Supporting Information

Structure and Property Based Design of Aminooxazoline Xanthenes as Selective and Orally Efficacious, CNS Penetrable BACE Inhibitors for the Treatment of Alzheimer's Disease

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Experimental Section

Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. Anhydrous solvents were obtained from Aldrich and used directly. All reactions involving air- or moisture–sensitive reagents were performed under a nitrogen or argon atmosphere. All

final compounds were purified to ≥95% purity as determined by high-performance liquid chromatography (HPLC). Purity was measured using Agilent 1100 Series high performance liquid chromatography (HPLC) systems with UV detection at 254 nm (System A: Agilent Zorbax Eclipse XDB-C8 4.6 x 150 mm, 5 micron, 5 to 100% CH_3CN in H_2O with 0.1% TFA for 15 min at 1.5 mL/min; System B: Zorbax SB-C8, 4.6 x 75 mm, 10 to 90% CH_3CN in H_2O with 0.1% formic acid for 12 min at 1.0 mL/min). Silica gel columns were performed using prepacked silica gel cartridges (Biotage). ^1H NMR spectra were recorded on a Bruker AV-400 (400 MHz) spectrometer or on a Bruker AV-500 (500 MHz) spectrometer at ambient temperature. NMR spectra were processed using ACD SpecManager (version 12; ACD, Toronto, Canada). All observed protons are reported as parts per million (ppm) downfield from tetramethylsilane (TMS) or other internal reference in the appropriate solvent indicated. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants, and number of protons. Melting points were determined on a Ta Instruments Q200 DSC (New Castle, DE, U.S.). Low-resolution mass spectral (MS) data were determined on an Agilent 1100 Series LCMS with UV detection at 254 nm and a low resonance electrospray mode (ESI). Exact mass confirmation was performed on an Agilent 1200 series high performance liquid chromatography (HPLC) system (Santa Clara, CA, U.S.) by flow injection analysis, eluting with a binary solvent system A and B (A, water with 0.1% FA; B, ACN with 0.1% FA) under gradient conditions (5-95% B over 3 min) at 0.3 mL/min with MS detection by an Agilent 6510-Q-TOF mass spectrometer (Santa Clara, CA, U.S.).

4-(5'-chloro-2'-fluorobiphenyl-3-yl)-4-(4-methoxyphenyl)-4,5-dihydrooxazol-2-amine (1) ^1H NMR (400 MHz, DMSO-d_6) δ 7.60 (d, *J* = 1.37 Hz, 1H), 7.53 (dd, *J* = 2.71, 6.75 Hz, 1H), 7.42 - 7.50 (m, 2H), 7.32 - 7.41 (m, 5H), 6.79 - 6.88 (m, 2H), 6.20 (s, 2H), 4.63 - 4.74 (m, 2H), 3.71 (br. s., 3H). MS *m/z* = 396.8.

4-(3'-chlorobiphenyl-3-yl)-4-(4-methoxyphenyl)-4,5-dihydrooxazol-2-amine (2) ^1H NMR (400 MHz, DMSO-d_6) δ 7.70 (t, *J* = 1.75 Hz, 1H), 7.65 (t, *J* = 1.91 Hz, 1H), 7.54 - 7.59 (m, 1H), 7.46 - 7.52

(m, 2H), 7.40 - 7.46 (m, 2H), 7.33 - 7.40 (m, 3H), 6.80 - 6.87 (m, 2H), 6.20 (s, 2H), 4.65 - 4.75 (m, 2H), 3.69 (s, 3H). MS *m/z* = 378.8.

4-(4-methoxyphenyl)-4-(3-(pyridin-3-yl)phenyl)-4,5-dihydrooxazol-2-amine (3) ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.83 (d, *J* = 1.68 Hz, 1H), 8.57 (dd, *J* = 1.53, 4.73 Hz, 1H), 8.00 (td, *J* = 1.94, 7.95 Hz, 1H), 7.72 (s, 1H), 7.52 (td, *J* = 1.36, 7.50 Hz, 1H), 7.44 - 7.50 (m, 2H), 7.34 - 7.44 (m, 3H), 6.79 - 6.89 (m, 2H), 6.23 (br. s., 2H), 4.64 - 4.79 (m, 2H), 3.70 (s, 3H). MS *m/z* = 346.0 $[M+H]^+$.

