

Biochemical and structural evaluation of highly selective 2-arylbenzoxazole-based transthyretin amyloidogenesis inhibitors

Supporting Information

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Figure S1: Inhibitor purities as determined using two distinct RP-HPLC conditions. Refer to the Experimental procedures for individual HPLC traces.

X	Substituent								
	a	b	c	d	e	f	g	h	i
1	>99%	95%	99%	95%	98%	>99%	>99%	98%	97%
	<i>99%</i>	<i>98%</i>	<i>99%</i>	<i>96%</i>	<i>98%</i>	<i>99%</i>	<i>99%</i>	<i>97%</i>	<i>96%</i>
2		98%	>99%	98%		>99%	98%	98%	>99%
		<i>>99%</i>	<i>97%</i>	<i>97%</i>		<i>>99%</i>	<i>97%</i>	<i>98%</i>	<i>98%</i>
3	>99%	>99%	>99%	>99%	97%	>99%	>99%	>99%	
	<i>96%</i>	<i>98%</i>	<i>98%</i>	<i>98%</i>	<i>96%</i>	<i>>99%</i>	<i>98%</i>	<i>98%</i>	
4		>99%	95%	>99%	>99%	>99%			
		<i>>99%</i>	<i>95%</i>	<i>96%</i>	<i>99%</i>	<i>98%</i>			
5	>99%	>99%	>99%	>99%	98%	>99%	>99%		>99%
	<i>98%</i>	<i>99%</i>	<i>>99%</i>	<i>99%</i>	<i>96%</i>	<i>99%</i>	<i>>99%</i>		<i>98%</i>
6		>99%	>99%	>99%	>99%	>99%			
		<i>98%</i>	<i>98%</i>	<i>97%</i>	<i>>99%</i>	<i>>99%</i>			

Primary RP-HPLC Conditions (Upper, black values):

Samples were chromatographically separated using a ThermoHypersil-Keystone Betabasic-18 column (model 71503-034630, 150 Å pore size, 3 µm particle size), eluting with a H₂O:CH₃CN gradient solvent system. Linear gradients were run from either 100:0, 80:20, or 60:40 A:B to 0:100 A:B (A = 95:5 H₂O:CH₃CN, 0.25% TFA; B = 5:95 H₂O:CH₃CN, 0.25% TFA).

Secondary RP-HPLC Conditions (Lower, red, italicized values):

Samples were chromatographically separated using a Vydac-C₄ column (model 214TP5415, 300 Å pore size, 5 µm particle size), eluting with a H₂O:MeOH gradient solvent system. Linear gradients were run from 100:0 to 0:100 C:D (C = 99.75% H₂O, 0.25% TFA; D = 100% MeOH).

Figure S2: Phenolic pKa values calculated using the SPARC V3.1 online pKa calculator (<http://ibmlc2.chem.uga.edu/sparc/>). Calculations were based on unbound compounds in aqueous conditions; however, in the case of compounds bound to TTR, the local protein environment will also contribute to the phenolic pKa's and thus the values may differ.

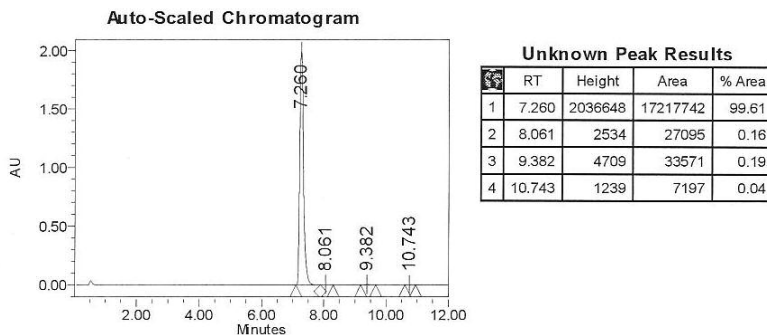
	a	b	c	d	e	f	g	h	i
1	8.43	7.08	6.82	6.86	6.83	8.85	6.94	<i>m</i> -8.33 <i>p</i> -7.69	
2									
3		5.77	5.24	5.35	5.29	9.21			
4									
5									
6									

Experimental:

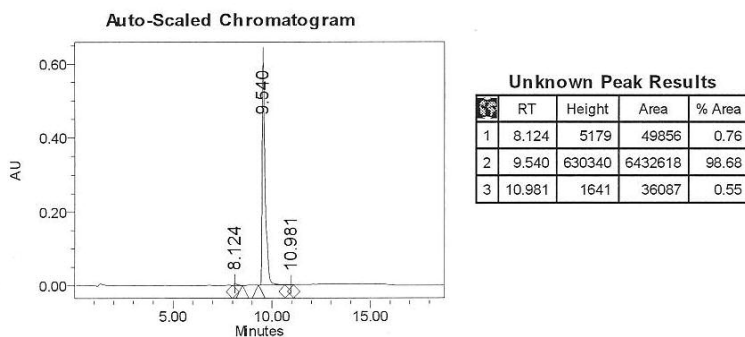
2-Phenylbenzoxazole (1a).

Refer to the main text for experimental procedures.

Primary RP-HPLC Conditions Chromatographic Trace:



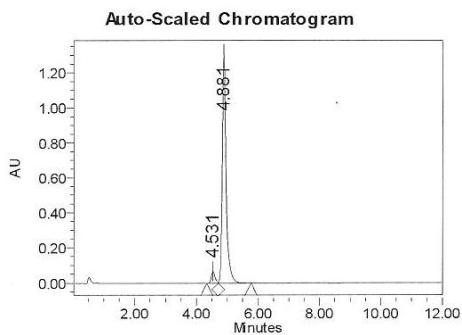
Secondary RP-HPLC Conditions Chromatographic Trace:



2-(3-Fluorophenyl)benzoxazole (1b).

3-Fluorobenzoic acid (165 mg, 1.18 mmol), 2-aminophenol (106 mg, 0.968 mmol), and *p*-TsOH·H₂O (928 mg, 4.88 mmol) were stirred in refluxing xylenes (10 mL). After 20 h the reaction was cooled, extracted into EtOAc (50 mL), and washed with saturated NaHCO₃ (2x25 mL) and brine (25 mL). The organics were then dried over Na₂SO₄, filtered, and concentrated. Flash chromatographic purification over silica (9:1 hexanes:EtOAc) afforded 2-(3-fluorophenyl)benzoxazole (**1b**) as a white solid (31.9 mg, 15%). ¹H-NMR (500 MHz, *d*₆-DMSO) δ 8.04 (ddd, *J*=1.0, 1.5, 7.8 Hz, 1H), 7.93 (ddd, *J*=1.5, 2.6, 9.6 Hz, 1H), 7.78-7.84 (m, 2H), 7.64-7.70 (m, 1H), 7.41-7.52 (m, 3H); ¹³C-NMR (125 MHz, *d*₆-DMSO) δ 162.32 (d, *J*=245 Hz), 161.07 (d, *J*=2.9 Hz), 150.27, 141.30, 131.69 (d, *J*=8.6 Hz), 128.56 (d, *J*=8.6 Hz), 125.97, 125.10, 123.50 (d, *J*=2.9 Hz), 120.05, 118.93 (d, *J*=20.0 Hz), 113.87 (d, *J*=24.0 Hz), 111.09; ESI-TOF 214.0658 *m/z* [MH]⁺, C₁₃H₉FNO requires 214.0663; RP-HPLC: 95% & 98% pure.

