An Efficient Assembly of Heterobenzazepine Ring Systems Utilizing an Intramolecular Palladium Catalyzed Cycloamination

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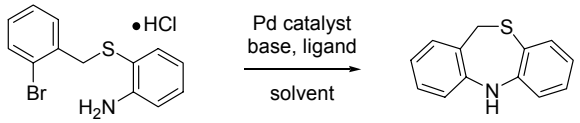
Supporting Information

A. Expanded version of Table I.

B. Experimental procedures and characterization for the preparation of all examples and their precursors listed in Table 2 (**7a-m** and **4a-m**).

C. Copy of the ^{1}H NMR spectra for compound **4F**.

Table 1: Expanded Table of Optimization of the Intramolecular Palladium-Catalyzed Amination



7a **4a**

Ex	Solvent	Base	Catalyst[b]	Ligand	Temp °C	Time[c]	% Yield[d]
1[a]	toluene	NaO-*t*-Bu	$Pd(PPh_3)_4$	None	95	48 h	22
2	dioxane	NaO-*t*-Bu	$Pd(PPh_3)_4$	None	105	48 h	32
3	THF	NaO-*t*-Bu	$Pd(PPh_3)_4$	None	75	48 h	7
4	toluene	NaO-*t*-Bu	$Pd(dba)_2$	P(*t*-Bu)$_3$	95	2.5 h	60
5	THF	NaO-*t*-Bu	$Pd(dba)_2$	P(*t*-Bu)$_3$	75	4.5 h	53
6	*o*-xylene	NaO-*t*-Bu	$Pd(dba)_2$	P(*t*-Bu)$_3$	110	1 h	53
7	dioxane	NaO-*t*-Bu	$Pd(dba)_2$	P(*t*-Bu)$_3$	105	2 h	59
8	DMF	NaO-*t*-Bu	$Pd(dba)_2$	P(*t*-Bu)$_3$	160	0.5 h	10
9	DMSO	NaO-*t*-Bu	$Pd_2(dba)_3$	P(*t*-Bu)$_3$	95	24 h	trace
10	MeOH	NaO-*t*-Bu	$Pd_2(dba)_3$	P(*t*-Bu)$_3$	95	24 h	13
11	toluene	NaO-*t*-Bu	$Pd_2(dba)_3$ (1%)	P(*t*-Bu)$_3$ (0.5%)	95	48 h	0
12	toluene	NaO-*t*-Bu	$Pd_2(dba)_3$ (3%)	P(*t*-Bu)$_3$ (1.5%)	95	48 h	0
13	toluene	NaO-*t*-Bu	$Pd_2(dba)_3$ (5%)	P(*t*-Bu)$_3$ (2.5%)	95	48 h	<5
14	toluene	K_2CO_3	$Pd(dba)_2$	P(*t*-Bu)$_3$	95	>48 h	0
15	toluene	Cs_2CO_3	$Pd(dba)_2$	P(*t*-Bu)$_3$	95	>48 h	0
16	toluene	Et_3N	$Pd(dba)_2$	P(*t*-Bu)$_3$	95	>48 h	0
17	toluene	NaO-*t*-Bu / K_2CO_3	$Pd(dba)_2$	P(*t*-Bu)$_3$	95	1 h	67
18	toluene	NaO-*t*-Bu / K_2CO_3	$Pd_2(dba)_3$	P(*t*-Bu)$_3$	95	2.5 h	65
19	THF	NaO-*t*-Bu / K_2CO_3	$Pd(dba)_2$	P(*t*-Bu)$_3$	75	12 h	55
20	dioxane	NaO-*t*-Bu / K_2CO_3	$Pd(dba)_2$	P(*t*-Bu)$_3$	105	1 h	62
21	toluene	NaO-*t*-Bu	$Pd(dba)_2$	P(*o*-tolyl)$_3$	95	>48 h	0
22	toluene	NaO-*t*-Bu	$Pd(dba)_2$	P(2-furyl)$_3$	95	>48 h	0
23	toluene	NaO-*t*-Bu	$Pd(dba)_2$	(+/-)-BINAP	95	4 h	59
24	toluene	NaO-*t*-Bu	$Pd(dba)_2$	dppf	95	4 h	49
25	toluene	NaO-*t*-Bu	$Pd_2(dba)_3$	DTBPBP	95	>48 h	trace
26	toluene	NaO-*t*-Bu	$Pd(OAc)_2$	P(*t*-Bu)$_3$	95	>48 h	16

[a] Conditions as described by Buchwald.[1] [b]Unless otherwise noted, 10 mol% catalyst and ligand were used in each case. When Pd_2dba_3 was used, 5 mol% phosphine was used. [c]Reactions were run to completion as indicated by consumption of starting material by HPLC. [d]All yields are for chromatographed reactions. DTBPBP = 2-(di-*t*-butylphosphino)biphenyl.

[1] Wolfe, J.P.; Rennels, R.A.; Buchwald, S.L. *Tetrahedron*, **1996**, *52*, 7525-46

NMR spectra were recorded at 400 and 100 MHz for the ^{1}H NMR and ^{13}C NMR, respectively unless otherwise noted. NMR chemical shifts are expressed in ppm relative to the internal solvent peak or TMS. Coupling constants were calculated in hertz. Most reactions were carried out under an atmosphere of nitrogen unless otherwise noted, using Aldrich SureSeal™ Solvents. The P(*t*-Bu)$_3$ was used as a 10% wt/wt solution in hexanes. All palladium catalyzed aminations were carried out under an atmosphere of argon. All melting points are uncorrected.

The requisite benzyl bromides were obtained through commercial sources, or prepared according to the literature, 2-bromo-1-(bromomethyl)-3-methylbenzene,[2] 1-bromo-2-(bromomethyl)-4-methoxybenzene,[3] and 4-bromo-3-(bromomethyl)benzonitrile.[4]

General Procedure A: Synthesis of thioether linked acyclic precursors.

Preparation of 2-[(2-bromobenzyl)thio]aniline hydrochloride (7a). To 2-nitrophenyl disulfide (6.0 g, 19.5 mmol, 1.0 eq.) was added a solution of sodium sulfide nonahydrate (15.0 g, 62 mmol, 3.2 eq.) in H_2O (200 mL). The resulting yellow suspension was heated to reflux for 60 minutes, and then cooled in an ice bath. A solution of 2-bromobenzyl bromide (10.2 g, 41 mmol, 2.1 eq.) in THF (150 mL) was slowly added, and the resulting biphasic mixture heated to reflux for 60 minutes. The mixture was cooled, diluted with EtOAc (100 mL), and the phases separated. The basic aqueous phase was extracted with EtOAc (3 x 100 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated to give an oil that was taken-up in MeOH and Et_2O. The hydrochloride was prepared by treatment with 2.0 N HCl in Et_2O followed by crystallization from MeOH and Et_2O to give a white solid (6.6 g, 51%): mp 189-193 °C; IR (diffuse reflectance) 2939, 2852 (s,b), 2813, 2736 (b), 2711 (b), 2684, 2529 (s,b), 2519 (s), 2338 (w), 2256 (w), 2228 (w), 1964 (w), 1939 (w), 1473, 757 (s), cm $^{-1}$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.61 (dd, J = 1, 8 Hz, 1 H), 7.26 - 7.09 (m, 5 H), 6.99 (d, J = 8 Hz, 1 H), 6.64 (m, 1 H), 4.07 (s, 2 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 137.6, 137.2, 134.3, 134.2, 132.6, 131.2, 130.7, 130.5, 130.3, 128.9, 125.7, 124.7, 41.4; MS (EI) m/z (rel. intensity) 293 (M+, 38), 295 (42), 214 (76), 171 (96), 169 (99), 124 (99), 90 (54), 86 (72), 84 (80), 80 (67), 51 (46). HRMS (EI) calcd for $C_{13}H_{12}BrNS$ 292.9874, found 292.9863; Anal. Calcd for $C_{13}H_{12}BrNS$•HCl: C, 47.22; H, 3.96; N, 4.24. Found: C, 47.03; H, 4.00; N, 4.17.

