19.8, 11.3; Calculated for $C_{20}H_{25}N_2O_2$ 325.2; Found MS (ESI): m/z 324.1 $[M-H-Br]^+$

3-Hexyl-1-isobutyl-2-methyl-4,9-dioxo-4,9-dihydro-1H-naphtho[2,3-d]imidazol-3-ium bromide (32)

Yellow solid; Yield: 38.7%; mp: 242.1-244.0 °C; ^{1}H NMR (400 MHz, MeOD) δ 8.34-8.30 (m, 2H), 8.01 – 7.99 (m, 2H), 4.76-4.72 (m, 2H), 4.60 (d, *J* = 7.6 Hz, 2H), 2.98(s, 3H), 2.37-2.30 (m, 1H), 2.01-1.93 (m, 2H), 1.60-1.54 (m, 2H), 1.50-1.44 (m, 4H), 1.12 (d, *J* = 6.7 Hz, 6H), 1.00 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, MeOD) δ 176.2, 176.1, 153.3, 136.2, 133.4, 133.3, 132.0, 131.9, 128.2, 128.2, 55.3, 49.2, 32.3, 30.6, 30.3, 27.2, 23.5, 19.8, 14.3, 10.9, 10.7; Calculated for $C_{22}H_{29}N_2O_2$ 353.2; Found MS (ESI): m/z 352.3 $[M-H-Br]^+$

1-Isobutyl-2-methyl-3-octyl-4,9-dioxo-4,9-dihydro-1H-naphtho[2,3-d]imidazol-3-ium bromide (33)

Yellow solid; Yield: 17.3 %; mp: 245.1-247.3 °C; ^{1}H NMR (400 MHz, MeOD) δ 8.34-8.30 (m, 2H), 8.01-7.98 (m, 2H), 4.76-4.72 (m, 2H), 4.60 (d, *J* = 7.6 Hz, 2H), 2.97 (s, 3H), 2.36-2.29 (m, 1H), 2.01-1.93 (m, 2H), 1.59-1.55 (m, 2H), 1.51-1 47 (m, 2H), 1.44-1.42 (m, 6H), 1.13-1.11 (d, *J* = 6.7 Hz, 6H), 0.98-0.94(m, 3H); ^{13}C NMR (101 MHz, MeOD) δ 176.4, 176.3, 153.5, 136.4, 133.6, 133.5, 132.2, 132.1, 128.5, 128.4, 55.5, 33.1, 30.8, 30.5, 30.4, 30.3, 27.7, 23.9, 20.1, 14.6, 11.1; Calculated for $C_{24}H_{33}N_2O_2$ 381.3; Found MS (ESI): m/z 380.2 $[M-H-Br]^+$

3-Decyl-1-isobutyl-2-methyl-4,9-dioxo-4,9-dihydro-1H-naphtho[2,3-d]imidazol-3-ium bromide (34)

Yellow solid; Yield: 27.1%; mp: 248.1.7-251.4 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.20-8.18 (m, 2H), 8.01 – 7.99 (m, 2H), 4.61 (t, *J* = 8.0, 2H) MHz, 2H), 4.50-4.48 (m, 2H), 2.93 (s, 3H), 2.17 (m, 1H), 1.97-1.81 (m, 2H), 1.39 – 1.25 (m, 14H), 0.98-0.96 (m, 6H), 0.85-0.83 (m, 3H); ^{13}C NMR (101 MHz DMSO-d_6) δ 174.8, 174.8, 151.9, 135.2, 131.6, 130.4, 130.2, 126.8, 126.8, 53.3, 47.3, 31.2, 28.9, 28.8, 28.7, 28.6, 28.5, 25.7, 22.1, 19.2, 13.9, 10.3. Calculated for $C_{26}H_{37}N_2O_2$ 409.2; Found MS (ESI): m/z 408.1 $[M-H-Br]^+$

3-Dodecyl-1-isobutyl-2-methyl-4,9-dioxo-4,9-dihydro-1H-naphtho[2,3-d]imidazol-3-ium bromide (35)

Yellow solid; Yield: 15.6 %; mp: 250.4-252.6 °C; ^{1}H NMR (400 MHz, MeOD) δ 8.33 – 8.29 (m, 2H), 7.99-7.97 (m, 2H), 4.75-4.71 (m, 2H), 4.59 (d, *J* = 7.6 Hz, 2H), 2.96 (s, 3H), 2.35-2.28 (m, 1H), 1.97 – 1.94 (m, 2H), 1.57 – 1.33 (m, 18H), 1.11 (d, *J* = 6.7 Hz, 6H), 0.95-0.92 (m, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.8, 174.8. 151.9. 135.2, 131.6, 130.4, 130.2, 126.8, 126.8, 53.3, 47.3, 31.3, 29.0, 29.0, 28.9, 28.8, 28.7, 28.6, 28.5, 22.1, 19.2, 13.9, 10.3. Calculated for $C_{28}H_{41}N_2O_2$ 437.3; Found MS (ESI): m/z 436.2 $[M\text{-}H\text{-}Br]^+$

4. Purity Determination of Series A-C

Compound purity was determined by reverse phase HPLC. Chromatograms were collected on a Shimadzu Nexera SR HPLC system (Shimadzu Scientific Instruments, Columbia, MD, USA). Separations were carried out on a Zorbax Eclipse XDB-C18 (150 x 4.6 mm, 5 µm; Agilent Tech. Inc., Loveland, CO) with eluents methanol-water (MeOH-H_2O) or acetonitrile-water (MeCN-H_2O) and detection at 254 nm and 280 nm. The mobile phase flow rate was 1.0 mL/min. The chromatogram was run for 15 min for the detection of the major peak of test compound which was expressed as a percentage of total peaks detected during the run. Compounds with peak areas ≥ 95% on both solvent systems were deemed sufficiently pure for biological investigations.