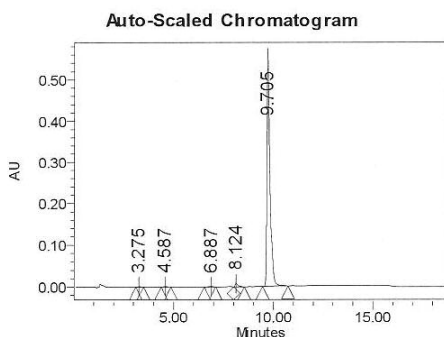
Primary RP-HPLC Conditions Chromatographic Trace:



Unknown Peak Results

RT	Height	Area	% Area
1 4.531	66099	546531	4.60
2 4.881	1312773	11322713	95.40

Secondary RP-HPLC Conditions Chromatographic Trace:



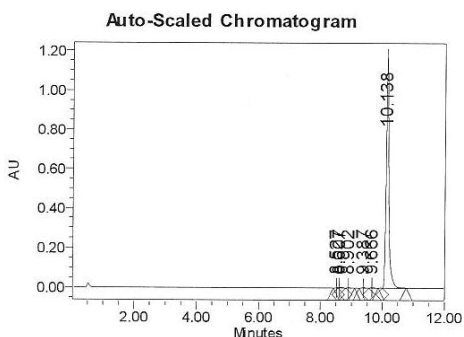
Unknown Peak Results

RT	Height	Area	% Area
1 3.275	1142	11788	0.20
2 4.587	1406	16213	0.27
3 6.887	1323	16488	0.28
4 8.124	8038	77312	1.31
5 9.705	560278	5775742	97.93

2-(3-Chlorophenyl)benzoxazole (1c).

Refer to the main text for experimental procedures.

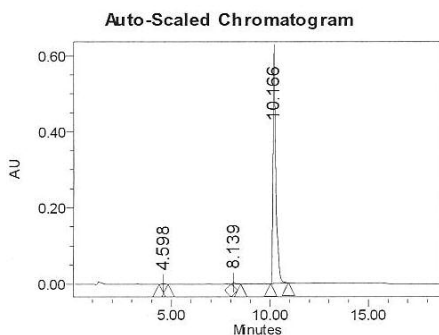
Primary RP-HPLC Conditions Chromatographic Trace:



Unknown Peak Results

RT	Height	Area	% Area
1 8.527	1700	8196	0.11
2 8.607	2010	18171	0.25
3 8.902	1313	9173	0.12
4 9.387	1867	13018	0.18
5 9.666	3694	21622	0.29
6 10.138	1170957	7290095	99.05

Secondary RP-HPLC Conditions Chromatographic Trace:



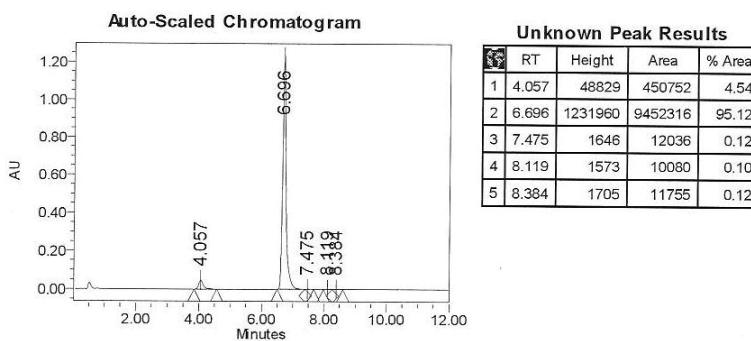
Unknown Peak Results

RT	Height	Area	% Area
1 4.598	1111	12044	0.19
2 8.139	4054	38995	0.63
3 10.166	604957	6179323	99.18

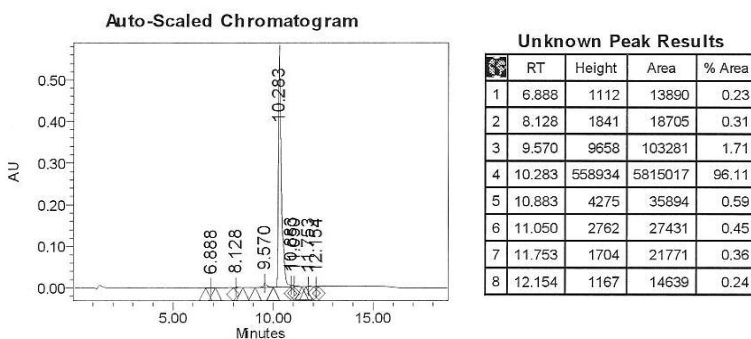
2-(3-Bromophenyl)benzoxazole (**1d**).

3-Bromobenzoic acid (196 mg, 0.975 mmol), 2-aminophenol (88.0 mg, 0.806 mmol), and *p*-TsOH•H₂O (769 mg, 4.04 mmol) were stirred in refluxing xylenes (10 mL). After 6 h the reaction was cooled, extracted into EtOAc (50 mL), and washed with saturated NaHCO₃ (2x25 mL) and brine (25 mL). The organics were then dried over Na₂SO₄, filtered, and concentrated. Flash chromatographic purification over silica (9:1-4:1 hexanes:EtOAc gradient elution) afforded 2-(3-bromophenyl)benzoxazole (**1d**) as an off-white solid (30.4 mg, 14%). ¹H-NMR (500 MHz, *d*₆-DMSO) δ 8.30 (t, *J*=1.8 Hz, 1H), 8.19 (ddd, *J*=1.0, 1.6, 7.8 Hz, 1H), 7.79-7.85 (m, 3H), 7.58 (dt, *J*=0.3, 7.9 Hz, 1H), 7.41-7.48 (m, 2H); ¹³C-NMR (125 MHz, *d*₆-DMSO) δ 160.76, 150.30, 141.30, 134.61, 131.61, 129.58, 128.61, 126.26, 126.00, 125.13, 122.39, 120.07, 111.14; ESI-TOF 214.0658 *m/z* [MH]⁺, C₁₃H₉FNO requires 214.0663; RP-HPLC: 95% & 96% pure.