General Procedure B: Cycloamination of thioethers.

Preparation of 5,11-dihydrodibenzo[b,e][1,4]thiazepine (4a). An oven dried 40 mL vial containing two 6 mm glass beads was charged with a mixture of **7a** (250 mg, 0.76 mmol, 1.0 eq.), sodium tert-butoxide (163 mg, 1.7 mmol, 2.2 eq.), K_2CO_3 (235 mg, 1.7 mmol, 2.2 eq.), and bis(dibenzylideneacetone)palladium (49 mg, 8.5 μmol, 0.1 eq.). After the air atomosphere was replaced with argon, toluene (9 mL) was added, followed by a solution of P(*t*-Bu)$_3$ (10% wt/wt in hexanes) (198 mg, 9.8 μmol, 0.1 eq.). The resulting purple mixture was capped, and placed on a shaker block heated to 95 °C. After 1 h, HPLC indicated consumption of starting material. The reaction mixture was

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2. Miyano, S.; Fukushima, H.; Inagawa, H.; Hasimoto H. *Bull. Chem. Soc. Jpn*., **1986**, *59*, 3285-6.

3. Miller, W.H.; Alberts, D.P.; Bhatnagar, P.K.; Bondinell, W.E.; Callahan, J.F.; Calvo, R.R.; Cousins, R.D.; Erhard, K.F.; Heerding, D.A.; Keenan, R.M.; Kwon, C.; Manley, P.J.;. Newlander, K.A.; Ross, S.T.; Samanen, J.M.; Uzinskas, I.N.; Venslavsky, J.W.; Yuan, C. C-K.; Haltiwanger, R.C.; Gowen, M.; Hwang, S-M.; James, I.E.; Lark, M.W.; Rieman, D.J.; Stroup, G.B.; Azzarano, L.M.; Salyers, K.L.; Smith, B.R.; Ward, K.W.; Johanson, K.O.; Huffman. W.F. *J. Med. Chem*. **2000**, *43*, 22-6.

4. Zhang, H-Y.; Yu, J-Q.; Bruice, T. C. *Tetrahedron* **1994**, *50*, 11339-62.

concentrated to dryness, and absorbed to silica gel. Purification was carried out using silica gel chromatography (30% CH_2Cl_2 in heptane to 50% CH_2Cl_2 in heptane as the eluent) and afforded the product as a pale brown solid (108 mg, 67%): IR (diffuse reflectance) 3344 (s), 2454 (w), 2420 (w), 2350 (w), 2326 (w), 2280 (w), 1580 (s), 1531, 1481 (s), 1441, 1349 (s), 1156, 754 (s), 742 (s), 691, cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.68 (s, 1 H), 7.15 - 7.01 (m, 6 H), 6.69 - 6.65 (m, 2 H), 3.98 (s, 2 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 144.2, 142.8, 131.9, 128.8, 128.3, 127.6, 127.4, 122.5, 119.7, 119.0, 118.3, 118.2, 38.4; MS (EI) m/z (rel. intensity) 213 (M+, 91), 214 (39), 213 (91), 212 (62), 198 (19), 181 (54), 180 (99), 179 (49), 178 (22), 167 (20), 152 (32); HRMS (FAB) calcd for $C_{13}H_{11}NS$+H 214.0690, found 214.0689. Anal. Calcd for $C_{13}H_{11}NS$: C, 73.20; H, 5.20; N, 6.57; Found: C, 72.83; H, 5.35; N, 6.28.

Preparation of 2-[(2-bromo-3-methylbenzyl)thio]aniline hydrochloride (7b). Following general procedure A, 2-[(2-bromo-3-methylbenzyl)thio]aniline hydrochloride was prepared (4.65 g, 45%): mp 202-205 °C; IR (diffuse reflectance) 3003 (b), 2801 (s,b), 2725 (s), 2666, 2602, 2582, 2523, 2285 (w), 2240 (w), 2014 (w), 1987 (w), 1906 (w), 1513, 1473, 766 (s), cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.36 - 7.29 (m, 2 H), 7.29 - 7.21 (m, 2 H), 7.16 (at, J = 7 Hz, 1 H), 7.09 (dd, J = 2, 7 Hz, 1 H), 6.98 - 7.08 (m, 1 H), 4.24 (s, 2 H), 2.39 (s, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 138.7, 138.2, 136.6, 134.8, 130.0, 129.3, 128.8, 126.9, 126.5, 124.3, 120.7, 40.0, 23.4; MS (EI) m/z (rel. intensity) 307 (M+, 0), 228 (36), 185 (73), 183 (79), 124 (56), 86 (64), 84 (92), 80 (35), 78 (91), 63 (99), 51 (49); HRMS (FAB) calcd for $C_{14}H_{14}BrNS$+H 308.0109, found 308.0108; Anal. Calcd for $C_{14}H_{14}BrNS$•HCl: C, 48.78; H, 4.39; N, 4.06. Found: C, 49.11; H, 4.48; N, 4.09.

Preparation of 2-[(2-bromobenzyl)thio]-5-chloroaniline hydrochloride (7c).[5] Following general procedure A (starting from 1,4-dichloro-2-nitrobenzene[6]), 2-[(2-bromobenzyl)thio]-5-chloroaniline hydrochloride was prepared (48.5 g, 94%): mp 179-182 °C; IR (diffuse reflectance) 2938, 2802 (s,b), 2600, 2568, 2539 (s), 2351 (w), 2339 (w), 2282 (w), 2171 (w), 1965 (w), 1550, 1471, 1101, 886, 735 (s), cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.59 (dd, J = 1, 8 Hz, 1 H), 7.27 - 7.14 (m, 3 H), 7.00 (d, J = 9 Hz, 1 H), 6.90 (d, J = 3 Hz, 1 H), 6.56 (dd, J = 3, 9 Hz, 1 H), 4.04 (s, 2 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 148.8, 136.9, 136.7, 134.0, 132.6, 131.2, 129.2, 127.5, 123.8, 117.3, 115.3, 114.6, 38.2; MS (EI) m/z (rel. intensity) 327 (M+, 0), 329 (17), 171 (67), 169 (62), 160 (16), 158 (43), 90 (32), 89 (27), 86 (65), 84 (99), 51 (40); HRMS (FAB) calcd for $C_{13}H_{11}BrClNS$+H 327.9563, found 327.9561; Anal. Calcd for $C_{13}H_{11}BrClNS$•HCl: C, 42.76; H, 3.31; N, 3.84; Found: C, 42.74; H, 3.34; N, 3.87.