Table S-1: HPLC Purity data of final compounds (Series A-C) based on % area of major peak

Series	Compound	MeOH-Water (3:2), 15 mM ammonium formate		MeOH-Acetonitrile-Water (3:3:4), 15 mM ammonium formate	
		254 nm	280 nm	254 nm	280 nm
A	5	98.2	99.3	98.8	98.9
A	6	98.9	98.9	98.8	98.9
A	7	98.8	98.9	98.7	98.8
A	8	98.5	98.6	98.8	98.8
A	9	98.9	98.9	98.8	98.8
A	10	96.2	96.2	97.3	97.5
A	11	98.8	98.7	98.8	98.7
A	12	98.3	98.3	98.3	98.1
A	13	99.0	99.0	98.0	98.9
A	14	98.5	98.5	98.9	98.9
A	15	98.9	98.7	98.6	98.5
A	16	99.0	96.5	97.9	98.0
A	17	98.8	98.8	98.7	98.7
A	18	98.4	98.4	98.9	98.6
A	19	97.5	97.6	95.8	95.7
A	20	98.8	98.9	98.8	98.9
A	21	98.8	98.8	96.5	96.4
A	22	99.0	99.0	99.0	99.0
A	23	98.7	98.9	98.9	98.9
A	24	98.8	98.9	98.7	98.7
B	36	95.7	96.7	97.0	96.1
B	37	97.1	97.8	97.1	97.3
B	38	96.4	97.2	96.0	95.2
B	39	96.4	96.7	98.0	97.9
B	40	96.7	97.1	95.9	97.3

Series	Compound	MeOH:Water (3:2), 25 mM ammonium formate		MeOH-Acetonitrile-Water (3:3:4), 25 mM ammonium formate	
		254 nm	280 nm	254 nm	280 nm
C	25	97.2	97.4	97.2	96.5
C	26	96.9	96.7	97.1	96.6
C	27	97.8	96.8	96.4	97.0
C	28	96.2	97.3	96.8	96.4
C	29	96.3	97.4	96.1	95.9
C	30	96.6	97.1	96.4	96.7
C	31	97.6	96.7	97.4	97.8

Series	Compound	MeOH:Water (9:1), 25 mM ammonium formate		Acetonitrile: Water (9:1), 25 mM ammonium formate	
		254 nm	280 nm	254 nm	280 nm
C	32	97.0	99.0	96.0	98.9
C	33	97.8	98.7	98.8	98.7
C	34	98.8	97.8	98.7	98.7
C	35	97.0	96.5	97.9	98.0

5. Synthesis of key compound 1,3-diisopropyl-2-methyl-4,9-dioxo-4,9-dihydro-1H-naphtho[2,3-d]imidazol-3-ium bromide (19)

5.1. (2-Chloro-3-(isopropylamino) naphthalene-1,4-dione (44a)

To 2,3-dichloro-1,4-naphthoquinone (1.5mmol, 341 mg) in 10mL ethanol was added isopropylamine (1.5mmol, 89 mg, 0.13 mL) and triethylamine (2.25mmol, 227 mg, 0.3 mL). The reaction mixture was stirred at room temperature (25^{o}C) for 24 h, after which the solid residue was filtered off, washed with water and recrystallized from ethanol. **44a** was obtained as a red solid in 87% yield (325mg). mp 122.8-123.1 ^{0}C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.97-7.96 (dd, J = 4.1, 1.2 Hz, 1H), 7.95-7.94 (dd, J = 4.2, 1.4 Hz, 1H), 7.83-7.79 (dt, J = 9.4, 1.6 Hz, 1H), 7.74-7.70 (dt, J = 9.4, 1.6 Hz, 1H), 6.71 (d, J = 11.1 Hz, 1H), 4.74-4.66 (m, 1H), 1.27 (d, J = 8 Hz, 6H); Calculated for $C_{13}H_{12}ClNO_2$ 249.1; Found MS (ESI): m/z 250.4 $[M+H]^+$

5.2. *N*-(3-Chloro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-N-isopropylacetamide (44b)

44a (0.4 mmol, 0.1g) was stirred in acetic anhydride (11 mmol, 1 mL) in the presence of 2 drops concentrated sulfuric acid for 1.5 h at room temperature. Distilled water (5 mL) was added dropwise to the stirred mixture, after which it was extracted with ethyl acetate (EtOAc). The organic layer was worked up as described in the General Procedure and the crude product purified by column chromatography (EtOAc-hexane 1:8 to 1:4). **44b** was obtained as a yellow oil in 67.5% yield (79 mg) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 – 8.13 (m, 2H), 7.88 – 7.79 (m, 2H), 4.50-4.42 (m, 1H), 1.84 (s, 3H), 1.24 – 1.19 (m, 6H). Calculated for $C_{15}H_{14}ClNO_3$ 291.1; Found MS (ESI): m/z 291.1 $[M]^-$

5.3. [N-Isopropyl-N-(3-(isopropylamino)-1,4-dioxo-1,4-dihydronaphthalen-2-yl]acetamide (19a)

To a stirred suspension of **44b** (0.3 mmol, 90 mg) in acetonitrile (5 mL) was added dropwise excess isopropylamine (0.9 mmol, 0.05 g, 0.08 mL). The reaction mixture was stirred at 45 ^{0}C for 4h, after which it was concentrated *in vacuo* and purified by column chromatography (EtOAc :DCM 1 : 8 to 1: 2) to afford **19a** as a red oil in 35.8% yield (33 mg). ^{1}H NMR (400 MHz, MeOD) δ 8.09-8.06 (m, 2H), 7.83-7.79 (td, *J* = 9.4, 1.65 Hz, 1H), 7.74-7.70 (td, *J* = 9.55, 1.45 Hz, 1H), 4.46-4.27 (m, 2H), 1.96 (s, 3H), 1.34 (d, *J* = 8.05 Hz, 3H), 1.27 (d, *J* = 8 Hz, 3H), 1.24 (d, *J* = 8 Hz, 3H), 1.12 (d, *J* = 8.6 Hz, 3H); Calculated for $C_{18}H_{22}N_2O_3$ 314.2; Found MS (ESI): m/z 313.2 $[M-H]^-$