Primary RP-HPLC Conditions Chromatographic Trace:



Secondary RP-HPLC Conditions Chromatographic Trace:

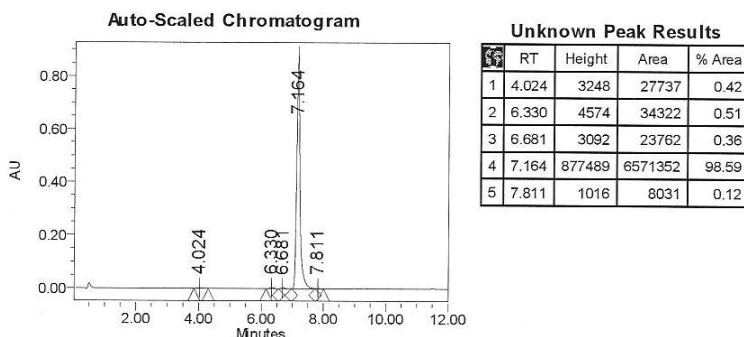


2-(3-Iodophenyl)benzoxazole (**1e**).

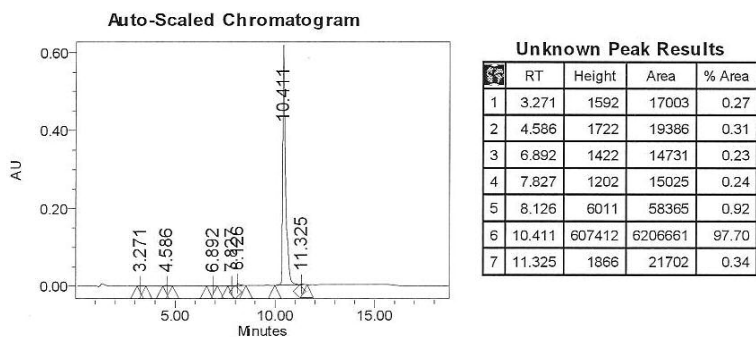
3-Iodobenzoic acid (289 mg, 1.16 mmol), 2-aminophenol (104 mg, 0.957 mmol), and *p*-TsOH•H₂O (910 mg, 4.78 mmol) were stirred in refluxing xylenes (10 mL). After 20 h the reaction was cooled, extracted into EtOAc (50 mL), and washed with saturated NaHCO₃ (2x25 mL) and brine (25 mL). The organics were then dried over Na₂SO₄, filtered, and concentrated. Flash chromatographic purification over silica (9:1 hexanes:EtOAc) afforded 2-(3-iodophenyl)benzoxazole (**1e**) as a pale yellow solid (27.1 mg, 9%). ¹H-NMR (500 MHz, *d*₆-DMSO) δ 8.48 (t, *J*=1.6 Hz, 1H), 8.20 (ddd, *J*=1.1, 1.6, 7.8 Hz, 1H), 7.99 (ddd, *J*=1.0, 1.7, 7.9 Hz, 1H), 7.78-7.83 (m, 2H), 7.39-7.47 (m, 3H); ¹³C-NMR (125 MHz, *d*₆-DMSO) δ 160.69, 150.29, 141.31, 140.42, 135.35, 131.44,

128.44, 126.52, 125.92, 125.09, 120.03, 111.12, 95.44; ESI-TOF 321.9718 m/z $[MH]^+$, $C_{13}H_9INO$ requires 321.9723; RP-HPLC: 98% & 98% pure.

Primary RP-HPLC Conditions Chromatographic Trace:



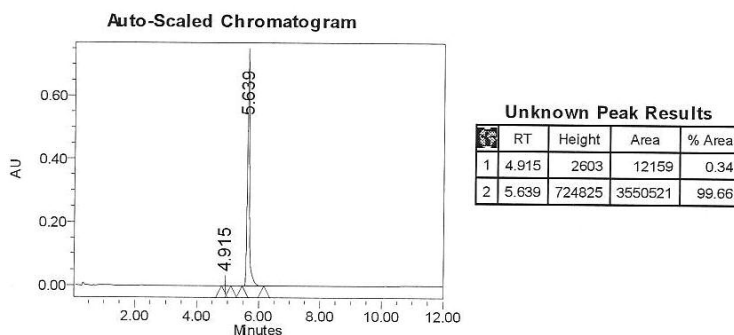
Secondary RP-HPLC Conditions Chromatographic Trace:



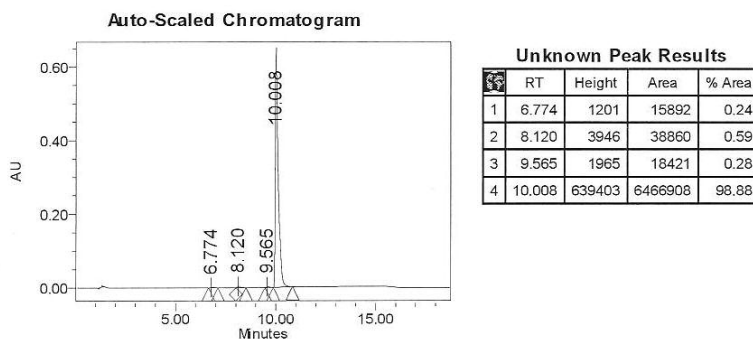
2-(3-Methylphenyl)benzoxazole (1f).

m-Toluoyl chloride (0.15 mL, 1.14 mmol), 2-aminophenol (105 mg, 0.961 mmol), and pyridine (78.5 μ L, 0.963 mmol) were stirred in xylenes (10 mL) at room temperature for 1 hour, then *p*-TsOH \cdot H₂O (915 mg, 4.81 mmol) was added and the reaction was stirred at reflux. After 18 h the reaction was cooled, extracted into EtOAc (50 mL), and washed with saturated NaHCO₃ (2x25 mL) and brine (25 mL). The organics were then dried over Na₂SO₄, filtered, and concentrated. Flash chromatographic purification over silica (9:1 hexanes:EtOAc) afforded 2-(3-methylphenyl)benzoxazole (**1f**) as a white solid (116 mg, 57%). ¹H-NMR (500 MHz, CDCl₃) δ 8.09-8.12 (m, 1H), 8.04-8.07 (m, 1H), 7.75-7.79 (m, 1H), 7.56-7.60 (m, 1H), 7.41 (t J =7.6 Hz, 1H), 7.33-7.37 (m, 3H), 2.46 (s, 3H); ¹³C-NMR (125 MHz, CDCl₃) δ 163.28, 150.77, 142.14, 138.76, 132.38, 128.84, 128.21, 127.05, 125.04, 124.78, 124.55, 119.98, 110.56, 21.36; ESI-TOF 210.0914 m/z $[MH]^+$, $C_{14}H_{12}NO$ requires 210.0913; RP-HPLC: >99% & 99% pure.

