Supporting Information

Discovery of Novel Benzo[a]phenoxazine SSJ-183 as Drug Candidate for Malaria

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Chemical Experiments

*General Procedure***.** Starting materials were obtained from Wako and Aldrich Companies and used as received. Melting points were determined on a Yanaco apparatus and are uncorrected. NMR spectra were recorded on a Bruker-400 or Vaian-500 spectrometer; TMS was used as an internal standard for ^{1}H NMR and solvent peak was used as an internal standard for ^{13}C NMR. Absorption spectra were taken on JASCO V-550 UV-vis spectrophotometer. IR and UV spectra were taken by

JASCO FT/IR-4100 and JASCO V-550, respectively. Mass spectra were recorded with JEOL JMS-600 and Shimadzu LCMS-2010 EV spectrometers. LC-MS (ESI^+) spectra were taken with a Shimadzu LCMS-2010EV spectrometry. The elemental analyses were performed with Yanaco CHN-MT-5 element analyzer. The purities (>96%) of products were determined by the LCMS spectrometer using Capcell pak C18 MGII 3 μm, 3.0 mm I.D. x 150 mm (Shiseido) eluting with 0.2 mL/min of 0.1% aqueous trifluoroacetic acid-acetonitrile (2 : 3 v/v).

Typical Procedure for the Synthesis of Tested Benzo[a]phenoxazines

To a solution of **6**[1] (X = NO_3, 365 mg, 1 mmol) in ethanol (5 mL) was added 4-aminopyridine (282 mg, 3 mmol) and the mixture was refluxed overnight and then stirred for 24 h at ambient temperature. After evaporation of the solvent, the residue was subjected to column chromatograph on silica gel. Elution with chloroform and methanol (10 : 0.3 and then 10 : 1, v/v) gave a product which was washed with ethyl acetate and then ether to give **5** (149.7 mg, 38%) as a purple powder.

The hydrochloride was prepared by treatment with conc. hydrochloric acid in ethanol, followed by addition of ether. The formed precipitate was recrystallized from ethanol and ether.

Physical and Spectral Data of New Benzo[a]phenoxazines

***N,N*-Diethyl-5-(pyridin-4-ylimino)-5H-benzo[a]phenoxazin-9-amine (5)**

Yield 38 %, mp 247-248 ^oC; IR ν (neat, cm^{-1}): 2975, 1640, 1595, 1575, 1490, 1455, 1270, 1220, 1110; UV-vis ($CHCl_3$): λ (nm) (log ε/L $mol^{-1}cm^{-1}$): 713 (4.48), 537 (4.49); ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.21 (t, J = 7.1 Hz, 6H), 3.41 (q, J = 7.1 Hz, 4H), 6.13 (s, 1H), 6.29 (d, J = 2.7 Hz, 1H), 6.57 (dd, J = 9.0, 2.7 Hz, 1H), 6.85-6.86 (m, 2H), 7.50 (d, J = 9.0 Hz, 1H), 7.61-7.69 (m, 2H), 8.50-8.52 (m, 2H), 8.54 (dd, J = 7.9, 1.4 Hz, 1H), 8.62 (dd, J = 7.9, 1.3 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 12.6, 44.9, 96.3, 97.7, 108.8, 116.0, 123.9, 124.7, 125.1, 129.9, 130.3, 130.5, 131.6, 132.2, 141.5, 146.6, 149.1, 150.0, 150.4, 156.8, 159.4; MS (EI^+): *m/z*: 394 $[M\cdot]^+$; HRMS (EI^+) 394.1793 $[M\cdot]^+$, found 394.1807; Anal. Calcd. For $C_{25}H_{22}N_4O\cdot0.25H_2O$: C, 75.26; H, 5.68; N, 14.04; Found: C, 75.31; H, 5.10; N, 13.88.