5.4. 1,3-Diisopropyl-2-methyl-4,9-dioxo-4,9-dihydro-1H-naphtho[2,3-d]imidazol-3-ium bromide (19)

48% aqueous hydrobromic acid (1.5 mmol, 0.16 mL) was added dropwise to a solution of **19a** (0.1 mmol, 30 mg) in 1:1 EtOH/EtOAc (8 mL) and stirred at 40 °C for 4h followed by stirring for 18 h at room temperature. The reaction mixture was concentrated *in vacuo* and

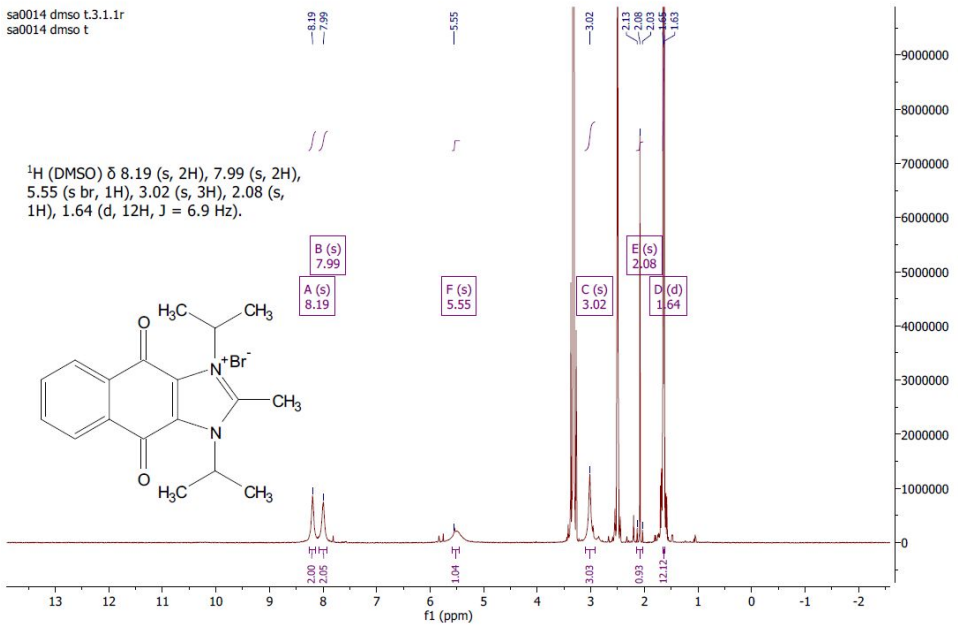
purified by column chromatography (2 % MeOH in DCM to 6% MeOH in DCM) to afford **19** as a yellow solid in 26,4% yield (10 mg); mp: 266.2-266.5 °C; ^{1}H NMR (400 MHz, DMSO)δ 8.19 (m, 2H), 7.99 (m, 2H), 5.55 (br s, 1H), 3.02 (s, 3H), 2.13-2.03 (m, 1H), 1.64 (d, J = 6.9 Hz, 12H); ^{13}CNMR (400 MHz, DMSO-d_6)δ 175.1, 175.1, 152.2, 135.7, 132.2, 131.8, , 127.5, 53.1, 31.2, 20.1, 13.3; Calculated for $C_{18}H_{21}N_2O_2$ 297.2; Found MS (ESI): m/z 297.1 $[M\text{-}Br]^+$. HRMS (ESI) calcd for $C_{18}H_{21}N_2O_2$ 297.1598. Found 297.1602.

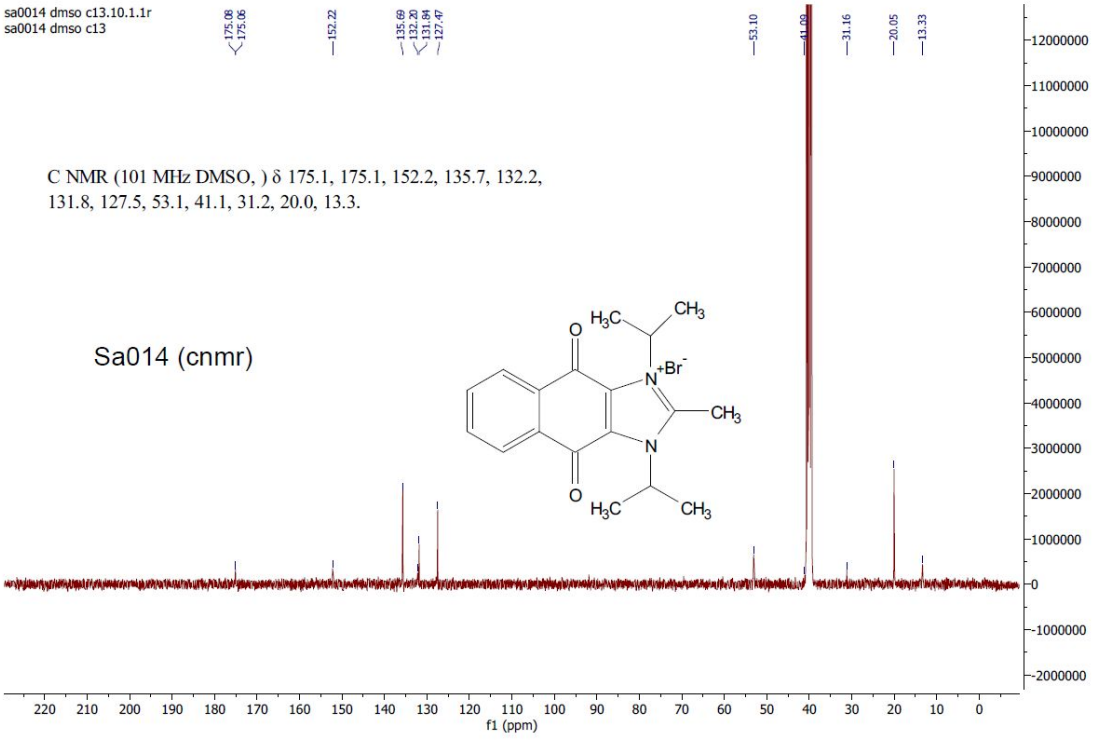
6. NMR and HPLC Spectra of Compound 19

19 is also called **SA014**

Both ^{1}H NMR and ^{13}C NMR were carried out in deuterated DMSO.