Primary RP-HPLC Conditions Chromatographic Trace:



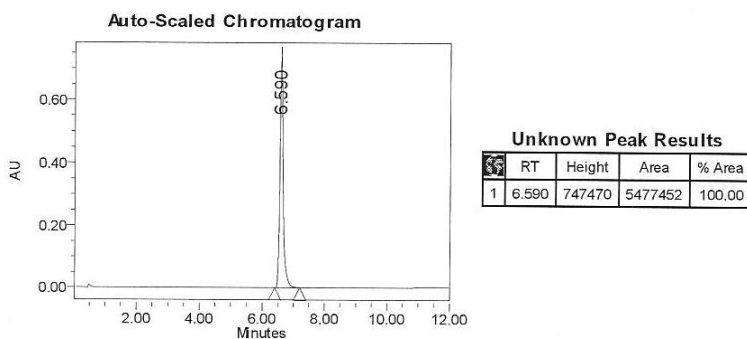
Secondary RP-HPLC Conditions Chromatographic Trace:



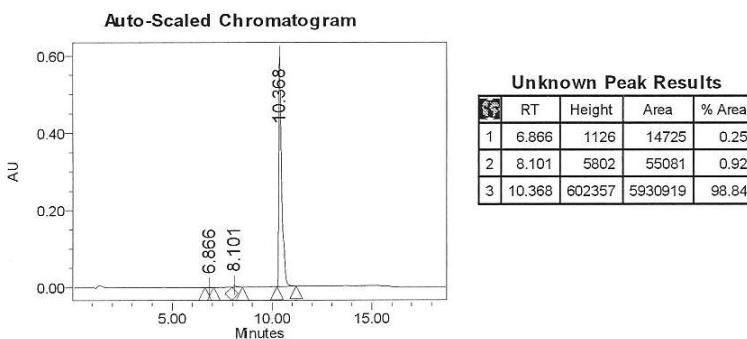
2-(3-Trifluoromethylphenyl)benzoxazole (1g**).**

3-Trifluoromethylbenzoyl chloride (0.19 mL, 1.26 mmol), 2-aminophenol (115 mg, 1.05 mmol), and pyridine (86.0 μ L, 1.05 mmol) were stirred in xylenes (10 mL) at room temperature for 1 hour, then *p*-TsOH \cdot H₂O (996 mg, 5.24 mmol) was added and the reaction was stirred at reflux. After 5 h the reaction was cooled, extracted into EtOAc (50 mL), and washed with saturated NaHCO₃ (2x25 mL) and brine (25 mL). The organics were then dried over Na₂SO₄, filtered, and concentrated. Flash chromatographic purification over silica (9:1 hexanes:EtOAc) afforded 2-(3-trifluoromethylphenyl)benzoxazole (**1g**) as a white solid (109 mg, 39%). ¹H-NMR (500 MHz, CDCl₃) δ 8.52-8.54 (m, 1H), 8.42-8.45 (m, *J*=7.9 Hz, 1H), 7.77-7.81 (m, 2H), 7.66 (tt, *J*=0.6, 7.8 Hz, 1H), 7.59-7.63 (m, 1H), 7.36-7.42 (m, 2H); ¹³C-NMR (125 MHz, CDCl₃) δ 161.52, 150.84, 141.91, 131.66 (q, *J*=33.0 Hz), 130.63, 129.56, 128.09, 127.94 (q, *J*=3.7 Hz), 125.74, 124.95, 124.53 (q, *J*=4.1 Hz), 123.72 (d, *J*=272 Hz), 120.35, 110.79; ESI-TOF 264.0636 *m/z* [MH]⁺, C₁₄H₉F₃NO requires 264.0631; RP-HPLC: >99% & 99% pure.

Primary RP-HPLC Conditions Chromatographic Trace:



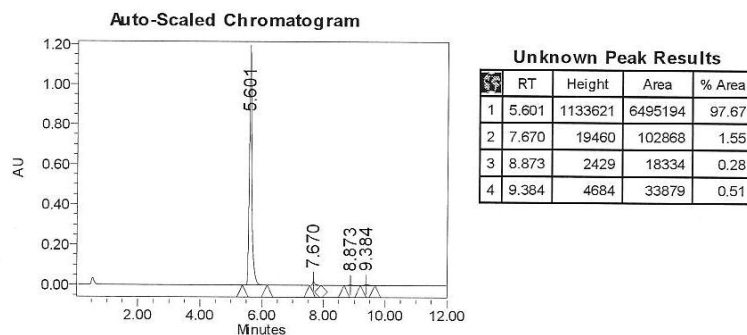
Secondary RP-HPLC Conditions Chromatographic Trace:



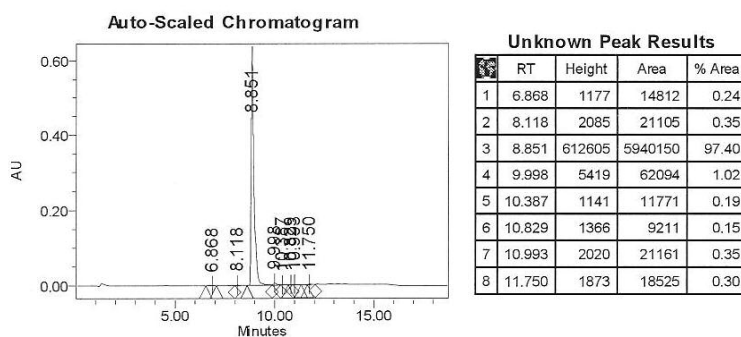
2-(3-Hydroxyphenyl)benzoxazole (1h).