Hydrochloride; mp > 300; IR ν (neat, cm^{-1}): 2920, 2850, 1638, 1579, 1518, 1318, 1251, 1162, 1077; UV-vis (*EtOH*): λ (nm) (log ε/L $mol^{-1}cm^{-1}$): 602 (4.64), 213 (4.63); ^{1}H NMR (400 MHz, *CD_3OD) δ* ppm 1.47 (t, *J* = 7.2 Hz, 6H), 4.02 (dd, *J* = 20.5, 7.1 Hz, 4H), 7.38 (d, *J* = 2.6 Hz, 1H), 7.60 (d, *J* = 7.5 Hz, 2H), 7.93-7.87 (m, 1H), 7.97 (dd, *J* =10.0, 2.6 Hz, 1H), 8.02 (d, *J* = 7.3 Hz, 1H), 8.05 (s, 1H), 8.15 (d, *J* = 10.0 Hz, 1H), 8.34 (d, *J* = 8.4 Hz, 1H), 8.46 (d, *J* = 7.5 Hz, 2H), 9.17 (d, *J* = 8.1 Hz, 1H); MS (ESI^+): m/z: 395.2 $[M\text{-}Cl]^+$; Anal. Calcd. For $C_{25}H_{22}N_4O{\cdot}2HCl{\cdot}H_2O$: C, 61.86; H, 5.40; N, 11.54; Found: C, 61.50; H, 5.29; N, 11.41.

5-(3,5-Dichloropyridin-2-ylimino)-*N,N*-diethyl-5H-benzo[a]phenoxazin-9-amine (10)

Yield 10 %, mp 192-193 ^oC; IR ν (neat, cm^{-1}): 2980, 1640, 1590, 1555, 1420, 1275, 1210, 1115; UV-vis (*$CHCl_3$*): λ (nm) (log ε/L $mol^{-1}cm^{-1}$): 547 (4.67); ^{1}H NMR (400 MHz, *$CDCl_3$*) δ ppm 1.22 (t, *J* = 7.1 Hz, 6H), 3.43 (q, *J* = 7.1 Hz, 4H), 6.34 (d, *J* = 2.6 Hz, 1H), 6.42 (s, 1H), 6.61 (dd, *J* = 9.0, 2.5 Hz, 1H), 7.54 (d, *J* = 9.0 Hz, 1H), 7.63-7.71 (m, 2H), 7.78 (d, *J* = 2.3 Hz, 1H), 8.34 (d, *J* = 2.3 Hz, 1H), 8.63-8.69 (m, 2H); ^{13}C NMR (101 MHz, *$CDCl_3$*) δ ppm 12.6, 45.0, 96.3, 98.8, 109.3, 123.7, 124.6, 125.2, 125.6, 125.8, 129.9, 130.4, 130.7, 131.6, 132.0, 137.3, 141.1, 145.4, 146.7, 149.4, 150.3, 158.5, 158.8; MS (EI^+): *m/z*: 462 $[M\cdot]^+$; HRMS (EI^+) 462.1014 $[M\cdot]^+$, found 462.0958; Anal. Calcd. For $C_{25}H_{20}Cl_2N_4O{\cdot}0.5H_2O$: C, 63.57; H, 4.48; N, 11.86; Found: C, 63.48; H, 4.30; N, 11.72.

***N,N*-Diethyl-5-(quinolin-2-ylimino)-5H-benzo[a]phenoxazin-9-amine (11)**

Yield 71 %, mp 234-236 ^oC; IR ν (neat, cm^{-1}): 2980, 1635, 1585, 1540, 1510, 1340, 1265, 1220, 1110; UV-vis (*$CHCl_3$*): λ (nm) (log ε/L $mol^{-1}cm^{-1}$): 691 (4.30), 539 (4.57); ^{1}H NMR (400 MHz, *$CDCl_3$*) δ ppm 1.19 (t, *J* = 7.1 Hz, 6H), 3.39 (q, *J* = 7.1 Hz, 4H), 6.26 (d, *J* = 2.7 Hz, 1H), 6.47 (s, 1H), 6.57 (dd, *J* = 9.0, 2.7 Hz, 1H), 7.20 (d, *J* = 8.5 Hz, 1H), 7.44-7.48 (m, 1H), 7.52 (d, *J* = 9.0 Hz, 1H), 7.63-7.70 (m, 3H), 7.79-7.83 (m, 1H), 8.03 (d, *J* = 8.4 Hz, 1H), 8.14-8.16 (m, 1H), 8.62-8.72 (m, 2H);

^{13}C NMR (101 MHz, *CDCl$_3$*) δ ppm 12.6, 44.9, 96.3, 99.3, 108.9, 117.6, 123.7, 124.8, 124.9, 125.6, 125.7, 127.4, 128.5, 129.5, 129.8, 130.3, 130.4, 130.5, 131.7, 132.5, 137.8, 146.7, 148.0, 149.2, 150.0, 156.4, 158.2; MS (EI$^+$): *m/z*: 444 [M·]$^+$; HRMS (EI$^+$) 444.1950 [M·]$^+$, found 444.1931; Anal. Calcd. For $C_{29}H_{24}N_4O·1.5H_2O$: C, 73.86; H, 5.77; N, 11.88; Found: C, 73.16; H, 5.29; N, 11.67.