Sa014 (pnmr)





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Batch Filename	: MEOH,ACN BATCH 28.10.16.lcb		
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Injection Volume	: 0.5 uL		
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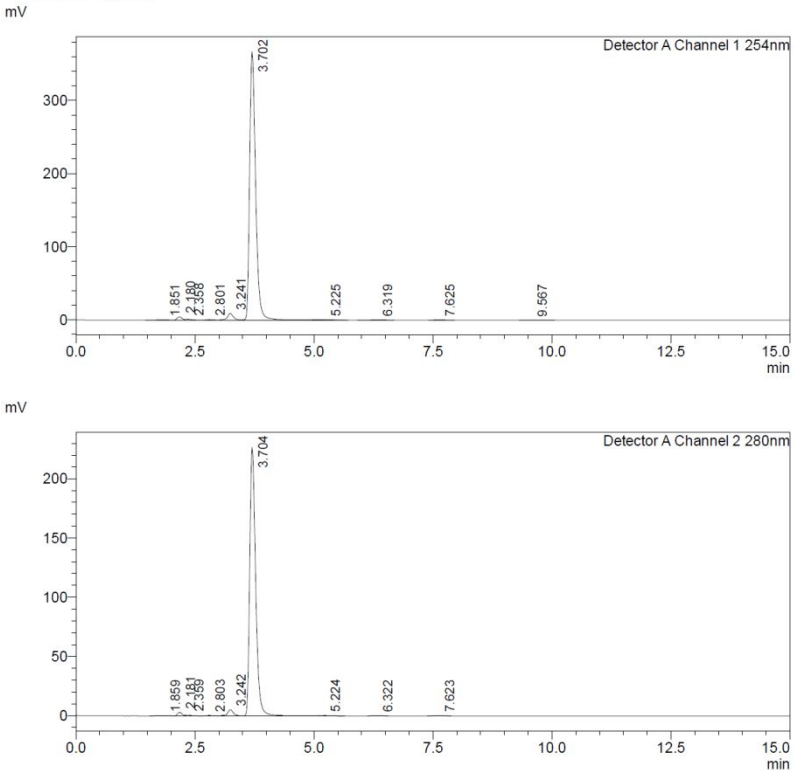


<Peak Table>

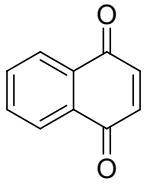
Detector A Channel 1 254nm

7. Activity of Series B on asexual stages of NF54 *P. falciparum*

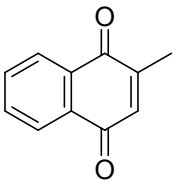
Table S-2: *In vitro* activity of Series B compounds (**36-40**) and commercially available quinones (1,4-naphthoquinone, menadione and 1,4 benzoquinone against asexual NF54 *P. falciparum* parasites at concentrations (5 µM, 1 µM, 100 nM, 20 nM).

Compound	% Inhibition of asexual proliferation [a]			
	5 µM	1 µM	100 nM	20 nM
36	31.8	22.3	29.6	21.0
37	34.0	27.5	28.0	32.1
38	33.6	28.5	24.2	16.8
39	23.6	13.0	12.2	18.8
40	83.3	47.3	19.0	21.9
1,4-Naphtho-quinone[b]	29.9	30.1	19.4	11.1
Menadione[b]	22.6	22.6	28.8	0
1,4-Benzo-quinone[b]	36.2	36.9	30.1	28.4

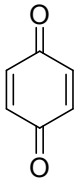
[a] Average from 3 independent biological repeats. IC_{50} of chloroquine (positive control) was 10 (± 3) nM [b] Commercially purchased, structures are as follows:



1,4-Naphthoquinone



Menadione



1,4-Benzoquinone

8. clog P of Series A and C

Table S-3: clog P of Series A and C compounds (**4-35**)

Compound	**clogP[a]**	**Compound**	**clogP[a]**	**Compound**	**clogP[a]**
4	-3.22	**15**	-1.10	**26**	-1.23
5	-2.69	**16**	-1.32	**27**	-0.70
6	-2.16	**17**	-1.58	**28**	-0.92
7	-2.38	**18**	-1.05	**29**	-1.18
8	-2.63	**19**	-1.54	**30**	-0.17
9	-1.63	**20**	-1.80	**31**	-0.30
10	-2.16	**21**	-0.79	**32**	0.88
11	-1.63	**22**	-2.05	**33**	1.94
12	-1.85	**23**	-1.04	**34**	3.0
13	-2.10	**24**	-0.05	**35**	4.06
14	-1.10	**25**	-1.76		

[a] clogP values were determined on ChemDraw Ultra Ver 12.0.0.1076, CambridgeSoft

9. Spearman ρ correlation coefficients of Series A and C

Table S-4: Non-parametric correlations of clogP versus plasmodial activities of Series A and C compounds as assessed by the Spearman ρ correlation coefficient, IBM SPSS Statistics Ver 25.

Parameters	Spearman ρ correlation coefficient	Significance (2-Tailed)
Series A (n = 21): clogP values versus IC_{50} Dd2	-0.209	0.363
Series A (n = 21): clogP values versus IC_{50} 3d7	0.101	0.664
Series C(n = 11): clogP values versus IC_{50} NF54	0.655	0.029 [a]
Series C (n = 11): clogP values versus IC_{50} K1	0.827	0.002 [b]
Series C (n = 11): clogP values versus IC_{50} W2	0.827	0.002 [b]
Series C(n = 11): clogP values versus IC_{50} EG	0.573	0.066 [c]
Series C (n = 11): clogP values versus IC_{50} LG	-0.918	0.0001 [b]

[a] Correlation is significant at the 0.05 level (2-tailed); [b] Correlation is significant at the 0.01 level (2-tailed). [c] No significant correlation.