3-Hydroxybenzoic acid (153 mg, 1.11 mmol), 2-aminophenol (100 mg, 0.916 mmol), and *p*-TsOH•H₂O (878 mg, 4.62 mmol) were stirred in refluxing xylenes (10 mL). After 4 h the reaction was cooled, extracted into EtOAc (50 mL), and washed with saturated NaHCO₃ (2x25 mL) and brine (25 mL). The organics were then dried over Na₂SO₄, filtered, and concentrated. Flash chromatographic purification over silica (4:1-1:1 hexanes:EtOAc gradient elution) afforded 2-(3-hydroxyphenyl)benzoxazole (**1h**) as a tan solid (77.0 mg, 40%). ¹H-NMR (500 MHz, *d*₆-DMSO) δ 9.95 (s, 1H), 7.76-7.81 (m, 2H), 7.63 (dt, *J*=1.2, 7.7 Hz, 1H), 7.59 (dd, *J*=1.7, 2.3 Hz, 1H), 7.37-7.44 (m, 3H), 7.02 (ddd, *J*=0.9, 2.5, 8.2 Hz, 1H); ¹³C-NMR (125 MHz, *d*₆-DMSO) δ 162.33, 157.92, 150.18, 141.49, 130.54, 127.53, 125.49, 124.87, 119.81, 119.16, 118.05, 113.66, 110.93; ESI-TOF 212.0699 *m/z* [MH]⁺, C₁₃H₁₀NO₂ requires 212.0706; RP-HPLC: 98% & 97% pure.

Primary RP-HPLC Conditions Chromatographic Trace:



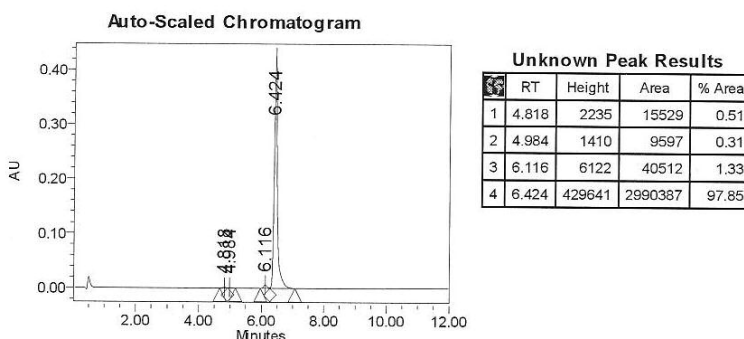
Secondary RP-HPLC Conditions Chromatographic Trace:



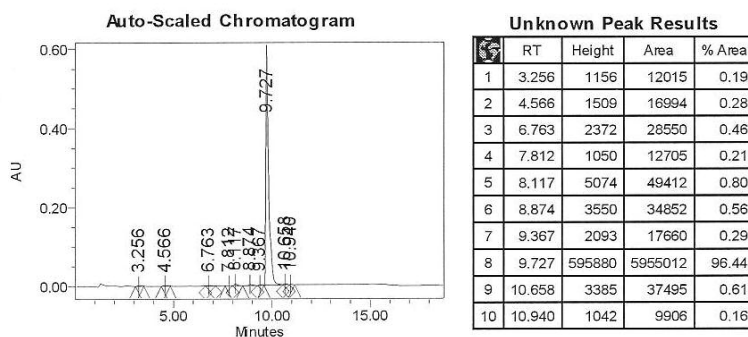
2-(3-Methoxyphenyl)benzoxazole (1i).

Refer to the main text for experimental procedures.

Primary RP-HPLC Conditions Chromatographic Trace:



Secondary RP-HPLC Conditions Chromatographic Trace:

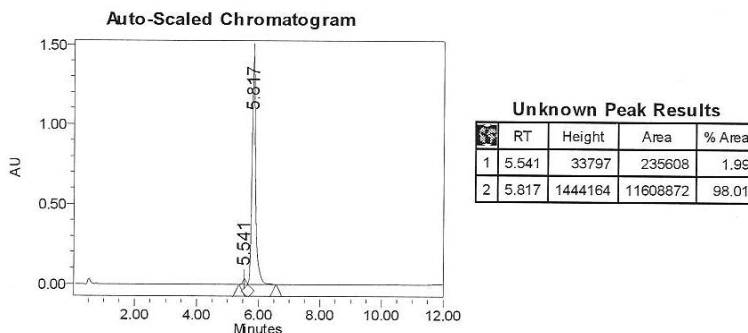


2-(3,5-Difluorophenyl)benzoxazole (2b).

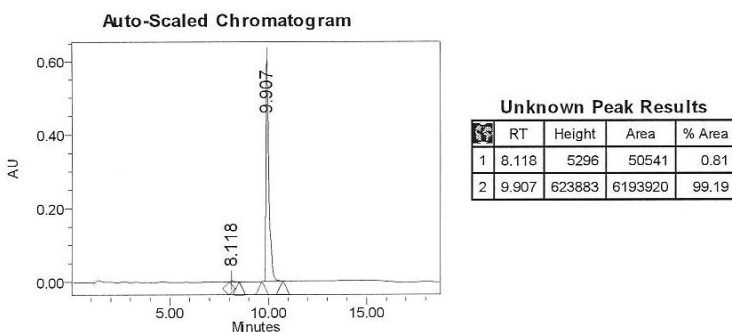
3,5-Difluorobenzoyl chloride (236 mg, 1.34 mmol) and 2-aminophenol (120 mg, 1.10 mmol), were stirred in xylenes (10 mL) at room temperature for 5 minutes, then *p*-TsOH•H₂O (1.06 g, 5.57 mmol) was added and the reaction was stirred at reflux. After 2 h the reaction was cooled, extracted into EtOAc (50 mL), and washed with saturated NaHCO₃ (2x25 mL) and brine (25 mL). The organics were then dried over Na₂SO₄, filtered, and concentrated. Flash chromatographic purification over silica (9:1 hexanes:EtOAc) afforded 2-(3,5-difluorophenyl)benzoxazole (**2b**) as a white solid (88.0 mg, 35%). ¹H-NMR (500 MHz, CDCl₃) δ 7.75-7.81 (m, 3H), 7.57-7.62 (m, 1H), 7.36-7.43 (m, 2H), 6.98 (tt, *J*=2.4, 8.7 Hz, 1H); ¹³C-NMR (125 MHz, CDCl₃) δ 163.24, (dd,

$J=12.4$, 250 Hz), 160.75 (t, $J=3.9$ Hz), 150.81, 141.81, 130.13 (t, $J=10.5$ Hz), 125.94, 125.02, 120.46, 110.81, 110.5-110.8 (m), 106.85 (t, $J=25.2$ Hz); ESI-TOF 232.0566 m/z $[MH]^+$, $C_{13}H_8F_2NO$ requires 232.0568; RP-HPLC: 98% & >99% pure.

Primary RP-HPLC Conditions Chromatographic Trace:



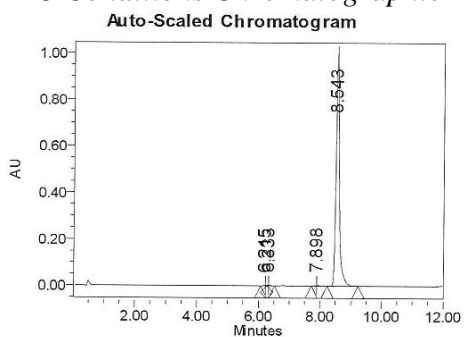
Secondary RP-HPLC Conditions Chromatographic Trace:



2-(3,5-Dichlorophenyl)benzoxazole (2c).