Preparation of 7-chloro-5,11-dihydrodibenzo[b,e][1,4]thiazepine (4c).[1] Following general procedure B, 7-chloro-5,11-dihydrodibenzo[b,e][1,4]thiazepine was prepared (22.4 g, 68%): IR (drift) 3345, 2361 (w), 2291 (w), 2249 (w), 2202 (w), 1916 (w), 1574, 1496, 1476 (s), 1385, 1339, 941, 852, 789, 741 (s), cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.16 (d, J = 8 Hz, 1 H), 7.14 (ddd, J = 1, 8, 8 Hz, 1 H), 7.01 (dd, J = 1, 7 Hz, 1 H), 8.84 - 6.78 (m, 3 H), 6.72 (dd, J = 2, 8 Hz, 1 H), 6.2 (s, 1 H), 3.99 (s, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.9, 142.0, 134.0, 133.6, 129.6, 129.4, 128.5, 122.7, 120.7, 120.2, 119.9, 119.5, 39.3; HRMS (FAB) calcd for $C_{13}H_{10}ClNS$+H 248.0301, found 248.0300; Anal. Calcd for $C_{13}H_{10}ClNS$: C, 63.03; H, 4.07; N, 5.65; Found: C, 62.97; H, 4.07; N, 5.67

Preparation of 2-[(2-bromobenzyl)thio]-5-(trifluoromethyl)aniline hydrochloride (7d).[1] Following general procedure A, 2-[(2-bromobenzyl)thio]-5-(trifluoromethyl)aniline hydrochloride was prepared (36.4 g, 70%): mp 168-170 °C; IR (diffuse reflectance) 2788 (s,b), 2581, 2540, 2424, 2292 (w), 2170 (w), 2135 (w), 1965 (w), 1327 (s), 1170 (s), 1144, 1132 (s), 1089, 898, 739 (s), cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.91 (br s, 2 H), 7.61 (1, J = 8 Hz, 1 H), 7.29 - 7.18 (m, 4 H), 7.11 (d, J = 2 Hz, 1 H), 6.82

[5] Yale, H.L.; Beer, B.; Pluscec, J.; Spitzmiller, E. R. *J. Med. Chem.* 13(4), **1970**, 713-722.

[6] Bogert, M. T.; Stull, A. *Org. Synth.*; Wiley & Sons: New York, **1941**; Collect. Vol. I., 220-221.

(dd, *J* = 2, 8 Hz, 1 H), 4.16 (s, 2 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 145.1, 136.6, 134.5, 133.1, 131.7, 129.6, 129.4 (q, *J* = 32 Hz), 128.1, 124.8, 124.4 (q, *J* = 272 Hz), 124.3, 115.9, 113.4, 38.2; MS (EI) m/z (rel. intensity) 361 (M+, 11), 282 (24), 193 (14), 192 (37), 173 (15), 171 (93), 169 (99), 148 (37), 90 (30), 89 (32), 63 (22); HRMS (FAB) calcd for $C_{14}H_{11}BrF_3NS$+H 361.9826, found 361.9819. Anal. Calcd for $C_{14}H_{11}BrF_3NS$•HCl: C, 42.18; H, 3.03; N, 3.51. Found: C, 42.13; H, 3.10; N, 3.54.

Preparation of 7-(trifluoromethyl)-5,11-dihydrodibenzo[b,e][1,4]thiazepine (4d).[1] Following general procedure B, 7-(trifluoromethyl)-5,11-dihydrodibenzo[b,e][1,4]thiazepine was prepared (198 mg, Yield 70%): IR (diffuse reflectance) 2350 (w), 2307 (w), 2265 (w), 2238 (w), 2160 (w), 1487 (s), 1401 (s), 1352 (s), 1323 (s), 1181 (s), 1140, 1123 (s), 1118 (s), 1094 (s), 950 (s), cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8 Hz, 1 H), 7.16 (ddd, *J* = 1, 8, 8 Hz, 1 H), 7.05 - 6.94 (m, 3 H), 6.86 (ddd, *J* = 1, 7, 7 Hz, 1 H), 6.86 - 6.82 (m, 1 H), 6.27 (s, 1 H), 4.05 (s, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.7, 142.7, 133.1, 129.7, 129.1, 128.5 (q, *J* = 32 Hz), 128.3, 127.0, 124.5 (q, *J* = 272 Hz), 120.0, 119.9, 116.2 (q, *J* = 4 Hz), 114.1 (q, *J* = 4 Hz), 38.1; MS (EI) m/z (rel. intensity) 281 (M+, 75), 282 (12), 281 (75), 280 (18), 249 (16), 248 (99), 228 (11), 212 (13), 179 (11), 86 (9), 84 (15); HRMS (EI) calcd for $C_{14}H_{10}F_3NS$ 281.0486, found 281.0475; Anal. Calcd for $C_{14}H_{10}F_3NS$: C, 59.78; H, 3.58; N, 4.98. Found: C, 59.76; H, 3.57; N, 5.00.

Preparation of 2-[(2-bromo-5-fluorobenzyl)thio]aniline hydrochloride (7e). Following general procedure A, 2-[(2-bromo-5-fluorobenzyl)thio]aniline hydrochloride was prepared (3.17 g, 51%): mp 201-204 °C; IR (diffuse reflectance) 2894 (s), 2805 (b), 2751, 2687, 2567, 2554, 2337 (w), 2258 (w), 2218 (w), 2172 (w), 2139 (w), 1473 (s), 822, 767 (s), 753, cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.36 (br s, 2 H), 7.65 (dd, *J* = 6, 9 Hz, 1 H), 7.31 (d, *J* = 4 Hz, 2 H), 7.19 (d, *J* = 8 Hz, 1 H), 7.15 - 7.07 (m, 2 H), 7.03 - 6.99 (m, 1 H), 4.20 (s, 2 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.9 (d, *J* = 245 Hz), 139.50, 138.8 (d, *J* = 8 Hz), 135.4, 134.1 (d, *J* = 8 Hz), 129.8, 124.1, 122.9, 120.7, 118.4 (d, *J* = 3 Hz), 118.1 (d, *J* = 23 Hz), 116.3 (d, *J* = 23 Hz), 38.7; MS (EI) m/z (rel. intensity) 311 (M+, 0), 313 (23), 311 (22), 232 (52), 189 (28), 187 (29), 125 (23), 124 (99), 108 (28), 80 (32), 51 (25); HRMS (FAB) calcd for $C_{13}H_{11}BrFNS$+H 311.9858, found 311.9847; Anal. Calcd for $C_{13}H_{11}BrFNS$•HCl: C, 44.78; H, 3.47; N, 4.02. Found: C, 44.57; H, 3.29; N, 3.92.

Preparation of 2-fluoro-5,11-dihydrodibenzo[b,e][1,4]thiazepine (4e). Following general procedure B, 2-fluoro-5,11-dihydrodibenzo[b,e][1,4]thiazepine was prepared (38 mg, 16%): IR (diffuse reflectance) 3366, 2446 (w), 2332 (w), 2264 (w), 2139 (w), 1927 (w), 1535, 1509, 1477, 1355, 1256, 1226, 811 (s), 754, 741 (s), cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.56 (s, 1 H), 7.12 - 7.02 (m, 4 H), 6.98 - 6.93 (m, 2 H), 6.65 (ddd, *J* = 1, 8, 8 Hz, 1 H), 4.00 (s, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5 (d, *J* = 237 Hz), 144.3, 139.9, 132.2, 131.1 (d, *J* = 7 Hz), 128.1, 122.3, 120.9 (d, *J* = 8 Hz), 120.0, 118.7, 115.2 (d, *J* = 22 Hz), 144.4 (d, *J* = 22 Hz), 37.9; MS (EI) m/z (rel. intensity) 231 (M+, 99), 232 (27), 231 (99), 230 (53), 199 (33), 198 (97), 197 (37), 196 (14), 170 (16), 109 (12), 84 (17); HRMS (FAB) calcd for $C_{13}H_{10}FNS$+H 232.0596, found 232.0589; Anal. Calcd for $C_{13}H_{10}FNS$: C, 67.51; H, 4.36; N, 6.06. Found: C, 67.48; H, 4.37; N, 6.00.