10. Determination of solubility, PAMPA permeability and microsomal stability of compound 19.

10.1. Solubility Determinations*:*

Solubility determinations (25°C, pH 7.4, 24 h) were carried out on Multiscreen Solubility filter plates (Millipore- MSSLBPC10) from Millipore Corporation (MA, USA) following the protocol (PC2445EN00) from the manufacturer.

10.2. PAMPA Permeability Determinations

Determinations were carried out on MultiScreen-IP PAMPA assay (donor) plates (MAIPNTR10) and MultiScreen Receiver Plates (MATRNPS50) from Millipore Corporation (USA) with 1 % lecithin (Sigma Aldrich, USA) in dodecane (Reagent Plus®, Sigma Aldrich USA) as the lipid barrier. Effective permeability Pe (25°C, pH7.4, 16 h) was determined following a reported method. [S2]

10.3. Microsomal Stability

A previously described method was followed.[S3] Internal standard used was another member of Series A. Chromatographic separation was performed on a Luna 5u C18 column (100 mm

x 4.60 i.d., 5 µm, Phenomenex, Torrance, CA, USA) with a Security Guard Cartridge (3.0 X 4 mm, Phenomenex, Torrance, CA, USA). The mobile phase was a mixture of (A) 0.1% formic acid in water and (B) 0.1% formic acid in acetonitrile. Solvent gradient was 80% A-20% B (1.3 min), 40% A-60% B (1.7 min) and 80%A-20%B for the remaining time (2 min). Flow rate was set at 0.8 mL/min. Sample injection was 1 µL and column temperature was ambient. Data processing was carried out on Analyst® 1.4.2 software package (Applied Biosystems, MA., USA). The corresponding multiple reaction monitoring (MRM) transition of the test compound was selected and used for peak configuration in Analyst® 1.4.2 for semi-quantification. The peak areas of the test compound at different time points were expressed as a % of the peak area of test compound at time zero. % Concentration of test compound was plotted against each time point to give the i*n vitro* half life ($t_{1/2}$ in min) which was determined from time required for initial compound to be reduced to 50 % of its original amount. Each determination was repeated separately on 3 different occasions and $t_{1/2}$ was reported as mean ± SD.

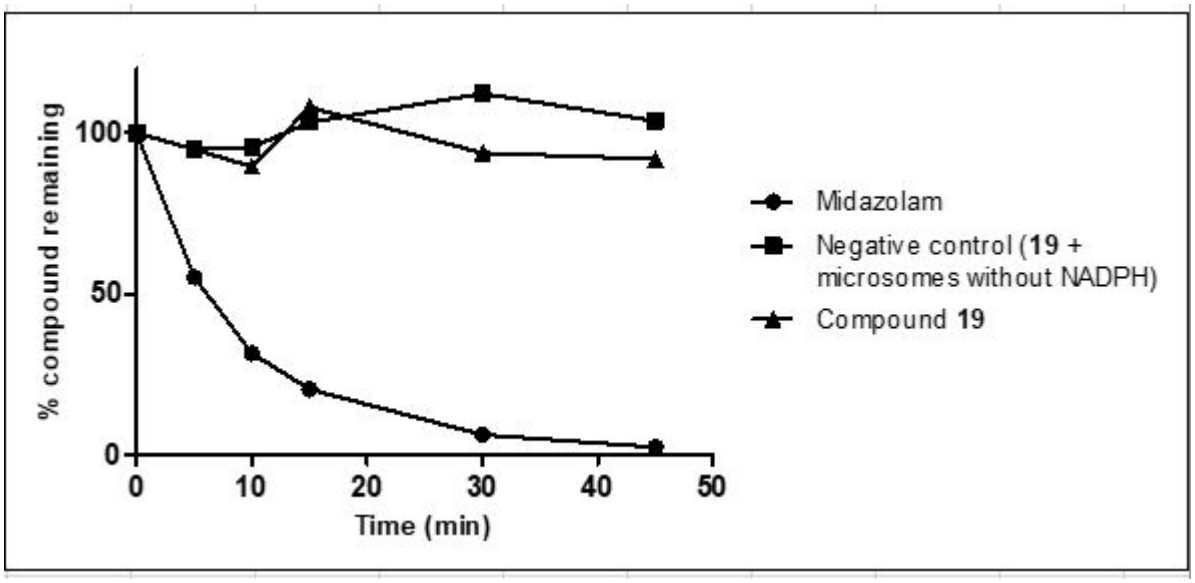


Figure S-1: NADPH-mediated degradation of **19** and midazolam (positive control) by male rat liver microsomes at 37°C over 45 min.

11. Redox cycling EC_{50} values of Series A and B as determined by the phenol red horse radish peroxidase (HRP) assay

A previously reported method was followed with modifications.[S4] 2 µL of test compound (200-fold concentration in DMSO), 18 µL Hank's Balanced Salt Solution (HBSS) and 40 µL dithiothreitol (DTT) solution (2.5 mM in HBSS) were sequentially added to each well in a 96-well clear plate. The contents were shaken for 45 min, 600 rpm on a plate shaker, after which was immediately added 40 µL of horse radish peroxidase-phenol red solution (150 µg/mL horseradish peroxidase, 1 mM phenol red sodium in HBSS) and the plate shaken again for another 10 min, 600 rpm. 15 µL 1M NaOH was then added to each well, agitated (1 min) and absorbance readings were read at 610nm on a microplate reader. DMSO content per well was kept at 1% v/v. Test compound and positive control naphthoquinone were tested over a range of concentrations**.** The absorbance at 610 nm was plotted against logarithmic concentration of test compound from which EC_{50} (concentration required to increase oxidized phenol red absorbance to 50% of maximum value) was determined.