***N,N*-Diethyl-5-(5-methylisoxazol-3-ylimino)-5H-benzo[a]phenoxazin-9-amine (12)**

Yield 34 %, mp 195-196 ^{o}C; IR *ν* (neat, cm^{-1}): 2975, 1635, 1590, 1560, 1490, 1275, 1110; UV-vis (*CHCl$_3$*): λ (nm) (log ε/L mol^{-1}cm^{-1}): 539 (4.65); ^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 1.23 (t, *J* = 7.1 Hz, 6H), 2.45 (s, 3H), 3.42 (q, *J* = 7.1 Hz, 4H), 5.92 (s, 1H), 6.33 (d, *J* = 2.7 Hz, 1H), 6.58 (dd, *J* = 9.0, 2.7 Hz, 1H), 6.77 (s, 1H), 7.51 (d, *J* = 9.0 Hz, 1H), 7.60-7.68 (m, 2H), 8.59-8.63 (m, 2H); ^{13}C NMR (101 MHz, *CDCl$_3$*) δ ppm 12.6, 12.7, 44.9, 96.3, 99.1, 99.6, 109.0, 123.7, 125.0, 125.5, 129.8, 130.3, 130.5, 131.5, 132.3, 141.3, 146.7, 149.2, 150.1, 160.3, 168.8, 169.6; MS (EI$^+$): *m/z*: 398 [M·]$^+$; HRMS (EI$^+$) 398.1742 [M·]$^+$, found 398.1721; Anal. Calcd. For $C_{24}H_{22}N_4O_2·2H_2O$: C, 66.34; H, 6.03; N, 12.89; Found: C, 66.54; H, 5.43; N, 12.67.

***N,N*-Diethyl-5-(6-methoxybenzo[d]thiazol-2-ylimino)-5H-benzo[a]phenoxazin-9-amine (13)**

Yield 52 %, mp 197-198 ^{o}C; IR *ν* (neat, cm^{-1}): 2975, 1635, 1585, 1430, 1320, 1270, 1110; UV-vis (CHCl3): λ (nm) (log ε/L mol^{-1}cm^{-1}): 582 (4.69); ^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 1.23 (t, *J* = 7.1 Hz, 6H), 3.43 (q, *J* = 7.1 Hz, 4H), 3.89 (s, 3H), 6.39 (d, *J* = 2.7 Hz, 1H), 6.62 (dd, *J* = 9.1, 2.7 Hz, 1H), 7.03 (dd, *J* = 8.9, 2.6 Hz, 1H), 7.29 (d, *J* = 2.5 Hz, 1H), 7.55 (d, *J* = 9.0 Hz, 1H), 7.62-7.70 (m, 3H), 7.81 (d, *J* = 8.9 Hz, 1H), 8.64-8.69 (m, 2H); ^{13}C NMR (101 MHz, *CDCl$_3$*) δ ppm 12.6, 45.0, 55.8, 96.2, 100.7, 104.2, 109.7, 114.7, 122.5, 123.7, 125.7, .125.8, 129.7, 130.4, 130.8, 131.6, 132.3, 136.3, 140.8, 146.9, 147.2, 150.2, 150.5, 156.5, 159.4, 160.3; MS (CI$^+$): *m/z*: 481 [MH]$^+$; HRMS (CI$^+$) 481.1698 [MH]$^+$, found 481.1691; Anal. Calcd. For

$C_{28}H_{24}N_4O_2S \cdot 0.5H_2O$: C, 68.69; H, 5.15; N, 11.44; Found: C, 68.41; H, 5.01; N, 11.23.