3,5-Dichlorobenzoyl chloride (270 mg, 1.29 mmol), 2-aminophenol (111 mg, 1.02 mmol), and pyridine (83.0 μ L, 1.02 mmol) were stirred in xylenes (10 mL) at room temperature for 1 hour, then *p*-TsOH \cdot H₂O (969 mg, 5.09 mmol) was added and the reaction was stirred at reflux. After 5 h the reaction was cooled, extracted into EtOAc (50 mL), and washed with saturated NaHCO₃ (2x25 mL) and brine (25 mL). The organics were then dried over Na₂SO₄, filtered, and concentrated. Flash chromatographic purification over silica (9:1 hexanes:EtOAc) afforded 2-(3,5-dichlorophenyl)benzoxazole (**2c**) as a pale yellow solid (112 mg, 41%). ¹H-NMR (500 MHz, CDCl₃) δ 8.14 (d, $J=1.9$ Hz, 2H), 7.77-7.80 (m, 1H), 7.58-7.62 (m, 1H), 7.50 (t, $J=1.9$ Hz, 1H), 7.37-7.42 (m, 2H); ¹³C-NMR (125 MHz, CDCl₃) δ 160.38, 150.80, 141.73, 135.80, 131.24, 129.88, 125.96, 125.83, 125.04, 120.43, 110.81; ESI-TOF 263.9976 m/z $[MH]^+$, $C_{13}H_8Cl_2NO$ requires 263.9976; RP-HPLC: >99% & 97% pure.

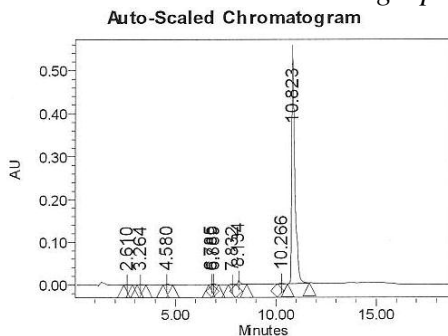
Primary RP-HPLC Conditions Chromatographic Trace:



Unknown Peak Results

RT	Height	Area	% Area
1 6.215	1271	7733	0.10
2 6.333	1486	10656	0.14
3 7.898	2996	21405	0.28
4 8.543	998188	7493110	99.47

Secondary RP-HPLC Conditions Chromatographic Trace:



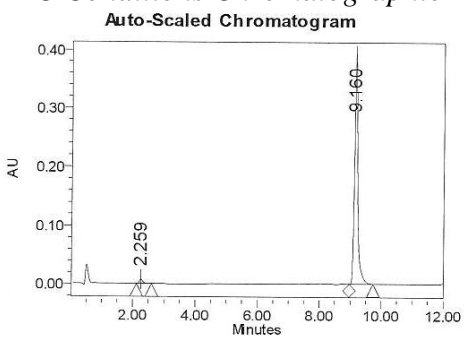
Unknown Peak Results

RT	Height	Area	% Area
1 2.610	1274	15262	0.25
2 3.264	1481	15787	0.26
3 4.580	1753	19957	0.33
4 6.785	1752	10621	0.17
5 6.889	1889	16530	0.27
6 7.832	1073	13169	0.22
7 8.134	9174	88368	1.45
8 10.266	1616	25057	0.41
9 10.823	543012	5907164	96.65

2-(3,5-Dibromophenyl)benzoxazole (2d).

Refer to the main text for experimental procedures.

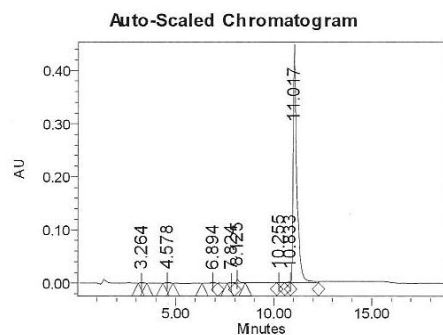
Primary RP-HPLC Conditions Chromatographic Trace:



Unknown Peak Results

RT	Height	Area	% Area
1 2.259	7848	59822	1.98
2 9.160	394219	2968164	98.02

Secondary RP-HPLC Conditions Chromatographic Trace:



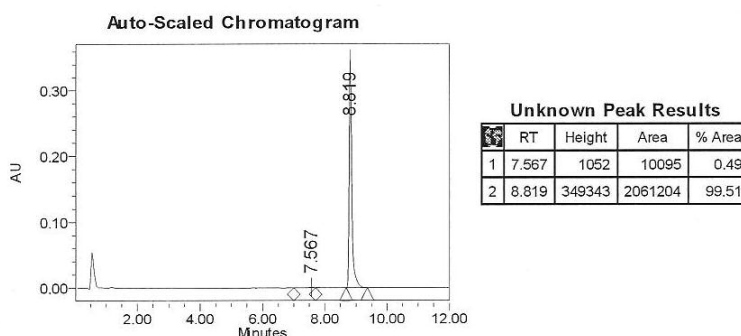
Unknown Peak Results

RT	Height	Area	% Area
1 3.264	1467	15691	0.27
2 4.578	1818	20656	0.35
3 6.894	1534	19280	0.33
4 7.824	1350	17006	0.29
5 8.125	6872	66390	1.13
6 10.255	1116	20328	0.35
7 10.833	1228	16582	0.28
8 11.017	430570	5685450	97.00

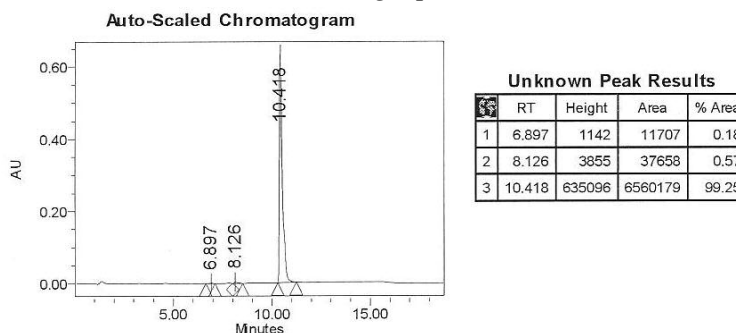
2-(3,5-Dimethylphenyl)benzoxazole (2f).