4-(4-methoxyphenyl)-4-(3-(pyrimidin-5-yl)phenyl)-4,5-dihydrooxazol-2-amine (4) ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.19 (s, 1H), 9.09 (s, 2H), 7.80 (t, *J* = 1.68 Hz, 1H), 7.61 (d, *J* = 7.55 Hz, 1H), 7.53 (td, *J* = 1.32, 7.90 Hz, 1H), 7.42 - 7.48 (m, 1H), 7.34 - 7.40 (m, 2H), 6.79 - 6.89 (m, 2H), 4.81 (d, *J* = 8.39 Hz, 1H), 4.70 (d, *J* = 8.32 Hz, 1H), 3.71 (s, 3H). MS *m/z* = 347.4 $[M+H]^+$.

4-(3-(6-fluoropyridin-3-yl)phenyl)-4-(4-methoxyphenyl)-4,5-dihydrooxazol-2-amine (5) ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.48 (d, *J* = 2.59 Hz, 1H), 8.21 (dt, *J* = 2.63, 8.18 Hz, 1H), 7.71 (t, *J* = 1.75 Hz, 1H), 7.51 (td, *J* = 1.39, 7.59 Hz, 1H), 7.47 (td, *J* = 1.30, 7.86 Hz, 1H), 7.34 - 7.43 (m, 3H), 7.28 (dd, *J* = 2.78, 8.51 Hz, 1H), 6.79 - 6.88 (m, 2H), 6.22 (br. s., 2H), 4.64 - 4.78 (m, 2H), 3.70 (s, 3H). MS *m/z* = 364.0 $[M+H]^+$.

4-(3-(2-fluoropyridin-3-yl)phenyl)-4-(4-methoxyphenyl)-4,5-dihydrooxazol-2-amine (6) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 - 8.13 (m, 1H), 7.76 (ddd, *J* = 1.96, 7.51, 9.71 Hz, 1H), 7.45 - 7.50 (m, 1H), 7.27 - 7.41 (m, 3H), 7.13 - 7.23 (m, 5H), 6.75 - 6.81 (m, 2H), 4.68 - 4.77 (m, 2H), 3.71 (s, 3H). MS *m/z* = 364.2 $[M+H]^+$.

2'-methoxy-7'-phenyl-5H-spiro[oxazole-4,9'-xanthen]-2-amine 2,2,2-trifluoroacetate (9a)

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.35 (br. s, 1H), 9.50 (br. s, 2H), 7.85 (d, *J* = 2.14 Hz, 1H), 7.79 (dd, *J* = 2.14, 8.55 Hz, 1H), 7.71 (d, *J* = 7.69 Hz, 2H), 7.50 (t, *J* = 7.69 Hz, 2H), 7.40 (s, 1H), 7.34 (d, *J* = 8.55 Hz, 1H), 7.27 (d, *J* = 9.08 Hz, 1H), 7.13 (dd, *J* = 2.94, 9.03 Hz, 1H), 7.08 (d, *J* = 2.89 Hz, 1H), 5.08 (d, *J* = 9.62 Hz, 2H), 3.82 (s, 3H). HRMS *m/z* = 359.1393 $[M+H]^+$. Calc'd for $C_{22}H_{19}N_2O_3$: 359.1395.

2'-methoxy-7'-o-tolyl-5H-spiro[oxazole-4,9'-xanthen]-2-amine 2,2,2-trifluoroacetate (9b)

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.33 (br. s, 1H), 9.50 (br. s, 2H), 7.50 (d, *J* = 1.92 Hz, 1H), 7.48 (dd, *J* = 1.98, 8.49 Hz, 1H), 7.23 - 7.36 (m, 6H), 7.13 (s, 2H), 5.05 (s, 2H), 3.82 (s, 3H), 2.26 (s, 3H). HRMS *m/z* = 373.1547 $[M+H]^+$. Calc'd for $C_{23}H_{21}N_2O_3$: 373.1552.