***N,N*-Diethyl-5-(pyrimidin-2-ylimino)-5H-benzo[a]phenoxazin-9-amine (14)**

Yield 24 %, mp 208-210 ^{o}C; IR ν (neat, cm^{-1}): 2975, 1640, 1590, 1550, 1395, 1275, 1110; UV-vis (*$CHCl_3$*): λ (nm) (log ε/L $mol^{-1}cm^{-1}$): 543 (4.62); ^{1}H NMR (400 MHz, *$CDCl_3$*) δ ppm 1.23 (t, *J* = 7.1 Hz, 6H), 3.43 (q, *J* = 6.9 Hz, 1H), 6.34 (d, *J* = 2.1 Hz, 1H), 6.58 (s, 1H), 6.63 (dd, *J* = 9.0, 2.3 Hz, 1H), 7.02 (t, *J* = 4.8 Hz, 1H), 7.54 (d, *J* = 9.0 Hz, 1H), 7.61-7.70 (m, 2H), 8.63 (d, *J* = 7.7 Hz, 1H), 8.67 (d, *J* = 8.1 Hz, 1H), 8.74 (d, *J* = 4.8 Hz, 2H); ^{13}C NMR (101 MHz, *$CDCl_3$*) δ ppm 12.6, 45.01, 96.2, 99.3, 109.6, 115.6, 123.6, 125.4, 125.7, 129.8, 130.5, 130.8, 131.6, 131.9, 140.9, 146.7, 149.4, 150.4, 158.6, 159.0, 168.1; MS (EI^+): *m/z*: 395 $[M\cdot]^+$; HRMS (CI^+) 396.1824 $[MH]^+$, found 396.1850; Anal. Calcd. For $C_{24}H_{21}N_5O \cdot 1.5H_2O$: C, 68.23; H, 5.73; N, 16.58; Found: C, 68.60; H, 5.29; N, 16.34.

***N,N*-Diethyl-5-(pyridin-2-ylimino)-5H-benzo[a]phenoxazin-9-amine (15)**

Yield 55 %, mp 169-170 ^{o}C; IR ν (neat, cm^{-1}): 2975, 1645, 1590, 1580, 1490, 1455, 1270, 1220, 1110; UV-vis (*$CHCl_3$*): λ (nm) (log ε/L $mol^{-1}cm^{-1}$): 532 (4.57); ^{1}H NMR (400 MHz, *$CDCl_3$*) δ ppm 1.20 (t, *J* = 7.1 Hz, 6H), 3.39 (q, *J* = 7.1 Hz, 4H), 6.27 (d, *J* = 2.7 Hz, 1H), 6.43 (s, 1H), 6.54 (dd, *J* = 9.0, 2.7 Hz, 1H), 6.99-7.03 (m, 2H), 7.49 (d, *J* = 9.0 Hz, 1H), 7.60-7.72 (m, 3H), 8.50-8.51 (m, 1H), 8.60-8.64 (m, 2H); ^{13}C NMR (101 MHz, *$CDCl_3$*) δ ppm 12.6, 44.9, 96.3, 99.1, 108.6, 117.0, 118.6, 123.7, 124.7, 125.3, 129.8, 130.1, 130.3, 131.6, 132.8, 137.6, 141.9, 146.6, 148.9, 149.0, 149.9, 157.9, 163.8; MS (EI^+): *m/z*: 394 $[M\cdot]^+$; HRMS (EI^+) 394.1793 $[M\cdot]^+$, found 394.1767; Anal. Calcd. For $C_{25}H_{22}N_4O \cdot 0.75H_2O$: C, 73.60; H, 5.81; N, 13.73; Found: C, 73.68; H, 5.57; N, 13.43.