3,5-Dimethylbenzoic acid (166 mg, 1.10 mmol), 2-aminophenol (100 mg, 0.920 mmol), and *p*-TsOH•H₂O (875 mg, 4.60 mmol) were stirred in refluxing xylenes (10 mL). After 18 h the reaction was cooled, extracted into EtOAc (50 mL), and washed with saturated NaHCO₃ (2x25 mL) and brine (25 mL). The organics were then dried over Na₂SO₄, filtered, and concentrated. Flash chromatographic purification over silica (9:1 hexanes:EtOAc) afforded 2-(3,5-dimethylphenyl)benzoxazole (**2f**) as a white solid (180 mg, 87%). ¹H-NMR (500 MHz, CDCl₃) δ 7.88-7.90 (m, 2H), 7.74-7.78 (m, 1H), 7.55-7.58 (m, 1H), 7.32-7.36 (m, 2H), 7.16-7.18 (m, 1H), 2.41 (s, 6H); ¹³C-NMR (125 MHz, CDCl₃) δ 163.47, 150.74, 142.14, 138.63, 133.33, 126.91, 125.40, 124.96, 124.51, 119.92, 110.52, 21.45; ESI-TOF 224.1069 *m/z* [MH]⁺, C₁₅H₁₄NO requires 224.1070; RP-HPLC: >99% & >99% pure.

Primary RP-HPLC Conditions Chromatographic Trace:



Secondary RP-HPLC Conditions Chromatographic Trace:

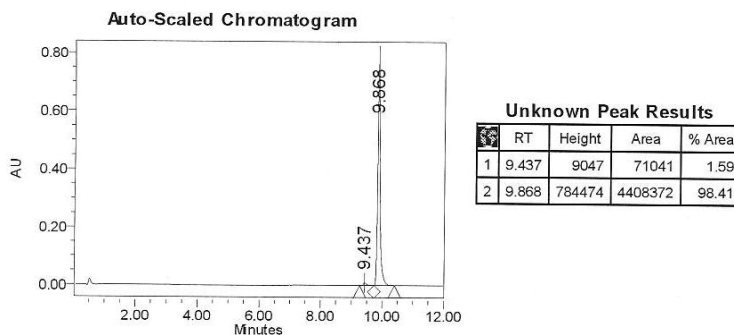


2-(3,5-Bis(trifluoromethyl)phenyl)benzoxazole (2g).

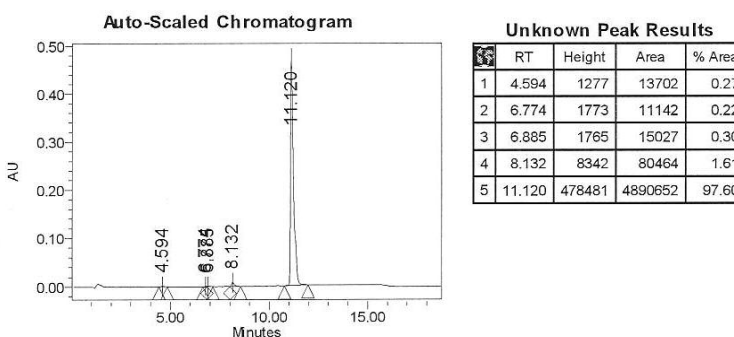
3,5-Bis(trifluoromethyl)benzoyl chloride (0.22 mL, 1.21 mmol), 2-aminophenol (109 mg, 1.00 mmol), and pyridine (82.0 μL, 1.01 mmol) were stirred in xylenes (10 mL) at room temperature for 1 hour, then *p*-TsOH•H₂O (952 mg, 5.00 mmol) was added and the reaction was stirred at reflux. After 4 h the reaction was cooled, extracted into EtOAc (50 mL), and washed with saturated NaHCO₃ (2x25 mL) and brine (25 mL). The organics were then dried over Na₂SO₄, filtered, and concentrated. Flash chromatographic purification over silica (9:1 hexanes:EtOAc) afforded 2-(3,5-bis(trifluoromethyl)phenyl)benzoxazole (**2g**) as a white solid (201 mg, 61%). ¹H-NMR (500 MHz, CDCl₃) δ 8.70-8.72 (m, 2H), 8.20-8.21 (m, 1H), 7.81-7.84 (m, 1H), 7.62-7.65 (m, 1H), 7.40-7.46 (m, 2H); ¹³C-NMR (125 MHz, CDCl₃) δ 160.00, 150.93, 141.70,

132.72 (q, $J=34.0$ Hz), 129.38, 127.52 (q, $J=3.4$ Hz), 126.40, 125.34, 124.55-124.75 (m), 122.96 (q, $J=273$ Hz), 120.68, 110.99; ESI-TOF 332.0507 m/z $[MH]^+$, $C_{15}H_7F_6NO$ requires 332.0505; RP-HPLC: 98% & 97% pure.

Primary RP-HPLC Conditions Chromatographic Trace:



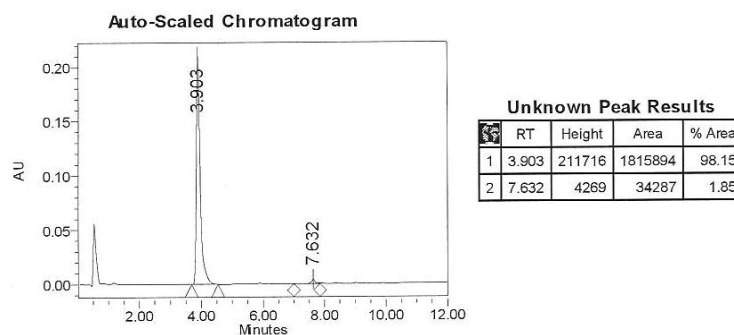
Secondary RP-HPLC Conditions Chromatographic Trace:



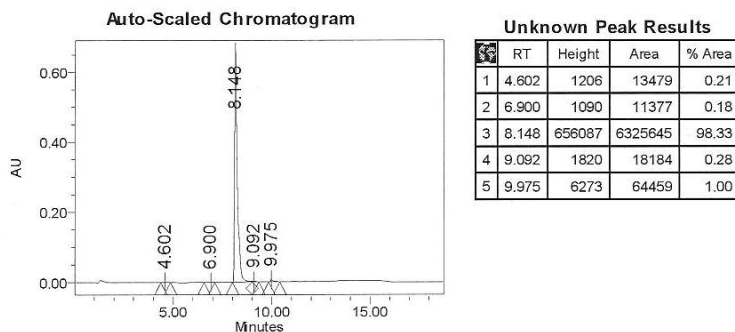
2-(3,5-Dihydroxyphenyl)benzoxazole (2h).

Refer to the main text for experimental procedures.