2'-methoxy-7'-m-tolyl-5H-spiro[oxazole-4,9'-xanthen]-2-amine 2,2,2-trifluoroacetate (9c)

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.28 (br. s, 1H), 9.53 (br. s, 2H), 7.82 (d, *J* = 2.03 Hz, 1H), 7.76 (dd, *J* = 2.14, 8.55 Hz, 1H), 7.52 (s, 1H), 7.49 (d, *J* = 7.80 Hz, 1H), 7.38 (t, *J* = 7.64 Hz, 1H), 7.33 (d, *J* = 8.55 Hz, 1H), 7.27 (d, *J* = 8.98 Hz, 1H), 7.21 (d, *J* = 7.37 Hz, 1H), 7.13 (dd, *J* = 2.83, 9.14 Hz, 1H), 7.08 (d, *J* = 2.78 Hz, 1H), 5.12 (d, *J* = 8.98 Hz, 1H), 5.07 (d, *J* = 9.30 Hz, 1H), 3.82 (s, 3H), 2.40 (s, 3H). HRMS *m/z* = 373.1558 $[M+H]^+$. Calc'd for $C_{23}H_{21}N_2O_3$: 373.1552.

2'-methoxy-7'-p-tolyl-5H-spiro[oxazole-4,9'-xanthen]-2-amine 2,2,2-trifluoroacetate (9d)

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.25 (br. s, 1H), 9.50 (br. s, 2H), 7.81 (d, *J* = 2.03 Hz, 1H), 7.75 (dd, *J* = 2.19, 8.60 Hz, 1H), 7.60 (d, *J* = 8.12 Hz, 2H), 7.31 (dd, *J* = 5.50, 8.28 Hz, 3H), 7.26 (d, *J* = 8.98 Hz, 1H), 7.11 - 7.16 (m, 1H), 7.08 (d, *J* = 2.88 Hz, 1H), 5.12 (d, *J* = 9.30 Hz, 1H), 5.07 (d, *J* = 10.04 Hz, 1H), 3.82 (s, 3H), 2.36 (s, 3H). HRMS *m/z* = 373.1549 $[M+H]^+$. Calc'd for $C_{23}H_{21}N_2O_3$: 373.1552.

2'-(2-chlorophenyl)-7'-methoxy-5H-spiro[oxazole-4,9'-xanthen]-2-amine 2,2,2-trifluoroacetate (9e)

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.31 (br. s, 1H), 9.47 (br. s, 2H), 7.66 (d, *J* = 1.92 Hz, 1H), 7.56 - 7.63 (m, 2H), 7.40 - 7.53 (m, 3H), 7.34 (d, *J* = 8.44 Hz, 1H), 7.27 (d, *J* = 8.98 Hz, 1H), 7.10 - 7.16 (m, 2H), 5.07 (br. s., 2H), 3.82 (s, 3H). HRMS *m/z* = 393.1012 $[M+H]^+$. Calc'd for $C_{22}H_{18}N_2O_3$: 393.1006.

2'-(3-chlorophenyl)-7'-methoxy-5H-spiro[oxazole-4,9'-xanthen]-2-amine 2,2,2-trifluoroacetate (9f)

mp 200.9 - 202.0 ºC. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.32 (br. s, 1H), 9.57 (br. s, 2H), 7.95 (d, *J* = 2.14 Hz, 1H), 7.78 - 7.87 (m, 2H), 7.69 (d, *J* = 8.01 Hz, 1H), 7.52 (t, *J* = 7.85 Hz, 1H), 7.45 (d, *J* = 7.48

Hz, 1H), 7.34 (d, *J* = 8.66 Hz, 1H), 7.27 (d, *J* = 8.98 Hz, 1H), 7.14 (dd, *J* = 2.94, 9.03 Hz, 1H), 7.02 (d, *J* = 2.88 Hz, 1H), 5.14 (d, *J* = 9.08 Hz, 1H), 5.07 (d, *J* = 9.83 Hz, 1H), 3.82 (s, 3H). HRMS *m/z* = 393.1014 $[M+H]^+$. Calc'd for $C_{22}H_{18}N_2O_3$: 393.1006.