Preparation of 2-[(2-bromo-5-methoxybenzyl)thio]aniline hydrochloride (7f). Following general procedure A, 2-[(2-bromo-5-methoxybenzyl)thio]aniline hydrochloride was prepared (808 mg, 39%): mp 189-193 °C; IR (diffuse reflectance) 3005, 2979, 2954, 2932 (s), 2836 (s), 2604, 2582, 2555, 2351 (w), 2339 (w), 2279 (w), 2221 (w), 2176 (w), 1474 (s), 772, cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.62 (s, 3 H) 4.12 (s, 2 H) 6.79 (m, 2 H) 6.92 (at, *J* = 8 Hz, 1 H) 7.19 (dd, *J* = 8, 2 Hz, 2 H) 7.26 (m, 1 H) 7.49 (m, 1 H); ^{13}C NMR (100 MHz, CD_3OD) δ 152.5, 142.4, 135.0, 131.0, 130.5, 126.5, 121.4, 119.7, 118.2, 118.0, 112.3, 112.0, 54.6, 36.0; MS (EI) m/z (rel. intensity) 323 (M+, 0), 325 (18), 323 (18), 244 (99), 211 (22), 201 (87), 199 (75), 124 (76), 85 (26), 83 (25), 77 (30). HRMS (FAB) calcd for $C_{14}H_{14}BrNOS$+H 324.0058, found 324.0051; Anal. Calcd for ($C_{14}H_{14}BrNOS$•HCl•0.3H_2O): C, 45.93; H, 4.29; N, 3.83. Found: C, 45.87; H, 4.15; N, 3.83.

Preparation of 2-methoxy-5,11-dihydrodibenzo[b,e][1,4]thiazepine (4f). Following general procedure B, 2-methoxy-5,11-dihydrodibenzo[b,e][1,4]thiazepine was prepared (20 mg, 8%): IR (diffuse reflectance) 3344, 2925, 2487 (w), 2457 (w), 2424 (w), 2401 (w), 2350 (w), 1502 (s), 1477 (s), 1317, 1259 (s), 1231, 1044, 813 (s), 750 (s), cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.19 (dd, *J* = 2, 8 Hz, 1 H), 7.06 (ddd, *J* = 1, 8, 8 Hz, 1 H), 6.78 - 6.69 (m, 4 H), 6.60 (d, *J* = 3 Hz, 1 H), 5.92 (s, 1 H), 4.02 (s, 2 H), 3.77 (s, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 152.1, 144.0, 136.5, 131.5, 130.8, 127.3, 120.9, 120.5, 119.0, 117.5, 113.4, 113.0, 55.1, 37.4; MS (EI) m/z (rel. intensity) 243 (M+, 0), 244 (16), 243 (99), 228 (36), 210 (58), 200 (14), 199 (20), 198 (11), 195 (16), 167 (66), 166 (24). HRMS (FAB) calcd for $C_{14}H_{13}NOS$+H 244.0796, found 244.0791.

General Procedure C: Preparation of nitro ethers.

Preparation of 2-bromobenzyl 2-nitrophenyl ether. To a flask containing 2-bromobenzyl bromide (10.0 g, 40 mmol, 1.05 eq.), 2-nitrophenol (5.3 g, 38 mmol, 1.0 eq.), and K_2CO_3 (13.1 g, 95 mmol, 2.5 eq) was added CH_3CN (75 mL). The solution was heated to 70 °C with an oil bath for 2 hours, at which time the reaction was complete as shown by HPLC. The reaction was quenched with H_2O (100 ml) and extracted with EtOAc (4 x 75 mL). The combine organics were washed with brine (2 x 50 mL), dried with Na_2SO_4, and the solvent removed under vacuum. The resulting solid was recrystallized from Hexane and EtOAc to afford an off-white solid (11.2 g, 96%): mp = 89-90 °C; IR (diffuse reflectance) 3385, 1934 (w), 1597, 1533, 1508 (s), 1450, 1348, 1197 (w), 989, 925 (w), 787, 749 (s), 736 (s), 722, 626, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.90 (dd, *J* = 2, 8 Hz, 1 H), 7.69 (d, *J* = 7 Hz, 1 H), 7.57 (dd, *J* = 1, 8 Hz, 1 H), 7.55 (m, 1 H), 7.37 (t, *J* = 8 Hz, 1 H), 7.20 (ddd, *J* = 1, 8, 9 Hz, 1 H), 7.17 (t, *J* = 9 Hz, 1 H), 7.07 (m, 1 H), 5.27 (s, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.6, 139.9, 134.9, 134.3, 132.8, 129.5, 128.5, 127.9, 125.9, 121.4, 120.9, 114.9, 70.3; MS (EI) *m/z* (rel. intensity) 171 (99), 169 (99), 123 (99), 90 (99), 77 (34), 76 (32), 64 (51), 63 (99), 52 (60), 51 (80). Anal. Calcd for $C_{13}H_{10}BrNO_3$: C, 50.67; H, 3.27; N, 4.55; Br, 25.93; Found: C, 50.64; H, 3.11; N, 4.54.

General Procedure D: Synthesis of ether linked acyclic precursors.

Preparation of 2-[(2-bromobenzyl)oxy]aniline hydrochloride (7h).[7] 2-Bromobenzyl 2-nitrophenyl ether (5.0 g, 16.2 mmol, 1 eq) was dissolved in IPA (100 mL) and heated to 60 °C with an oil bath. To this solution was added HCl (2.5 mL, 12 N) followed by Fe (13.5 g, 242 mmol, 15 eq). The reaction was allowed to stir for 17 hours at 60 °C, at which time it was filtered hot through a pad of celite. The solution was reduced to about 20 mL under vacuum at which time 2.0 N HCl in Et_2O was added until a ppt formed. The resulting off-white solid was recrystallized from MeOH and EtOAc to afford a white solid (4.4 g, 80 %): mp 194-196 °C; ^1H NMR (400 MHz, CD_3OD) δ 7.68 (t, *J* = 10 Hz, 2 H), 7.46 (m, 3 H), 7.30 (m, 2 H), 7.13 (dt, *J* = 2, 10 Hz, 1 H), 5.37 (s, 2 H); ^{13}C NMR (100 MHz, CD_3OD) δ 152.9, 136.5, 134.0, 131.7, 131.2, 130.8, 129.0, 125.2, 123.9, 122.8, 120.8, 114.6, 71.5; MS (ESI+) for $C_{13}H_{12}BrNO$ *m/z* 278.1 $(M+H)^+$; MS (EI) *m/z* (rel. intensity) 279 (13), 277 (14), 171 (23), 169 (26), 109 (12), 108 (99), 91 (17), 90 (19), 89 (18), 80 (50); % Water (KF): 4.93. Anal. Calcd for $C_{13}H_{12}BrNO•HCl•H_2O$: C, 46.94; H, 4.55; N, 4.21. Found: C, 46.89; H, 4.57; N, 4.16.

General Procedure E: Cycloamination of cthers.

Preparation of 5,11-dihydrodibenzo[b,e][1,4]oxazepine (**4h**).[7] An argon purged vial was charged with the chlorophenylamine hydrochloride (345 mg, 1.1 mmol, 1.0 eq), sodium tert-butoxide (192 mg, 2.0 mmol, 2.0 eq), potassium carbonate (276 mg, 2.0 mmol, 2.0 eq), and tris(dibenzylideneacetone) dipalladium (92 mg, 0.1 mmol, 0.1 eq). Toluene (10 mL) was added followed by tri-tert-butyl phosphine

[7] Yale, H. L.; Sowinski F. *J. Med. Chem*. **1964**, *7*, 609-14.