***N,N*-Diethyl-5-(pyridin-3-ylimino)-5H-benzo[a]phenoxazin-9-amine (16)**

Yield 43 %, mp 198-199 ^{o}C; IR ν (neat, cm^{-1}): 2971, 1636, 1589, 1564, 1488, 1469, 1408,1352, 1271, 1218, 1109, 1014; UV-vis (*CHCl$_3$*): λ (nm) (log ε/L mol^{-1}cm^{-1}): 533 (4.46), 240 (4.36); ^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 1.21 (t, *J* = 7.1 Hz, 6H), 3.42 (q, *J* = 7.1 Hz, 4H), 6.24 (s, 1H), 6.29 (d, *J* = 2.7 Hz, 1H), 6.57 (dd, *J* = 9.0, 2.7 Hz, 1H), 7.29-7.31(m, 2H), 7.50 (d, *J* = 9.0 Hz, 1H), 7.63-7.69 (m, 2H), 8.28 (d, J = 1.47 HZ,1H), 8.37(dd, J = 4.33, 1.80 HZ), 8.57 (d, *J* = 7.62 Hz, 1H), 8.64 (dd, *J* = 7.9, 1.3 Hz, 1H); ^{13}C NMR (101 MHz, *CDCl$_3$*) δ ppm 12.58, 44.92, 96.3, 97.7, 108.8, 123.6, 123.8, 124.8, 125.07, 128.1, 129.9, 130.2, 130.4, 131.5, 132.4, 141.8, 142.4, 144.5, 146.6, 149.1, 150.02; MS (EI^{+}): *m/z*: 395.1 [M+1]$^{+}$; HRMS (EI^{+}) 394.1793 [M·]$^{+}$, found 394.1792.

_N,N_-Dimethyl-5-(pyridin-4-ylimino)-5H-benzo[a]phenoxazin-9-amine (17)

Yield 44 %, mp 217-218 ^{o}C; IR ν (neat, cm^{-1}): 2954, 2887, 1628, 1592, 1577, 1447, 1442, 1359, 1200, 1111, 1002, 746; UV-vis (*CHCl$_3$*): λ (nm) (log ε/L mol^{-1}cm^{-1}): 546 (4.42), 236 (4.21); ^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 3.07 (s, 6H), 6.14 (s, 1H), 6.33 (d, *J* = 2.9 Hz, 1H), 6.61 (dd, *J* = 9.0, 2.7 Hz, 1H), 6.85-6.87 (m, 2H), 7.48 (d, *J* = 9.0 Hz, 1H), 7.53-7.55 (m, 2H), 7.66-7.7 (m, 2H), 8.53 (dd, *J* = 7.9, 1.4 Hz, 1H), 8.64 (dd, *J* = 7.9, 1.3 Hz, 1H); ^{13}C NMR (101 MHz, *CDCl$_3$*) δ ppm 40.3, 96.9, 97.9, 109.1, 112.9, 116.9, 123.9, 125.1, 129.2, 130.1, 130.4, 131.5, 132.2, 142.1, 146.2, 149.08, 152.2, 156.8, 159.4; MS (EI^{+}): *m/z*: 367.1 [M+1]$^{+}$; HRMS (EI^{+}) 366.1478 [M·]$^{+}$, found 366.1480.

_N,N_-Dipropyl-5-(pyridin-4-ylimino)-5H-benzo[a]phenoxazin-9-amine (18)

Yield 39 %, mp 215-216 ^{o}C; IR ν (neat, cm^{-1}): 2962, 2876, 1635, 1580, 1547, 1483, 1458, 1361, 1238, 1112, 772; UV-vis (*CHCl$_3$*): λ (nm) (log ε/L mol^{-1}cm^{-1}): 716 (4.97), 550 (5); ^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 1.051 (t, *J* = 7.2 Hz, 6H), 1.57(m,4H), 3.5 (t, *J* = 7.1 Hz, 4H), 6.31 (s, 1H), 6.6 (d, *J* = 2.6 Hz, 1H), 6.99 (dd, *J* = 8.9, 2.7 Hz, 1H),7.14-7.16 (m, 2H) 7.71-7.77 (m, 2H), 7.8 (d, *J* = 9.0 Hz, 1H), 8.45 (dd, *J* = 7.9, 1.4 Hz, 1H), 8.72-8.76 (m, 2H), 8.9 (dd, *J* = 7.9, 1.3 Hz, 1H); ^{13}C NMR (101 MHz,

CDCl₃) δ ppm 11.3, 20.5, 53.1, 96.4, 97.2, 109.6, 116.8, 123.9, 125.1, 125.3, 129.9, 130.6, 130.7, 131.7, 132.4, 140.7, 146.6, 149.7, 150.9, 151.7, 152.2, 157.4; MS (EI^+): *m/z*: 422 $[M\cdot+1]^+$; HRMS (EI^+) 422.2106 $[M\cdot]^+$, found 422.2128.