2'-(4-chlorophenyl)-7'-methoxy-5H-spiro[oxazole-4,9'-xanthen]-2-amine 2,2,2-trifluoroacetate (9g)

mp 189.3 – 196.0 ºC. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.20 (br. s, 1H), 9.42 (br. s, 2H), 7.89 (d, *J* = 2.24 Hz, 1H), 7.79 (dd, *J* = 2.19, 8.60 Hz, 1H), 7.76 (d, *J* = 8.55 Hz, 2H), 7.55 (d, *J* = 8.55 Hz, 2H), 7.34 (d, *J* = 8.66 Hz, 1H), 7.27 (d, *J* = 8.98 Hz, 1H), 7.13 (dd, *J* = 2.94, 9.03 Hz, 1H), 7.04 (d, *J* = 2.88 Hz, 1H), 5.07 (d, *J* = 9.51 Hz, 2H), 3.82 (s, 3H). HRMS *m/z* = 393.0998 $[M+H]^+$. Calc'd for $C_{22}H_{18}N_2O_3$: 393.1006.

2'-methoxy-7'-(4-(trifluoromethoxy)phenyl)-5H-spiro[oxazole-4,9'-xanthen]-2-amine 2,2,2-trifluoroacetate (9h)

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.31 (br. s, 1H), 9.52 (br. s, 2H), 7.92 (d, *J* = 2.03 Hz, 1H), 7.85 (d, *J* = 8.76 Hz, 2H), 7.80 (dd, *J* = 2.14, 8.66 Hz, 1H), 7.49 (d, *J* = 8.12 Hz, 2H), 7.35 (d, *J* = 8.55 Hz, 1H), 7.27 (d, *J* = 8.98 Hz, 1H), 7.14 (dd, *J* = 2.94, 9.03 Hz, 1H), 7.04 (d, *J* = 2.88 Hz, 1H), 5.11 (q, *J* = 9.40 Hz, 2H), 3.82 (s, 3H). HRMS *m/z* = 443.1218 $[M+H]^+$. Calc'd for $C_{23}H_{18}N_2O_4$: 443.1218.

2'-methoxy-7'-(3-(trifluoromethoxy)phenyl)-5H-spiro[oxazole-4,9'-xanthen]-2-amine 2,2,2-trifluoroacetate (9i)

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.20 (br. s, 1H), 9.52 (br. s, 2H), 7.96 (d, *J* = 1.92 Hz, 1H), 7.85 (dd, *J* = 1.98, 8.49 Hz, 1H), 7.78 (d, *J* = 7.91 Hz, 1H), 7.74 (s, 1H), 7.64 (t, *J* = 7.96 Hz, 1H), 7.40 (d, *J* = 8.23 Hz, 1H), 7.36 (d, *J* = 8.55 Hz, 1H), 7.28 (d, *J* = 9.08 Hz, 1H), 7.14 (dd, *J* = 2.99, 9.08 Hz, 1H), 7.03 (d, *J* = 2.88 Hz, 1H), 5.12 (q, *J* = 9.50 Hz, 2H), 3.82 (s, 3H). HRMS *m/z* = 443.1221 $[M+H]^+$. Calc'd for $C_{23}H_{18}N_2O_4$: 443.1218.

2'-(3-chloro-2-fluorophenyl)-7'-methoxy-5H-spiro[oxazole-4,9'-xanthen]-2-amine 2,2,2-trifluoroacetate (9j)

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.23 (br. s, 1H), 9.51 (br. s, 2H), 7.81 (br. s, 1H), 7.69 (d, *J* = 9.62 Hz, 1H), 7.63 (t, *J* = 6.73 Hz, 1H), 7.57 (t, *J* = 6.79 Hz, 1H), 7.36 (s, 2H), 7.27 (d, *J* = 9.08 Hz, 1H), 7.07 - 7.16 (m, 2H), 5.08 (br. s, 2H), 3.82 (s, 3H). HRMS *m/z* = 411.0907 $[M+H]^+$. Calc'd for $C_{22}H_{17}ClFN_2O_3$: 411.0911.