(10 mg, 0.05 mmol, 0.05 eq). The reaction vessel was again purged with argon, and heated to 95°C. After 2.5 hours, the reaction was cooled, concentrated, absorbed onto silica gel, and purified with Biotage chromatography (20% CH_2Cl_2 in heptane to 40% CH_2Cl_2 in heptane gradient) to give an off-white solid (186 mg, 86%): mp 119-120 °C; IR (diffuse reflectance) 3385, 1934 (w), 1597, 1533, 1508 (s), 1450, 1348, 1197 (w), 989, 925 (w), 787, 749 (s), 736 (s), 722, 626, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.18 (t, *J* = 7 Hz, 1 H), 7.08 (d, *J* = 7 Hz, 1 H), 6.96 (dd, *J* = 1, 8 Hz, 1 H), 6.90 (t, *J* = 7 Hz, 1 H), 6.75 (m, 4 H), 5.95 (br s, 1 H), 5.03 (s, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.3, 143.7, 134.9, 129.5, 129.2, 126.0, 123.8, 121.9, 119.9, 119.6, 118.8, 117.1, 74.7; MS (EI) *m/z* (rel. intensity) 197 (99), 168 (99), 117 (42), 89 (51), 84 (50), 77 (26), 65 (20), 63 (45), 52 (28), 51 (46); Anal. Calcd for $C_{13}H_{11}NO$: C, 79.16; H, 5.62; N, 7.10; Found: C, 78.94; H, 5.63; N, 7.10.

Preparation of 1-chloro-2-[(2-nitrophenoxy)methyl]benzene. Following General Procedure C, 1-chloro-2-[(2-nitrophenoxy)methyl]benzene was prepared (12.0 g, 95%): mp 85-87 °C; IR (diffuse reflectance) 2449, 2428, 2350, 2334, 2311, 1608 (s), 1531 (s), 1525 (s), 1519 (s), 1490 (s), 1450, 1346 (s), 1292 (s), 1271 (s), 1259 (s), cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (dd, *J* = 2, 8 Hz, 1 H), 7.70 (d, *J* = 7 Hz, 1 H), 7.54 (dd, *J* = 1, 8 Hz, 1 H), 7.40 (dd, *J* = 1, 8 Hz, 1 H), 7.34-7.26 (m, 2 H), 7.16 (d, *J* = 8 Hz, 1 H), 7.08 (dt, *J* = 1, 8 Hz, 1 H), 5.31 (s, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.7, 139.9, 134.3, 133.3, 131.8, 129.2, 129.2, 128.3, 127.3, 125.9, 120.9, 114.8, 68.1; HRMS (EI) calcd for $C_{13}H_{10}ClO_3$ 263.0349, found 263.0353; Anal. Calcd for $C_{13}H_{10}ClNO_3$: C, 59.22; H, 3.82; N, 5.31. Found: C, 59.18; H, 3.71; N, 5.26.

Preparation of 2-[(2-chlorobenzyl)oxy]aniline hydrochloride (7g). Following General Procedure D, 2-[(2-chlorobenzyl)oxy]aniline hydrochloride was prepared (4.0 g, 78%): mp 197-198 °C; IR (diffuse reflectance) 2872, 2843, 2622, 2595, 2473 (w), 2301 (w), 2247 (w), 2210 (w), 1969 (w), 1500, 1261, 1238, 1049, 998, 755 (s), cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.79 (dd, *J* = 4, 5 Hz, 1 H), 7.53 (m, 1 H), 7.41 (m, 3 H), 7.31 (t, *J* = 7 Hz, 1 H), 7.23 (d, *J* = 7 Hz, 1 H), 7.04 (dt, *J* = 1, 8 Hz, 1 H), 5.30 (s, 2 H), 3.8 (br s, 2 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 150.7, 133.6, 131.8, 129.7, 129.6, 129.1, 128.6, 127.2, 123.7, 121.6, 121.3, 113.4, 67.1; MS (EI) m/z (rel. intensity) 233 (M+, 0), 235 (48), 233 (99), 127 (60), 125 (84), 109 (43), 108 (88), 89 (46), 80 (73), 78 (27), 63 (34); HRMS (FAB) calcd for $C_{13}H_{12}ClNO$ +H 234.0686, found 234.0690; Anal. Calcd for $C_{13}H_{12}ClNO•HCl•0.2H_2O$: C, 57.04; H, 4.93; N, 5.12. Found: C, 56.91; H, 4.88; N, 5.12.

Preparation of 1-[(2-bromobenzyl)oxy]-3-methyl-2-nitrobenzene. Following General Procedure C, 1-[(2-bromobenzyl)oxy]-3-methyl-2-nitrobenzene was prepared (5.5 g, 87%): mp 94-95 °C; IR (diffuse reflectance) 2432 (w), 2402 (w), 2368 (w), 2353, 2323 (w), 1531 (s), 1476 (s), 1377 (s), 1372 (s), 1284 (s), 1272 (s), 849 (s), 771 (s), 760 (s), 750 (s), cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 (dd, *J* = 1, 8 Hz, 1 H), 7.47 (d, *J* = 7 Hz, 1 H), 7.34 (dt, *J* = 1, 8 Hz, 1 H), 7.27 (m, 1 H), 7.18 (dt, *J* = 2, 8 Hz, 1 H), 6.82 (t, *J* = 8 Hz, 2 H), 5.21 (s, 2 H), 2.33 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.5, 142.3, 134.9, 132.5, 131.3, 130.7, 129.5, 128.4, 127.8, 123.2, 121.7, 111.4, 70.1, 17.1; MS (EI) m/z (rel. intensity) 321 (M+, 0), 172 (25), 171 (99), 170 (24), 169 (99), 137 (34), 90 (70), 89 (67), 78 (23), 63 (33), 51 (25); HRMS (EI) calcd for $C_{14}H_{12}BrO_3$ 321.0001, found 320.9991; Anal. Calcd for $C_{14}H_{12}BrNO_3$: C, 52.20; H, 3.75; N, 4.35. Found: C, 52.16; H, 3.73; N, 4.33.

Preparation of 2-[(2-bromobenzyl)oxy]-6-methylaniline hydrochloride (**7i**). Following General Procedure D, 2-[(2-bromobenzyl)oxy]-6-methylaniline hydrochloride was prepared (2.82 g, 92%): mp 177-180 °C; IR (diffuse reflectance) 2946, 2917 (b), 2907 (b), 2890, 2860 (b), 2741 (b), 2557 (s), 2353 (w), 2341 (w), 2239 (w), 2214 (w), 2162 (w), 1481 (s), 768 (s), 752 (s), cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.70 (m, 2 H), 7.44 (t, *J* = 7 Hz, 1 H), 7.33 (t, *J* = 8 Hz, 1 H), 7.14 (t, *J* = 8 Hz, 1 H), 7.02 (d, *J* = 8 Hz, 1 H), 6.88 (d, *J* = 7 Hz, 1 H), 5.23 (s, 2 H), 2.34 (s, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 149.8, 135.2, 132.5, 131.3, 130.2, 130.1, 127.8, 216.3, 123.3, 122.6, 121.9, 110.8, 69.9, 17.3; MS (EI) m/z (rel. intensity) 291 (M+, 0), 293 (54), 291 (54), 169 (42), 123 (45), 122 (99), 94 (83), 84 (48), 78

(62), 77 (41), 63 (62); HRMS (FAB) calcd for $C_{14}H_{14}BrNO$ +H 292.0337, found 292.0341; Anal. Calcd for $C_{14}H_{14}BrNO$•HCl: C, 51.17; H, 4.60; N, 4.26. Found: C, 50.88; H, 4.73; N, 4.22.