_N,N_-Dibutyl-5-(pyridin-4-ylimino)-5H-benzo[a]phenoxazin-9-amine (19)

Yield 25 %, mp 188-189 °C; IR ν (neat, cm^{-1}): 2950, 2872, 1626, 1581, 1514, 1457, 1365, 1324, 1285, 1218, 772; UV-vis (*CHCl₃*): λ (nm) (log ε/L $mol^{-1}cm^{-1}$): 545 (4.06), 222 (3.92); ^1H NMR (400 MHz, *CDCl₃*) δ ppm 0.97 (t, *J* = 7.3 Hz, 6H), 1.37 (m, 4H), 1.6 (m, 4H), 3.3 (t, *J* = 7.2 Hz, 4H), 6.13 (s, 1H), 6.27 (d, *J* = 2.7 Hz, 1H), 6.55 (dd, *J* = 9, 2.7 Hz, 1H),7.39-7.34 (m, 2H) 7.62-7.7 (m, 2H), 7.84-7.89 (m, 2H), 8.2 (d, *J* = 9.0 Hz, 1H), 8.5 (dd, *J* = 7.9, 1.4 Hz, 1H), 8.6 (dd, *J* = 7.9, 1.3 Hz, 1H); ^{13}C NMR (101 MHz, *CDCl₃*) δ ppm 13.9, 20.2, 29.4, 50.9, 51.1, 96.3, 97.3, 109.4, 116.6, 123.8, 123.9, 124.0, 125.0, 125.3, 127.3, 128.3, 129.9, 130.1, 130.5, 130.6, 131.0,146.6, 149.5, 150.7, 157.2; MS (EI^+): *m/z*: 451 $[M\cdot+1]^+$; HRMS (EI^+) 450.2406 $[M\cdot]^+$, found 450.2409

9-Morpholino-5-(pyridin-4-ylimino)-5H-benzo[a]phenoxazine (20)

Yield 14.5 %, mp >300 °C; IR ν (neat, cm^{-1}): 2968, 2835, 1635, 1595, 1578, 1510, 1488, 1239, 1121, 1110, 1043, 1003, 827, 755; UV-vis (*CHCl₃*): λ (nm) (log ε/L $mol^{-1}cm^{-1}$): 502 (4.49); ^1H NMR (400 MHz, *CDCl₃*) δ ppm 8.69-8.62 (m, 1H), 8.54 (dd, *J* = 4.8, 1.5 Hz, 2H), 8.51 (d, *J* = 2.2 Hz, 1H), 7.77-7.63 (m, 2H), 7.58 (d, *J* = 8.9, 1H), 6.85 (dd, *J* = 4.8, 1.5 Hz, 2H), 6.78 (dd, *J* = 8.9, 2.6 Hz, 1H), 6.52 (d, *J* = 2.6, 1H), 6.15 (s, 1H), 3.86 (t, *J* = 4.8 Hz, 4H), 3.29 (t, *J* = 4.8 Hz, 4H); ^{13}C NMR (101 MHz, *CDCl₃*) δ ppm 159.1, 156.5, 152.8, 150.2, 148.7, 145.8, 144.0, 132.4, 131.2, 130.5, 130.4, 130.1, 126.6, 125.2, 124.1, 115.9, 111.2, 99.7, 98.4, 66.4, 47.6; MS (ESI^+): *m/z*: 409.2 $[M+H]^+$; Anal. Calcd. For $C_{25}H_{20}N_4O_2\cdot0.5H_2O$: C, 71.93; H, 5.07; N, 13.42; Found: C, 72.15; H, 5.08; N, 12.23.

N,N-Diethyl-11-methyl-5-(pyridin-4-ylamino)-5H-benzo[a]phenoxazin-9-amine (21)