2'-(4-chloro-2-fluorophenyl)-7'-methoxy-5H-spiro[oxazole-4,9'-xanthen]-2-amine 2,2,2-trifluoroacetate (9k)

mp 189.8 – 194.9 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.28 (br. s., 1H), 9.51 (br. s., 2H), 7.76 (s, 1H), 7.62 - 7.71 (m, 2H), 7.60 (dd, *J* = 2.05, 10.76 Hz, 1H), 7.44 (dd, *J* = 1.86, 8.31 Hz, 1H), 7.36 (d, *J* = 8.61 Hz, 1H), 7.24 - 7.31 (m, 1H), 7.09 - 7.17 (m, 2H), 5.08 (br. s, 2H), 3.82 (s, 3H). HRMS *m/z* = 411.0907 $[M+H]^+$. Calc'd for $C_{22}H_{17}ClFN_2O_3$: 411.0911.

2'-(5-chloro-2-fluorophenyl)-7'-methoxy-5H-spiro[oxazole-4,9'-xanthen]-2-amine 2,2,2-trifluoroacetate (9l)

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.18 (br. s, 1H), 9.46 (br. s, 2H), 7.82 (br. s, 1H), 7.67 - 7.74 (m, 2H), 7.48 - 7.54 (m, 1H), 7.41 (t, *J* = 9.51 Hz, 1H), 7.36 (d, *J* = 8.44 Hz, 1H), 7.27 (d, *J* = 9.08 Hz, 1H), 7.14 (dd, *J* = 2.83, 9.03 Hz, 1H), 7.08 (d, *J* = 2.78 Hz, 1H), 5.11 (d, *J* = 9.19 Hz, 1H), 5.07 (d, *J* = 8.66 Hz, 1H), 3.82 (s, 3H). HRMS *m/z* = 411.0908 $[M+H]^+$. Calc'd for $C_{22}H_{17}ClFN_2O_3$: 411.0911.

2'-(2-fluoro-3-methoxyphenyl)-7'-methoxy-5H-spiro[oxazole-4,9'-xanthen]-2-amine 2,2,2-trifluoroacetate (9m)

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.25 (br. s, 1H), 9.51 (br. s, 2H), 7.71 (s, 1H), 7.65 (d, *J* = 8.98 Hz, 1H), 7.35 (d, *J* = 8.55 Hz, 1H), 7.24 (s, 3H), 7.07 - 7.16 (m, 3H), 5.07 (q, *J* = 9.00 Hz, 2H), 3.89 (s, 3H), 3.82 (s, 3H). HRMS *m/z* = 407.1402 $[M+H]^+$. Calc'd for $C_{23}H_{20}N_2O_4$: 407.1407.

2'-(2-fluoro-5-methoxyphenyl)-7'-methoxy-5H-spiro[oxazole-4,9'-xanthen]-2-amine 2,2,2-trifluoroacetate (9n)

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.33 (br. s, 1H), 9.54 (br. s, 2H), 7.74 (s, 1H), 7.69 (d, *J* = 8.65 Hz, 1H), 7.35 (d, *J* = 8.55 Hz, 1H), 7.23 - 7.31 (m, 2H), 7.07 - 7.17 (m, 3H), 6.99 (td, *J* = 3.41, 8.79 Hz, 1H), 5.08 (q, *J* = 9.30 Hz, 2H), 3.82 (s, 3H), 3.81 (s, 3H). HRMS *m/z* = 407.1410 $[M+H]^+$. Calc'd for $C_{23}H_{20}N_2O_4$: 407.1407.