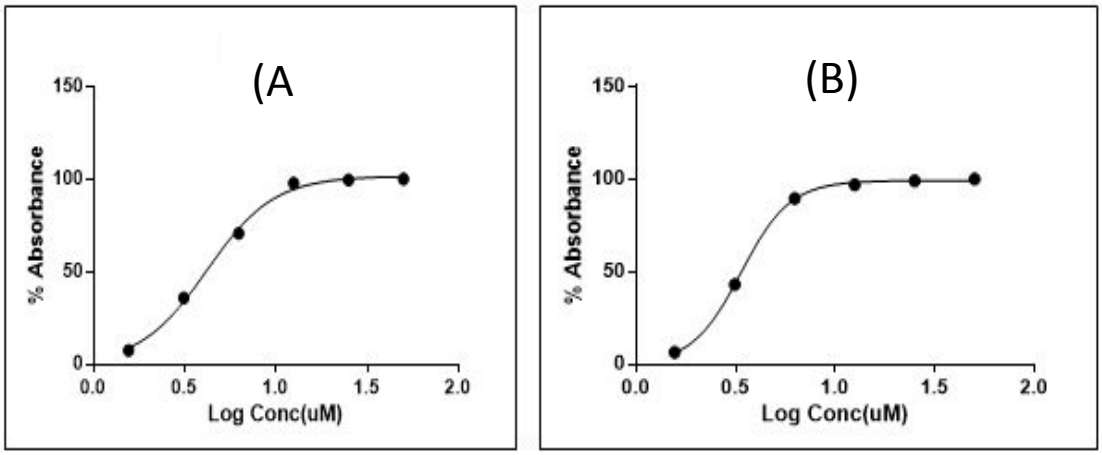
Table S-5: *Redox cycling EC_{50} values of Series A (5-24) and B (36-40)*

Compound	EC_{50} (µM)[a]	Compound	EC_{50} (µM)[a]
5	5.2 ± 0.3	**19**	3.7 ± 0.1
6	5.4 ± 0.3	**20**	3.9 ± 0.2
7	4.6 ± 0.1	**21**	4 ± 0.2
8	5.5 ± 0.3	**22**	3.9 ± 0.1
9	3.7 ± 0.1	**23**	5.6 ± 0.2
10	4.3 ± 0.3	**24**	3.4 ± 0.0
11	3.8 ± 0.1	**36**	> 400
12	2.8 ± 0.1	**37**	> 400
13	3.8 ± 0.1	**38**	> 400
14	4.1 ± 0.2	**39**	> 400
15	3.8 ± 0.1	**40**	> 400
16	5.2 ± 0.3		

17	3.7 ± 0.2	Naphthoquinone	0.35 ± 0.1
18	4.6 ± 0.1		

[a] EC_{50}: Concentration required to reduce oxidized phenol red absorbance to 50% of control values. Mean and SD of n=3 separate determinations.

Figure S-2: *Representative EC_{50} sigmoidal curves for (A)* ***19****; (B) naphthoquinone*



12. Determination of cytotoxicity of compounds Series A compounds on Chinese Hamster Ovary (CHO) cells

CHO-K1 (ATCC CCL-61) cells were grown in Ham's F12 Nutrient Mix (Ham's, ThermoFisher Scientific) supplemented with 10% heat-inactivated fetal bovine serum (Gibco) and 1% penicillin/streptomycin (GE Healthcare Life Sciences). They were seeded at a density of 1000 cells/well in 96-well plates containing 100 µL media per well and incubated for 24 h (37°C, 5% CO_2) for adherence. Thereafter, media in each well was removed by aspiration, 99.5µL of fresh media was added to each well followed by 0.5µL of test compound (prepared in DMSO stock solution at a 200-fold higher concentration) .The final DMSO concentration in each well was kept at 0.5% v/v. The compound-treated cells were incubated for 48 h (37°C, 5% CO_2) after which aliquots (0.5uL) of Celltitre 96 ®Aqueous One Solution (Promega, Madison, WS) were added to each well and incubated for a further 4 h. Plates were then agitated at 600 rpm, 1 min on a plate shaker before absorbance readings were read at 490 nm on a Tecan InfiniteTM M200 Pro plate reader. Viability of cells were determined from the following expression:

$$\text{Percentage viability} = [(Ab_{compound} - Ab_{blank})/(Ab_{control} - Ab_{blank})] \times 100\%$$

where $Ab_{compound}$ = Absorbance of compound-treated cells, $Ab_{control}$ = Absorbance of untreated/control cells and Ab_{blank} = Absorbance of growth media containing 0.5% w/v DMSO. Each test compound was assessed at 6 concentrations in at least 3 separate experiments carried out at different times. % Viability readings were plotted against log concentration on GraphPad Prism (Version 5.0, San Diego, CA) to give a sigmoidal curve from which IC_{50} (concentration required to reduce viability by 50% compared to control/untreated cells) was obtained.

13. In vitro assessment of antimalarial activity

13.1. In vitro assessment of antimalarial activity against asexual 3D7 and Dd2 *P. falciparum*

In vitro activity against asexual stages of *P. falciparum* parasites (3D7, Dd2) was determined using a previously described Hoechst 33342-based method to measure DNA content of infected erythrocytes.[S5] A 10x master drug plate was prepared by performing 11-point serial dilution from 1 µM DMSO stock solutions of **4-24** (Series A) with sterile PBS. 20 µL of the diluted test compound was added to 180 µL of parasite suspension in a 96-well plate. Control drugs were artesunate and chloroquine (CQ). DMSO content per well was kept at 0.1% v/v. The plates (protected from light) were incubated for 48h at 37 °C under hypoxic conditions (5% CO_2, 5% O_2, 90% N_2). Thereafter, parasites were labelled with Hoechst 33342 (Ex/Em: 350/461) for 15 minutes. At least 100,000 events were collected on the Attune NxT flow cytometer (Invitrogen, CA) using a 405-nm violet excitation laser fitted with a 417LP 440/50BP filter for Hoechst 33342 detection. Parasitemia was quantified using FlowJo software. Growth inhibitory IC_{50}s were determined on Graphpad Prism 5.0.