Preparation of 6-methyl-5,11-dihydrodibenzo[b,e][1,4]oxazepine (**4i**). Following General Procedure E, 6-methyl-5,11-dihydrodibenzo[b,e][1,4]oxazepine was prepared (138 mg, 65%): mp 103-104 °C; IR (diffuse reflectance) 3421, 2458 (w), 2410 (w), 2351 (w), 2332 (w), 2314 (w), 1518 (s), 1494 (s), 1480 (s), 1335 (s), 1311, 792, 752 (s), 748 (s), 733, cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.24 (d, J = 8 Hz, 1 H), 7.15 (t, J = 7 Hz, 1 H), 7.06 (m, 2 H), 6.82 (d, J = 7 Hz, 1 H), 6.76 (d, J = 8 Hz, 1 H), 6.70 (t, J = 7 Hz, 1 H), 6.59 (t, J = 8 Hz, 1 H), 4.94 (s, 2 H), 2.34 (s, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 149.9, 142.9, 133.6, 128.4, 128.0, 126.0, 125.3, 124.8, 119.0, 118.5, 118.0, 117.9, 74.7, 18.5; MS (EI) *m/z* (rel. intensity) 211 (M^+, 0), 211 (99), 196 (24), 182 (58), 180 (15), 168 (36), 167 (57), 117 (42), 86 (41), 84 (70), 51 (39); HRMS (FAB) calcd for $C_{14}H_{13}NO$+H 212.1075, found 212.1081; Anal. Calcd for $C_{14}H_{13}NO$•0.15H_2O: C, 78.59; H, 6.27; N, 6.55. Found: C, 78.47; H, 6.20; N, 6.48.

Preparation of 1-[(2-bromobenzyl)oxy]-4-methyl-2-nitrobenzene. Following General Procedure C, 1-[(2-bromobenzyl)oxy]-4-methyl-2-nitrobenzene was prepared (6.05 g, 98%): mp 111-113 °C; IR (diffuse reflectance) 2473 (w), 2430 (w), 2416 (w), 2385 (w), 2361 (w), 1573, 1524 (s), 1493, 1379, 1344 (s), 1291, 1287, 1258 (s), 800 (s), 750 (s), cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 (m, 2 H), 7.57 (d, J = 8 Hz, 1 H), 7.35 (m, 2 H), 7.20 (t, J = 8 Hz, 1 H), 7.03 (d, J = 9 Hz, 1 H), 5.24 (s, 2 H), 2.36 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.6, 139.6, 135.1, 134.9, 132.4, 130.9, 129.4, 128.5, 127.9, 126.0, 121.4, 114.9, 70.4, 20.2; HRMS (EI) calcd for $C_{14}H_{12}BrO_3$ 321.0001, found 320.9998; Anal. Calcd for $C_{14}H_{12}BrNO_3$: C, 52.20; H, 3.75; N, 4.35. Found: C, 52.12; H, 3.67; N, 4.32.

Preparation of 2-[(2-bromobenzyl)oxy]-5-methylaniline hydrochloride (**7j**). Following General Procedure D, 2-[(2-bromobenzyl)oxy]-5-methylaniline hydrochloride was prepared (4.0 g, 79%): mp 211-214 °C; IR (diffuse reflectance) 2805 (b), 2763, 2740 (b), 2551, 2269 (w), 2194 (w), 2095 (w), 2046 (w), 1983 (w), 1483 (s), 1277 (s), 1271 (s), 1237, 807 (s), 756 (s), cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 9.95 (br s, 2 H), 7.77 (d, J = 8 Hz, 1 H), 7.68 (d, J = 8 Hz, 1 H), 7.44 (t, J = 13 Hz, 1 H), 7.31 (t, J = 8 Hz, 1 H), 7.25 (s, 1 H), 7.12 (m, 2 H), 5.95 (br s, 1 H), 5.22 (s, 2 H), 2.26 (s, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 148.4, 135.3, 132.3, 130.5, 129.9, 129.7, 128.6, 127.7, 123.8, 121.9, 121.6, 113.4, 69.5, 19.9; MS (EI) m/z (rel. intensity) 291 (M+, 0), 293 (34), 291 (35), 171 (39), 169 (41), 123 (33), 122 (99), 94 (68), 84 (37), 78 (45), 63 (49); HRMS (FAB) calcd for $C_{14}H_{14}BrNO$ +H 292.0337, found 292.0333; Anal. Calcd for $C_{14}H_{14}BrNO$•HCl: C, 51.17; H, 4.60; N, 4.26. Found: C, 51.16; H, 4.67; N, 4.25.

Preparation of 7-methyl-5,11-dihydrodibenzo[b,e][1,4]oxazepine (**4j**). Following General Procedure E, 7-methyl-5,11-dihydrodibenzo[b,e][1,4]oxazepine was prepared (184 mg, 87%): mp 178-179 °C; IR (diffuse reflectance) 3382, 2437 (w), 2380 (w), 2324 (w), 2221 (w), 2059 (w), 1593, 1516, 1349, 933, 869, 810 (s), 742 (s), 732, 628, cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.49 (s, 1 H), 7.13 (dt, J = 2, 9 Hz, 1 H), 7.06 (d, J = 6 Hz, 1 H), 6.93 (d, J = 8 Hz, 1 H), 6.79 (d, J = 2 Hz, 1 H), 6.73 (d, J = 8 Hz, 1 H), 6.67 (dd, J = 6, 7 Hz, 1 H), 6.42 (dd, J = 2, 8 Hz, 1 H), 4.89 (s, 2 H), 2.18 (s, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 146.5, 143.6, 134.8, 131.9, 128.7, 128.4, 124.9, 120.6, 118.9, 118.7, 117.6, 116.6, 73.9, 20.2; MS (EI) m/z (rel. intensity) 211 (M+, 99), 212 (37), 211 (99), 210 (90), 196 (51), 182 (86), 180 (41), 168 (67), 167 (84), 117 (67), 84 (26); HRMS (FAB) calcd for $C_{14}H_{13}NO$ +H 212.1075, found 212.1071; Anal. Calcd for $C_{14}H_{13}NO$: C, 79.59; H, 6.20; N, 6.63. Found: C, 79.58; H, 6.29; N, 6.62.

Preparation of 4-bromo-3-[(2-nitrophenoxy)methyl]benzonitrile. Following General Procedure C, 4-bromo-3-[(2-nitrophenoxy)methyl]benzonitrile was prepared (0.87 g, 82%): mp 185-187 °C; IR (diffuse reflectance) 2439 (w), 2238, 2186 (w), 1966 (w), 1924 (w), 1527 (s), 1350 (s), 1285, 1271, 1260, 1022, 907, 829 (s), 776, 739 (s), cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1 H), 7.96 (dd, J = 2, 9 Hz, 1 H), 7.72 (d, J = 8 Hz, 1 H), 7.59 (ddd, J = 2, 8, 9 Hz, 1 H), 7.51 (dd, J = 2, 8 Hz, 1 H), 7.14 (dd, J = 7, 8

Hz, 2 H), 5.25 (s, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.1, 139.9, 136.9, 134.5, 133.5, 132.6, 131.7, 126.5, 126.2, 121.7, 117.9, 114.9, 112.3, 69.7; HRMS (FAB) calcd for $C_{14}H_9BrN_2O_3$ +H 332.9875, found 332.9887. Anal. Calcd for $C_{14}H_9BrN_2O_3$: C, 50.48; H, 2.72; N, 8.41. Found: C, 50.45; H, 2.71; N, 8.40.

Preparation of 3-[(2-aminophenoxy)methyl]-4-bromobenzonitrile (7k). Following General Procedure D, 3-[(2-aminophenoxy)methyl]-4-bromobenzonitrile as an amorphous solid (0.30 g, 82%): IR (diffuse reflectance) 2470 (w), 2446 (w), 2363 (w), 2307 (w), 2231, 2231, 1508, 1459, 1280 (s), 1234 (s), 1221, 1023 (s), 883, 818 (s), 739 (s), cm $^{-1}$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.21 (d, J = 2 Hz, 1 H), 7.91 (d, J = 8 Hz, 1 H), 7.77 (dd, J = 2, 8 Hz, 1 H), 6.88 (d, J = 7 Hz, 1 H), 6.74-6.67 (m, 2 H), 6.51 (dt, J = 2, 8 Hz, 1 H), 5.10 (s, 2 H), 4.95 (br s, 2 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 144.5, 138.1, 138.0, 133.6, 132.9, 132.4, 127.5, 121.8, 118.1, 115.9, 114.3, 112.3, 110.8, 68.3; MS (EI) m/z (rel. intensity) 302 (M+, 7), 196 (9), 194 (10), 115 (14), 114 (9), 108 (81), 80 (99), 63 (9), 53 (30), 52 (18), 51 (11); HRMS calcd for $C_{14}H_{11}BrN_2O$+H 303.0133, found 303.0133; Anal. Calcd for $C_{14}H_{11}BrN_2O$: C, 55.47; H, 3.66; N, 9.24; Found: C, 55.39; H, 3.73; N, 9.11.