Yield 26.6 %, hydrochloride; mp >300 ^{o}C; IR ν (neat, cm^{-1}): 2977, 1639, 1579, 1513, 1443, 1324, 1249, 1199, 1072, 946, 823, 780; UV-vis (*MeOH*): λ (nm) (log ε/L mol^{-1}cm^{-1}): 594 (4.22); ^{1}H NMR (400 MHz, *CD_3OD*) δ ppm 9.16 (d, *J* = 8.4 Hz, 1H), 8.43 (d, *J* = 7.4 Hz, 2H), 8.31 (d, *J* = 8.4 Hz, 1H), 8.06-7.96 (m, 2H), 7.86-7.90 (m, 1H), 7.79 (s, 1H), 7.56 (d, *J* = 7.4 Hz, 2H), 7.25 (d, *J* = 2.5 Hz, 1H), 4.0 (q, *J* = 7.0 Hz, 4H), 2.89 (s, 3H), 1.46 (t, *J* = 7.0 Hz, 6H); ^{13}C NMR (101 MHz, *CD_3OD*) δ ppm 160.2, 158.7, 152.0, 147.3, 146.5, 144.6, 144.4, 142.5, 132.9, 131.9, 131.5, 130.0, 127.9, 124.8, 124.7, 123.4, 112.9, 110.5, 97.6, 39.5, 17.5, 14.1; MS (ESI^{+}): *m/z*: 394 [M^{+}]; Anal. Calcd. For $C_{26}H_{24}N_4O{\cdot}2HCl{\cdot}3H_2O$: C, 58.32; H, 6.06; N, 10.46; Found: C, 58.51; H, 5.57; N, 10.52.

***N*-Ethyl-*N*-(2-methansulfonamidylethyl)-11-methyl-5-(pyridine-4-ylimino)-5H-benzo[a]phenoxazin-9-amine (22)**

Yield 38 %, mp 235-236 ^{o}C; IR ν (neat, cm^{-1}): 3633, 3023, 2972, 1639, 1605, 1581, 1556, 1491, 1412, 1370, 1313, 1219, 1136; ^{1}H NMR (400 MHz, *$CDCl_3$*) δ ppm 1.21 (t, *J* = 7.01 Hz, 3H), 2.6 (s, 3H), 2.97 (s, 3H), 3.35 (q, *J* = 6.62 Hz, 2H), 3.47 (q, *J* = 7.0 Hz, 2H), 3.58 (t, *J* = 6.62 Hz, 2H), 6.13 (s, 1H), 6.24 (d, *J* = 2.41 Hz, 1H), 6.51 (s, 1H), 6.86 (d, *J* = 5.58 Hz, 1H), 7.65-7.69 (m, 2H), 8.51-8.54 (m, 3H), 8.68 (dd *J* = 7.46, Hz, 1H); MS (EI^{+}): *m/z*: 502.3 [M·+1]$^{+}$

***3*-Bromo-*N,N*-diethyl-5-(pyridin-2-ylimino)-5H-benzo[a]phenoxazin-9-amine (23)**

Yield 73 %, mp 204-205 ^{o}C; IR ν (neat, cm^{-1}): 2980, 1640, 1590, 1580, 1490, 1455, 1320, 1250, 1115; UV-vis (*$CHCl_3$*): λ (nm) (log ε/L mol^{-1}cm^{-1}): 544 (4.62); ^{1}H NMR (400 MHz, *$CDCl_3$*) δ ppm 1.21 (t, *J* = 7.1 Hz, 6H), 3.40 (q, *J* = 7.1 Hz, 4H), 6.26 (d, *J* = 2.6 Hz, 1H), 6.47 (s, 1H), 6.55 (dd, *J* = 9.0, 2.7 Hz, 1H), 7.04 (t, *J* = 6.3 Hz, 2H), 7.46 (d, *J* = 9.0 Hz, 1H), 7.70-7.74 (m, 2H), 8.44 (d, *J* = 8.6 Hz, 1H), 8.50-8.51 (m, 1H), 8.78 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR (101 MHz, *$CDCl_3$*) δ ppm 12.6, 45.0, 96.3,

99.1, 108.9, 117.2, 118.9, 124.7, 124.8, 125.5, 128.2, 130.4, 133.1, 134.1, 137.7, 140.8, 146.7, 148.9, 149.0, 150.2, 156.7, 163.2; MS (CI^+): *m/z*: 473 $[MH]^+$; HRMS (CI^+) 473.0976 $[MH]^+$, found 473.0981; Anal. Calcd. For $C_{25}H_{21}BrN_4O{\cdot}3H_2O$: C, 56.93; H, 5.16; N, 10.62; Found: C, 57.41; H, 4.35; N, 10.01.