2'-(5-chloro-2-fluoro-4-methylphenyl)-7'-methoxy-5H-spiro[oxazole-4,9'-xanthen]-2-amine 2,2,2-trifluoroacetate (9o)

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.34 (br. s, 1H), 9.56 (br. s, 2H), 7.77 (d, *J* = 1.18 Hz, 1H), 7.64 - 7.72 (m, 2H), 7.41 (d, *J* = 11.43 Hz, 1H), 7.34 (d, *J* = 8.65 Hz, 1H), 7.27 (d, *J* = 8.98 Hz, 1H), 7.13 (dd, *J* = 2.78, 7.69 Hz, 1H), 7.10 (d, *J* = 2.78 Hz, 1H), 5.08 (qd, *J* = 1.00, 8.33 Hz, 2H), 3.82 (s, 3H), 2.38 (s, 3H). HRMS *m/z* = 425.1066 $[M+H]^+$. Calc'd for $C_{23}H_{19}ClFN_2O_3$: 425.1068.

2'-(2-fluoropyridin-3-yl)-7'-methoxy-5H-spiro[oxazole-4,9'-xanthen]-2-amine 2,2,2-trifluoroacetate (9p)

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.27 (s, 1H), 9.49 (s, 2H), 8.27 (d, *J* = 4.59 Hz, 1H), 8.19 (s, 1H), 7.87 (s, 1H), 7.74 (d, *J* = 8.76 Hz, 1H), 7.49 - 7.54 (m, 1H), 7.38 (d, *J* = 8.55 Hz, 1H), 7.28 (d, *J* = 8.98 Hz, 1H), 7.14 (dd, *J* = 2.78, 9.08 Hz, 1H), 7.10 (d, *J* = 2.88 Hz, 1H), 5.08 (br. s., 2H), 3.82 (s, 3H). HRMS *m/z* = 378.1250 $[M+H]^+$. Calc'd for $C_{21}H_{17}FN_3O_3$: 378.1254.

2'-(4-fluoropyridin-3-yl)-7'-methoxy-5H-spiro[oxazole-4,9'-xanthen]-2-amine 2,2,2-trifluoroacetate (9q)

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.22 (br. s, 1H), 9.47 (br. s, 2H), 8.63 (d, *J* = 2.46 Hz, 1H), 8.36 (d, *J* = 2.56 Hz, 1H), 8.02 (d, *J* = 2.14 Hz, 1H), 7.84 (dd, *J* = 2.24, 8.65 Hz, 1H), 7.37 (d, *J* = 8.66 Hz, 1H), 7.32 (dd, *J* = 2.88, 8.55 Hz, 1H), 7.27 (d, *J* = 8.98 Hz, 1H), 7.14 (dd, *J* = 2.94, 9.03 Hz, 1H), 7.00 (d, *J* =

2.88 Hz, 1H), 5.11 (d, *J* = 9.19 Hz, 2H), 3.82 (s, 3H). HRMS *m/z* = 378.1249 $[M+H]^+$. Calc'd for $C_{21}H_{17}FN_3O_3$: 378.1254.

2'-(2-chloropyridin-4-yl)-7'-methoxy-5H-spiro[oxazole-4,9'-xanthen]-2-amine 2,2,2-trifluoroacetate (9r)

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.22 (br. s, 1H), 9.67 (br. s, 1H), 9.49 (br. s, 1H), 8.50 (d, *J* = 5.34 Hz, 1H), 8.20 (d, *J* = 2.14 Hz, 1H), 7.96 - 8.03 (m, 2H), 7.84 (dd, *J* = 1.50, 5.24 Hz, 1H), 7.39 (d, *J* = 8.66 Hz, 1H), 7.29 (d, *J* = 8.98 Hz, 1H), 7.15 (dd, *J* = 2.89, 9.08 Hz, 1H), 6.97 (d, *J* = 2.88 Hz, 1H), 5.14 (d, *J* = 9.40 Hz, 2H), 3.82 (s, 3H). HRMS *m/z* = 394.0952 $[M+H]^+$. Calc'd for $C_{21}H_{17}ClN_3O_3$: 394.0958.