Preparation of 5,11-dihydrodibenzo[b,e][1,4]oxazepine-2-carbonitrile (4k). Following General Procedure E, 5,11-dihydrodibenzo[b,e][1,4]oxazepine-2-carbonitrile was prepared (0.13 g, 79%): mp 174-175 °C; IR (diffuse reflectance) 3345, 2480 (w), 2434 (w), 2391 (w), 2350 (w), 2214 (s), 2214 (s), 1614, 1596, 1531 (s), 1504 (s), 1365, 1350, 808, 760, cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.35 (s, 1 H), 7.56 (d, J = 8 Hz, 2 H), 7.08-7.04 (m, 2 H), 6.99-6.93 (m, 2 H), 6.76 (t, J = 7 Hz, 1 H), 4.96 (s, 2 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 148.0, 145.9, 132.6, 131.4, 131.3, 123.5, 122.3, 119.8, 118.8, 118.3, 118.1, 115.8, 96.8, 72.1; MS (EI) m/z (rel. intensity) 222 (M+, 84), 222 (84), 221 (51), 193 (99), 192 (25), 140 (15), 105 (15), 91 (37), 84 (23), 77 (16), 51 (22); HRMS calcd for $C_{14}H_{10}N_2O$+ 222.0793, found 222.0788. Anal. Calcd for $C_{14}H_{10}N_2O$: C, 75.66; H, 4.54; N, 12.60. Found: C, 75.84; H, 4.59; N, 12.23.

Preparation of 1-bromo-4-fluoro-2-[(2-nitrophenoxy)methyl]benzene. Following General Procedure C, 1-bromo-4-fluoro-2-[(2-nitrophenoxy)methyl]benzene was prepared (5.22 g, 95%): mp 122-123 °C; IR (diffuse reflectance) 2455 (w), 2434, 2407, 2372 (w), 2349, 1531 (s), 1525 (s), 1467 (s), 1265 (s), 879 (s), 812 (s), 774 (s), 739 (s), 626 (s), 601 (s), cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (dd, J = 2, 8 Hz, 1 H), 7.59-7.51 (m, 2 H), 7.48 (dd, J = 3, 9 Hz, 1 H), 7.15-7.09 (m, 2 H), 6.94 (dt, J = 3, 8 Hz, 1 H), 5.22 (s, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4 (d, J = 246 Hz), 151.4, 139.8, 137.1 (d, J = 8 Hz), 134.4, 133.6 (d, J = 8 Hz), 126.1, 121.2, 116.5 (d, J = 23 Hz), 115.7 (d, J = 25 Hz), 114.9 (d, J = 3 Hz), 114.7, 69.8; HRMS (EI) calcd for $C_{13}H_9BrFO_3$ 324.9750, found 324.9749; Anal. Calcd for $C_{13}H_9BrFNO_3$: C, 47.88; H, 2.78; N, 4.29. Found: C, 47.81; H, 2.79; N, 4.29.

Preparation of 2-[(2-bromo-5-fluorobenzyl)oxy]aniline hydrochloride (**7l**). Following General Procedure D, 2-[(2-bromo-5-fluorobenzyl)oxy]aniline hydrochloride was prepared (3.3 g, 82%): mp 211-215 °C; IR (diffuse reflectance) 2862 (s), 2842 (s,b), 2652, 2624, 2384 (w), 2356 (w), 2298 (w), 2247 (w), 2194 (w), 1497, 1466, 1256, 1240, 818, 753 (s), cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.05 (br s, 2 H), 7.78-7.71 (m, 2 H), 7.51 (dd, J = 1, 8 Hz, 1 H), 7.35 (dt, J = 1, 9 Hz, 1 H), 7.24-7.19 (m, 2 H), 7.08 (dt, J = 1, 8 Hz, 1 H), 5.24 (s, 2 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.6 (d, J = 243 Hz), 150.3, 137.7 (d, J = 8 Hz), 133.9 (d, J = 8 Hz), 128.5, 123.7, 121.9, 121.5, 116.7 (d, J = 23 Hz), 116.5 (d, J = 24 Hz), 115.6 (d, J = 3 Hz), 113.4, 68.8; MS (EI) m/z (rel. intensity) 295 (M+, 0), 297 (42), 295 (40), 187 (20), 109 (30), 108 (99), 107 (22), 84 (28), 80 (80), 78 (44), 63 (49); HRMS (FAB) calcd for $C_{13}H_{11}BrFNO$ +H 296.0087, found 296.0088; Anal. Calcd for $C_{13}H_{11}BrFNO$•HCl: C, 46.95; H, 3.64; N, 4.21. Found: C, 47.08; H, 3.69; N, 4.20.

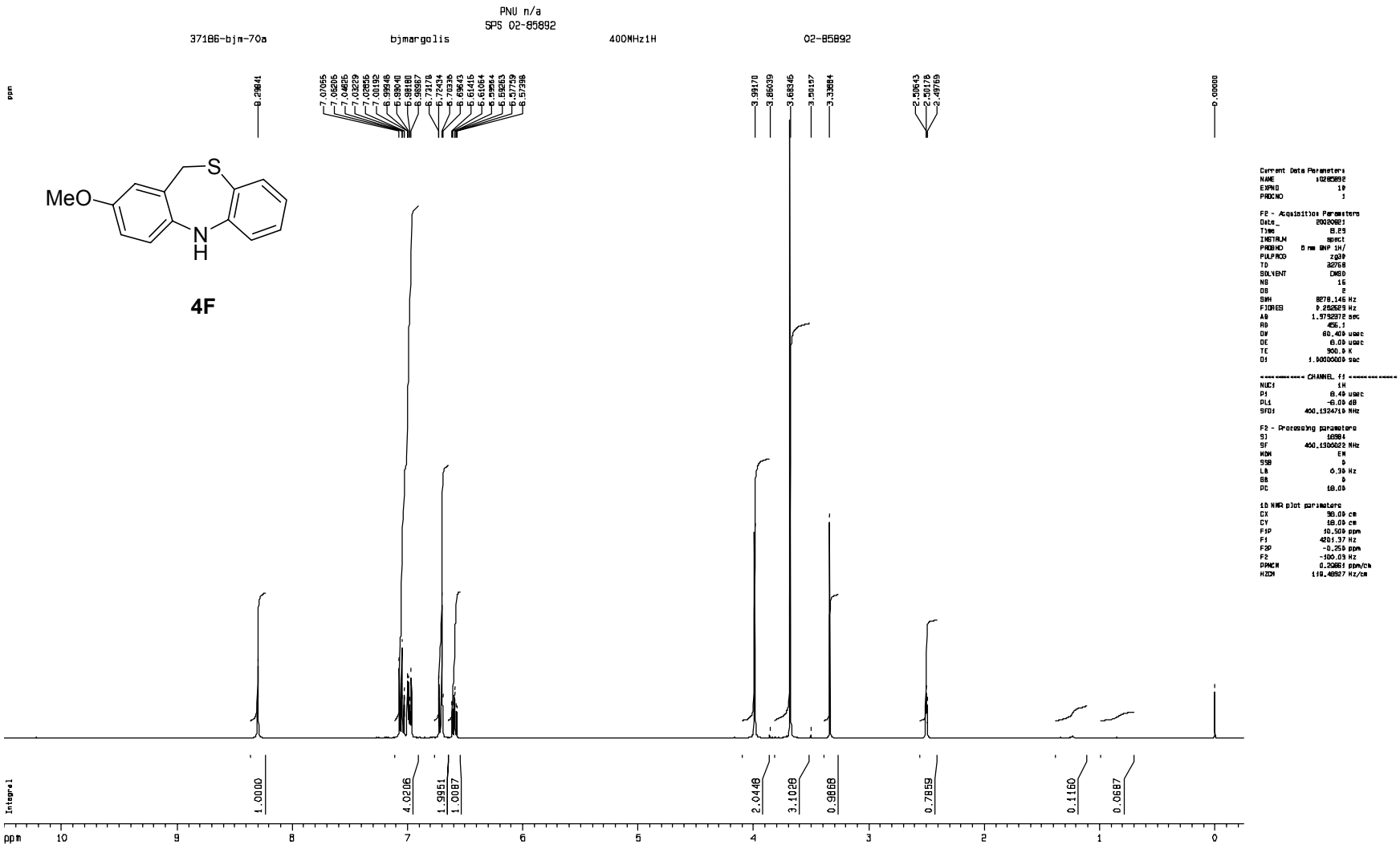
Preparation of 2-fluoro-5,11-dihydrodibenzo[b,e][1,4]oxazepine (**4l**). Following General Procedure E, 2-fluoro-5,11-dihydrodibenzo[b,e][1,4]oxazepine was prepared (200 mg, 93%): mp 109-111 °C; IR (diffuse reflectance) 3391, 2482 (w), 2437 (w), 2409 (w), 2374 (w), 2315 (w), 1502 (s), 1341, 1255,