13.2. In vitro assessment of antimalarial activity against asexual NF54, W2 and K1 *P. falciparum*

In vitro activity against asexual stages of *P. falciparum* parasites (NF54, K1, W2) was determined using the proliferative SYBR Green I-based fluorescence assay as described previously.[S6] Stock solutions of test compounds in DMSO were serially diluted in supplemented RPMI 1640 medium containing AlbuMAX II, with content of DMSO per well kept at 0.1% v/v or lower, parasitemia at 1% and hematocrit at 1%. Artesunate and CQ were used as reference drugs. Drug treated parasites were incubated for 96 h (37 °C) under hypoxic conditions (5% CO_2, 5% O_2, 90% N_2). Subsequently, 100 µL of the parasite suspension was added to 100 µL SYBR Green I lysis buffer which comprised 0.2 µL/mL 10 000x SYBR Green I (Invitrogen), 20 mM Tris, pH 7.5, 5 mM EDTA, 0.008% w/v saponin and 0.08% v/v Triton X-100. The treated plates were then incubated at 37 °C for 1 h, after which fluorescence was

read on a Fluoroskan Ascent FL microplate reader (Thermo Scientific) at Ex/Em wavelengths of 485 nm /538 nm. Readings were corrected for background fluorescence (using CQ-treated infected erythrocytes) in which parasite proliferation was completely inhibited. Corrected readings were expressed as % proliferation normalized to an untreated control. Sigmoidal dose-response curves were plotted using GraphPad 5.0 from which 50% growth inhibitory concentrations (IC_{50}) were determined.

13.3. In vitro assessment of antimalarial activity against *P. falciparum* TM90C2B asexual parasites using the modified [^{3}H]-hypoxanthine incorporation assay

The modified [^{3}H]-hypoxanthine incorporation assay was used to test compounds against drug-sensitive (NF54), drug resistant (K1) strains of *P. falciparum* and the atovaquone resistant *P. falciparum* clinical isolate TM90C2B. The parasites were cultivated in human erythrocytes as previously described [S7,S8] but with some variations to the medium which comprised RPMI 1640 supplemented with 0.5% ALBUMAX® II, 25 mM Hepes, 25 mM $NaHCO_3$ (pH 7.3), 0.36 mM hypoxanthine, and 100 µg/ml neomycin. Parasite cultures were maintained in an environment of 37 °C, 3% O_2, 4% CO_2, and 93% N_2 in humidified modular chambers.

Test compounds were dissolved in 100% DMSO, by sonication, to give 10 mg/ml stock solutions and diluted in culture medium devoid of hypoxanthine. Infected erythrocytes (100 microliter per well with 2.5% hematocrit and 0.3% parasitemia) were added to each compound titrated in 100 microliter duplicates over a 64-fold range and incubated for 48 h. After this period, 0.5 microCi of [^{3}H] hypoxanthine in 50 microliter media was added and the culture plates allowed to incubate for a further 24 h. From the parasites harvested on glass-fiber filters at the end of the total incubation period, radioactivity was determined using a Betaplate liquid scintillation counter (Wallac, Zurich). The radioactivity was recorded as counts per minute per well at each concentration of test compound and presented as percentage relative to the untreated controls. The concentrations resulting in 50% inhibition (IC_{50}) was determined by linear interpolation. [S9]

13.4. In vitro activity assay against *P. falciparum* NF54 gametocytes

A transgenic parasite line NF54-Pfs16-GFP-Luc which expressed a green fluorescent protein (GFP)-luciferase reporter construct controlled by the gametocyte marker Pfs16 was employed. [S10] Gametogenesis was induced in the transgenic parasite cell line through a combination of glucose depletion and a decrease in haematocrit from a >95% synchronized, ring-stage asexual population (~10% parasitemia) as described previously. [S10, S11] Drug assays were set up on days 5 and 10 (representing >90% of either early stage II/III or mature stage IV/V

gametocytes, respectively). In each instance, gametocytes (2-3% in media containing 1.5% hematocrit) were treated with test compound for 48h at 37 °C under hypoxic conditions. Cell viability was determined by a luciferase reporter assay. The parasite lysate (20 µL) was added to luciferin substrate (50 µL, Promega Luciferase Assay System) and the resultant bioluminescence was detected at an integration constant of 10s on the GloMax®-Multi+ Detection System with Instinct® Software. Methylene blue and aretesunate were routinely included as controls. Three independent biological replicates were carried out for each compound, each performed in technical triplicates. The compound concentration at which 50% parasite viability was affected (IC_{50}) was determined from dose response curves plotted on GraphPad 5.0.

14. PK of 19 in mice

This work was carried out under contract to H3D, University of Cape Town, South Africa. The procedure was conducted with the approval of the Animal Ethics Committee of the University of Cape Town (Approval No. 017/026, 017/025) in accordance with the South African National Standard for the Care and Use of Animals for Scientific Purposes and guidelines from the Department of Health.

Healthy male C57/BL6 mice weighing approximately 25 g were used. The mice were housed in cages (27x21x18 cm) under controlled environmental conditions (22±2^{o}C, 40-70% humidty12 h dark/light cycle). Their diet consisted of standard laboratory food. Water was available *ad libitum.*

The compound was dissolved in dimethylacetamine (DMA)/polyethyleneglycol (PEG)/ polypropyleneglycol (PPG) (10:30:60) for iv dosing at 2 mg/kg and in 0.5% (w/v) hydroxypropylmethylcellulose - 0.2% Tween 80 aqueous solution for oral dosing (20 mg/kg). The doses were compensated for the presence of the bromide anion. A group of 3 animals were used for each dosing route. Blood samples were collected via tail bleeds at predetermined times which were 0.17h, 0.5h, 1h, 3h, 5h, 7h, 9h, 24h for iv dosing and 0.5h, 1h, 3h, 5h, 7h, 9h, 24h for oral dosing. The blood was collected in heparinized tubes and stored at -80^{o}C until extraction.