2'-methoxy-7'-(pyridin-4-yl)-5H-spiro[oxazole-4,9'-xanthen]-2-amine 2,2,2-trifluoroacetate (9s)

^{1}H NMR (500 MHz, DMSO-d_6) δ 9.61 (br. s, 2H), 8.79 (br. d, *J* = 4.80 Hz, 2H), 8.21 (s, 1H), 7.95 - 8.11 (m, 3H), 7.43 (d, *J* = 8.76 Hz, 1H), 7.29 (d, *J* = 9.08 Hz, 1H), 7.16 (dd, *J* = 2.94, 9.03 Hz, 1H), 7.01 (d, *J* = 2.89 Hz, 1H), 5.09 - 5.19 (m, 2H), 5.12 (d, *J* = 9.62 Hz, 2H), 3.82 (s, 3H). HRMS *m/z* = 360.1346 $[M+H]^+$. Calc'd for $C_{21}H_{18}N_3O_3$: 360.1348.

2'-methoxy-7'-(pyrimidin-5-yl)-5H-spiro[oxazole-4,9'-xanthen]-2-amine 2,2,2-trifluoroacetate (9t)

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.25 (br. s, 1H), 9.61 (br. s, 1H), 9.43 (br. s, 1H), 9.24 (s, 2H), 9.21 (s, 1H), 8.20 (d, *J* = 2.14 Hz, 1H), 7.95 (dd, *J* = 2.19, 8.60 Hz, 1H), 7.41 (d, *J* = 8.65 Hz, 1H), 7.29 (d, *J* = 8.98 Hz, 1H), 7.15 (dd, *J* = 2.94, 9.03 Hz, 1H), 6.98 (d, *J* = 2.88 Hz, 1H), 5.14 (s, 2H), 3.82 (s, 3H). HRMS *m/z* = 361.1293 $[M+H]^+$. Calc'd for $C_{20}H_{17}N_4O_3$: 361.1300.

2'-(2-methylpropoxy)-7'-(5-pyrimidinyl)spiro[1,3-oxazole-4,9'-xanthen]-2-amine (11a)

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.18 (s, 1H), 9.08 (s, 2H), 7.75 (dd, *J* = 2.35, 10.86 Hz, 1H), 7.66 (d, *J* = 2.25 Hz, 1H), 7.28 (d, *J* = 8.51 Hz, 1H), 7.12 (d, *J* = 8.90 Hz, 1H), 6.93 (dd, *J* = 3.03, 4.69 Hz, 1H), 6.83 (d, *J* = 2.93 Hz, 1H), 6.45 (s, 2H), 4.25 (d, *J* = 8.22 Hz, 1H), 4.20 (d, *J* = 8.31 Hz, 1H), 3.63 - 3.81

(m, 2H), 1.96 - 2.08 (m, 1H), 0.99 (d, J = 6.65 Hz, 6H). HRMS m/z = 403.1775 $[M+H]^+$. Calc'd for $C_{23}H_{23}N_4O_3$: 403.1770.

X-Ray Crystal Structure Information

Table S1. Data collection and refinement statistics

	BACE + **6**	BACE + **9l**	BACE + **11a**
Data Collection			
Space group	$P6_122$	$P6_122$	$P6_122$
Cell dimensions			
a, b, c (Å)	101.5, 101.5, 170.7	101.5, 101.5, 168.5	102.3, 102.3, 171.4
α, β, γ (°)	90, 90, 120	90, 90, 120	90, 90, 120
Resolution (Å)	30–2.30 (2.35–2.30)	30-1.95 (2.02-1.95)	30-2.10 (2.18-2.10)
Total reflections	235003	300367	170098
Unique reflections	23047	36345	29870
Completeness (%)†	96.7 (94.3)	95.3 (71.7)	94.3 (93.7)
R_{merge}†	0.143 (0.916)	0.090 (0.802)	0.086 (0.546)
I/σ(I)†	18.9 (2.2)	21.5 (2.0)	18.4 (2.2)
Refinement			
Reflections used	21369	34510	28104
R_{work}/R_{free}	0.197/0.246	0.186/0.219	0.184/0.223
Average B-value ($Å^2$)	38.7	29.3	36.4

Number of atoms			
Protein	2931	2938	2906
Ligand	27	29	30
Solvent	220	342	306
R.m.s. deviations			
Bond lengths (Å)	0.008	0.008	0.008
Bond angles (°)	1.23	1.29	1.24
PDB ID code	4FRI	4FRJ	4FRK

[†]Values in parentheses are for the highest resolution shell.