1153, 877, 825, 811, 763, 751 (s), cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.54 (s, 1 H), 7.03-6.99 (m, 2 H), 6.96-6.92 (m, 2 H), 6.89-6.83 (m, 2 H), 6.60 (dt, *J* = 2, 8 Hz, 1 H), 4.93 (s, 2 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.6 (d, *J* = 234 Hz), 148.3, 140.3 (d, *J* = 2 Hz), 135.1, 126.5 (d, *J* = 6 Hz), 123.3, 120.8, 118.2 (d, *J* = 18 Hz), 117.8 (d, *J* = 8 Hz), 115.2 (d, *J* = 22 Hz), 114.7, 114.5, 72.9; MS (EI) m/z (rel. intensity) 215 (M+, 99), 216 (25), 215 (99), 214 (86), 187 (27), 186 (92), 185 (76), 184 (18), 135 (26), 86 (24), 84 (41); HRMS (FAB) calcd for $C_{13}H_{10}FNO$ +H 216.0825, found 216.0814; Anal. Calcd for $C_{13}H_{10}FNO•0.1H_2O$: C, 71.95; H, 4.71; N, 6.45. Found: C, 71.94; H, 4.78; N, 6.41.

Preparation of 1-bromo-4-methoxy-2-[(2-nitrophenoxy)methyl]benzene. Following General Procedure C, 1-bromo-4-methoxy-2-[(2-nitrophenoxy)methyl]benzene was prepared (2.2 g, 90%): mp 90-91 °C; IR (diffuse reflectance) 2492 (w), 2430 (w), 2350 (w), 2341 (w), 2310 (w), 1608 (s), 1520 (s), 1482 (s), 1352, 1303, 1284 (s), 1249 (s), 865 (s), 771, 742 (s), cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.93 (dd, *J* = 2, 8 Hz, 1 H), 7.56 (dt, *J* = 2, 8 Hz, 1 H), 7.43 (d, *J* = 9 Hz, 1 H), 7.36 (d, *J* = 1 Hz, 1 H), 7.16 (d, *J* = 8 Hz, 1 H), 7.08 (m, 1 H), 7.76 (dd, *J* = 3, 9 Hz, 1 H), 5.23 (s, 2 H), 3.84 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 151.6, 139.8, 135.9, 134.5, 133.0, 126.0, 120.9, 116.1, 114.8, 113.1, 111.2, 70.1, 55.6; MS (EI) m/z (rel. intensity) 337 (M+, 0), 201 (99), 199 (99), 120 (46), 91 (48), 90 (42), 80 (41), 78 (99), 77 (45), 63 (87), 61 (58); HRMS (EI) calcd for $C_{14}H_{12}BrNO_4$ 336.9950, found 336.9940; Anal. Calcd for $C_{14}H_{12}BrNO_4$: C, 49.73; H, 3.58; N, 4.14. Found: C, 49.70; H, 3.55; N, 4.14.

Preparation of 2-[(2-bromo-5-methoxybenzyl)oxy]aniline hydrochloride (**7m**). Following General Procedure D, 2-[(2-bromo-5-methoxybenzyl)oxy]aniline hydro chloride was prepared (1.68 g, 92%): mp 222-225 °C; IR (diffuse reflectance) 2975, 2897 (s,b), 2838 (s), 2650, 2616, 2355 (w), 2291 (w), 2247 (w), 2192 (w), 2128 (w), 1497, 1300, 1240 (s), 810, 742 (s), cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.57 (d, *J* = 9 Hz, 1 H), 7.46 (d, *J* = 6 Hz, 1 H), 7.36 (d, *J* = 3 Hz, 1 H), 7.33 (m, 1 H), 7.20 (d, *J* = 7 Hz, 1 H), 7.05 (dt, *J* = 7, 8 Hz, 1 H), 6.91 (dd, *J* = 3, 9 Hz, 1 H), 5.21 (s, 2 H), 3.79 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8, 150.4, 136.1, 133.0, 128.3, 123.4, 122.1, 121.4, 115.4, 115.3, 113.4, 111.8, 69.3, 55.5; MS (EI) m/z (rel. intensity) 307 (M+, 73), 309 (79), 307 (73), 228 (56), 201 (99), 199 (99), 108 (95), 91 (49), 80 (82), 77 (63), 53 (48); HRMS (FAB) calcd for $C_{14}H_{14}BrNO_2$ +H 308.0287, found 308.0281; Anal. Calcd for $C_{14}H_{14}BrNO_2$•HCl: C, 48.79; H, 4.39; N, 4.06. Found: C, 48.89; H, 4.54; N, 4.03.

Preparation of 2-methoxy-5,11-dihydrodibenzo[b,e][1,4]oxazepine (**4m**). Following General Procedure E, 2-methoxy-5,11-dihydrodibenzo[b,e][1,4]oxazepine was prepared (158 mg, 69%); mp 99-100 °C; IR (diffuse reflectance) 2477 (w), 2443 (w), 2351 (w), 2328 (w), 2232 (w), 1531, 1507 (s), 1319, 1276, 1265, 1232, 1041, 823, 757 (s), 745 (s), cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.28 (s, 1 H), 6.93-6.57 (m, 6 H), 6.53 (dd, *J* = 2, 8 Hz, 1 H), 4.92 (s, 2 H), 3.69 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.6, 147.9, 137.5, 135.6, 126.3, 123.1, 120.7, 118.1, 117.7, 117.5, 114.6, 113.4, 73.4, 55.2; MS (EI) m/z (rel. intensity) 227 (M+, 99), 227 (99), 226 (68), 198 (65), 184 (19), 183 (38), 155 (21), 154 (24), 86 (31), 84 (45), 51 (22); HRMS (FAB) calcd for $C_{14}H_{13}NO_2$ +H 228.1024, found 228.1030; Anal. Calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 74.00; H, 5.83; N, 6.14.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