3-Bromo-*N,N*-diethyl-5-(pyridin-4-ylimino)-5H-benzo[a]phenoxazin-9-amine (24)

Yield 28 %, mp 269-271 ^oC; IR ν (neat, cm^{-1}): 2980, 1635, 1590, 1575, 1490, 1410, 1355, 1250, 1115; UV-vis (*$CHCl_3$*): λ (nm) (log ε/L $mol^{-1}cm^{-1}$): 720 (4.44), 547 (4.43); ^1H NMR (400 MHz, *$CDCl_3$*) δ ppm 1.22 (t, *J* = 7.1 Hz, 6H), 3.41 (q, *J* = 7.1 Hz, 4H), 6.08 (s, 1H), 6.27 (d, *J* = 2.6 Hz, 1H), 6.56 (dd, *J* = 9.0, 2.7 Hz, 1H), 6.84-6.86 (m, 2H), 7.47 (d, *J* = 9.0 Hz, 1H), 7.73 (dd, *J* = 8.6, 2.1 Hz, 1H), 8.44 (d, *J* = 8.6 Hz, 1H), 8.53-8.55 (m, 2H), 8.63 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR (101 MHz, *$CDCl_3$*) δ ppm 12.6, 45.0, 96.2, 97.5, 109.1, 116.0, 124.81, 124.85, 125.6, 128.0, 130.3, 130.6, 133.3, 133.5, 140.4, 146.6, 149.1, 150.2, 150.3, 155.7, 159.2; MS (CI^+): *m/z*: 473 $[MH]^+$; HRMS (CI^+) 473.0976 $[MH]^+$, found 473.1017; Anal. Calcd. For $C_{25}H_{21}BrN_4O{\cdot}4H_2O$: C, 73.86; H, 5.77; N, 11.88; Found: C, 73.16; H, 5.29; N, 11.67.

***N,N*-Diethyl-5-(1-methylpyridin-4-ylimino)-5H-benzo[a]phenoxazin-9-ammonium Iodide (25)**

Yield 72%, mp >300 ºC. ^1H NMR (400 MHz, CD_3OD) δ ppm 1.25 (t, *J* = 7.10 Hz, 6H), 3.54 (q, *J* = 7.10 Hz, 4H), 4.24 (s, 3H), 6.35 (s, 1H), 6.56 (d, *J* = 2.73 Hz, 1H), 6.89 (dd, *J* = 9.21, 2.73 Hz, 1H), 7.43-7.41 (m, 2H), 7.73-7.63 (m, 2H), 7.82-7.76 (m, 1H), 8.47 (dd, *J* = 8.04, 0.87 Hz, 1H), 8.55 (d, *J* = 7.06 Hz, 2H), 8.71 (dd, *J* = 8.04 , 0.87 Hz, 1H). MS (ESI^+) m/z: 409.2 (M^+). Anal. Cacld. for $C_{26}H_{25}IN_4O{\cdot}H_2O$: C, 56.32; H, 4.91; N, 10.11. Found C, 55.80; H, 4.66; N, 9.85.

5-(1-Benzylpyridin-4-ylimino)-*N,N*-diethyl-5H-benzo[a]phenoxazin-9-ammonium Chloride (26)

Yield 82%, mp >300 ℃. ^{1}H NMR (400 MHz, *CD_3OD*) δ ppm 1.25 (t, *J* = 7.09 Hz, 6H), 3.55 (q, *J* = 7.09 Hz, 4H), 5.64 (s, 2H), 6.37 (s, 1H), 6.57 (d, *J* = 2.56 Hz, 1H), 6.91 (dd, *J* = 9.10, 2.20 Hz, 1H), 7.44 (d, *J* = 7.19 Hz, 2H), 7.54-7.46 (m, 5H), 7.72-7.62 (m, 2H), 7.81-7.75 (m, 1H), 8.45 (dd, *J* = 8.03, 0.85 Hz, 1H), 8.66 (d, *J* = 7.19 Hz, 2H), 8.70 (d, *J* = 7.53 Hz, 1H). MS (ESI^+) m/z: 485.2 (M^+). Anal. Cacld. for $C_{32}H_{29}ClN_4O \cdot H_2O$: C, 71.30; H, 5.80; N, 10.39. Found C, 71.04; H, 5.78; N, 10.39.

Biological Experiments

All animal studies including *in vivo* and PK studies were approved by the institutional animal experimentation ethics committees.