For extraction, an aliquot of blood (20 µL) was extracted with an aliquot (100 µL) of acetonitrile-0.1% formic acid containing the internal standard (10ng/mL MMV394902). The mixture was vortexed and centrifuged to remove precipitated protein. Calibration standards and quality controls were extracted by the same method. Supernatants were analysed for 19 by LCMS which was carried out using a AB SCIEX 4000 QTRAP system equipped with a

Turbo V TM ion source coupled to an Agilent 1100 HPLC. Ion detection was via positive electrospray ionization under multiple reaction monitoring (MRM) scans. Chromatographic separation was carried out on a Poroshell 120 EC-C18 column from Agilent (100x4.6 mm, 2.7 µM particle size), using gradient elution of mobile phases (A: 0.1% formic acid; B: 0.1% formic acid in acetonitrile) at the following settings : 0.5 mL/min flow rate, 10 min run, injection volume 5 µL, column temperature 40^{o}C, sample tray temperature 8^{o}C. The

19 was quantifiable up to 24h in 2 mice dosed PO and all mice dosed iv. The LLOQ was 0.007 µM. Circulating concentrations of **19** in mice after iv and po dosing are given in Table S-6. A non-compartmental analysis was performed for the determination of PK parameters using the software PK Solutions v2.0 (Summit Research Service). PK parameters were analysed up to 7 h only for iv dosing because of concerns over the reliabilities of the 9h and 24 h values. It was analysed up to 24 h for oral dosing.

Table S-6: Circulating concentrations of **19** in mice over 24 h after i.v. /p.o. dosing (n=3 per sampling time)

	Circulating concentrations (µM) Mean (SD) for n=3	
Time (h)	I.V dosing (2 mg/kg)	Oral dosing (20 mg/kg)
0.17	0.762 (0.637)	Not done
0.5	0.886 (0.549)	0.350 (0.012)
1	0.913 (0.725)	0.335 (0.186)
3	0.152 (0.073)	0.098 (0.044)
5	0.036 (0.022)	0.028 (0.020)
7	0.022 (0.011)	0.033 (0.005)
9	0.033 (0.004)	0.020 (0.010)
24	0.010 (0.004)	0.013 (0.004)

15. *In vivo* efficacy of 19 in a humanized mouse model of *P.falciparum*

This work was carried out under contract to H3D, University of Cape Town, South Africa. The procedure was conducted with the approval of the Animal Ethics Committee of the University of Cape Town (Approval No. 017/026, 017/025) in accordance with the South African National Standard for the Care and Use of Animals for Scientific Purposes and guidelines from the Department of Health.

The therapeutic efficacy of **19** was evaluated using a “4-day” test.

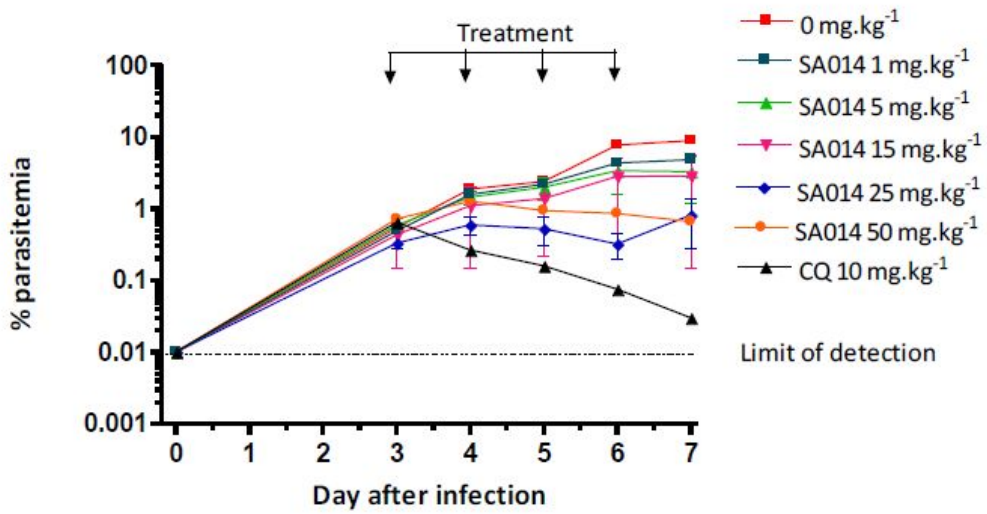
Briefly, NOD-*scid IL-2Ry* ^{null} mice engrafted with human erythrocytes (~60%) were infected with 2 x 10^7 *P. falciparum*-infected erythrocytes from a donor mouse. Infections were done intravenously (Day 0). Mice were housed in ventilated cages filled with autoclaved wood shavings in an air-conditioned facility (22 ± 0.3^{o}C, 40-70% relative humidity, 12 h light/dark cycle, 20 air changes per h) and fed with autoclaved pellets and sterile water *ad libitum*.

Compound **19** was dissolved in a solution of 0.5% hydroxypropyl methylcellulose and 0.2% Tween 80 in distilled water for oral administration to infected animals. 5 doses (1, 5, 15, 25 and 50 mg/kg) of **19** were administered to mice (2 mice per dose), with each dose given consecutively to the same group of mice on Days 3, 4, 5 and 6. Chloroquine phosphate (positive control) was dissolved in PBS and given orally to mice at 10 mg/kg following the same treatment schedule as19.

Parasitemia was assessed in samples drawn from peripheral blood of treated animals on days 0, 3,4,5,6 and 7. The blood sample was stained with TER-119-PE (marker for murine erythrocytes) and SYTO-19 (nucleic acid dye) and analysed by flow cytometry (BD Accuri C6 Plus).

Figure 4 is a plot of % parasitemia at days 3,4,5,6 and 7 in mice administered with **19** at po doses of 1,5,15, 25 and 50 mg/kg.

Figure S-3: % Parasitemia versus days after infection at various doses of **19** (SA014).



To determine ED_{90}, non-linear fitting to a sigmoid dose-response curve of log_{10} Parasitemia on day 7 following infection versus dose of **19** was used.

16. References

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