Primary RP-HPLC Conditions Chromatographic Trace:



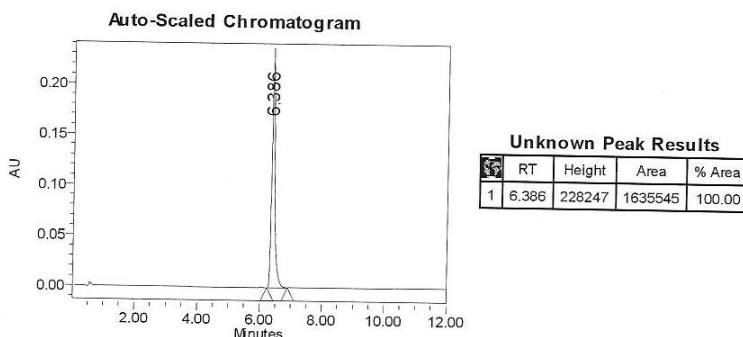
Secondary RP-HPLC Conditions Chromatographic Trace:



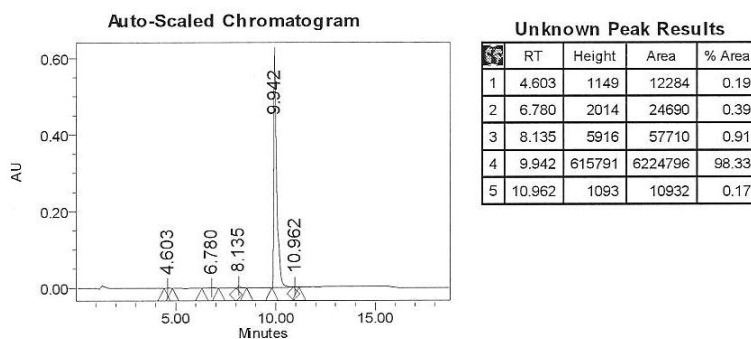
2-(3,5-Dimethoxyphenyl)benzoxazole (2i).

3,5-Dimethoxybenzoyl chloride (636 mg, 3.17 mmol), 2-aminophenol (287 mg, 2.63 mmol), and pyridine (0.22 mL, 2.70 mmol) were stirred in xylenes (10 mL) at room temperature for 1 hour, then *p*-TsOH•H₂O (2.50 g, 13.1 mmol) was added and the reaction was stirred at reflux. After 3 h the reaction was cooled, extracted into EtOAc (100 mL), and washed with saturated NaHCO₃ (2x50 mL) and brine (50 mL). The organics were then dried over Na₂SO₄, filtered, and concentrated. Flash chromatographic purification over silica (2:1 hexanes:EtOAc) afforded 2-(3,5-dimethoxyphenyl)benzoxazole (**2i**) as a pale yellow solid (402 mg, 60%). ¹H-NMR (500 MHz, *d*₆-DMSO) δ 7.76-7.81 (m, 2H), 7.38-7.45 (m, 2H), 7.29 (d, *J*=2.3 Hz, 2H), 6.34 (t, *J*=2.3 Hz, 1H), 3.84 (s, 6H); ¹³C-NMR (125 MHz, *d*₆-DMSO) δ 162.01, 160.92, 150.19, 141.36, 128.12, 125.68, 124.95, 119.88, 111.01, 104.85, 104.19, 55.57; ESI-TOF 256.0970 *m/z* [MH]⁺, C₁₅H₁₄NO₃ requires 256.0968; RP-HPLC: >99% & 98% pure.

Primary RP-HPLC Conditions Chromatographic Trace:



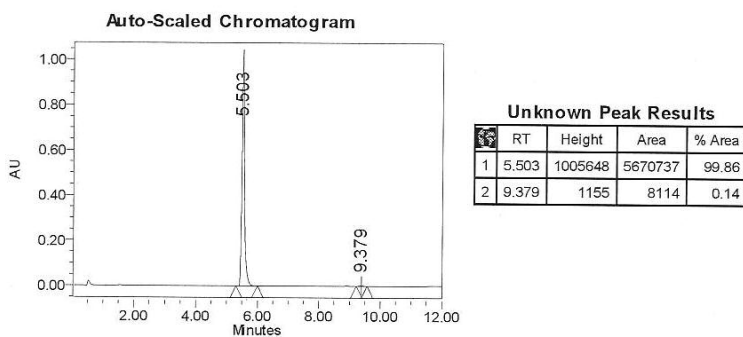
Secondary RP-HPLC Conditions Chromatographic Trace:



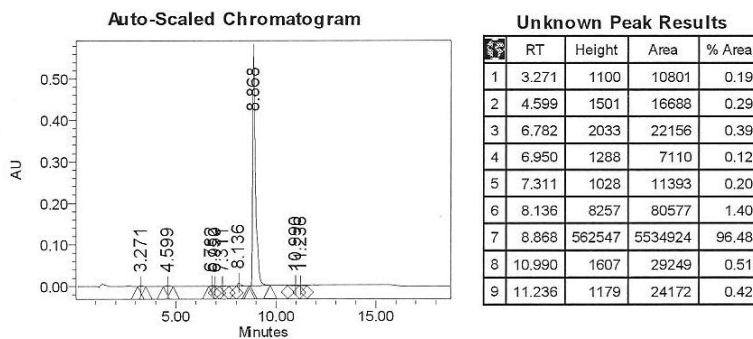
2-(4-Hydroxyphenyl)benzoxazole (3a).

4-Hydroxybenzoic acid (134 mg, 0.972 mmol), 2-aminophenol (88.0 mg, 0.806 mmol), and *p*-TsOH·H₂O (765 mg, 4.02 mmol) were stirred in refluxing xylenes (10 mL). After 4 h the reaction was cooled, extracted into EtOAc (50 mL), and washed with saturated NaHCO₃ (2x25 mL) and brine (25 mL). The organics were then dried over Na₂SO₄, filtered, and concentrated. Flash chromatographic purification over silica (2:1:1:1 hexanes:EtOAc gradient elution) afforded 2-(4-hydroxyphenyl)benzoxazole (**3a**) as an off-white solid (78.8 mg, 46%). ¹H-NMR (500 MHz, *d*₆-DMSO) δ 10.32 (s, 1H), 8.01-8.05 (m, 2H), 7.70-7.74 (m, 2H), 7.33-7.38 (m, 2H), 6.94-6.98 (m, 2H); ¹³C-NMR (125 MHz, *d*₆-DMSO) δ 162.77, 160.96, 150.05, 141.78, 129.33, 124.75, 124.61, 119.27, 117.17, 116.13, 110.60; ESI-TOF 212.0707 *m/z* [MH]⁺, C₁₃H₁₀NO₂ requires 212.0706; RP-HPLC: >99% & 96% pure.

Primary RP-HPLC Conditions Chromatographic Trace:



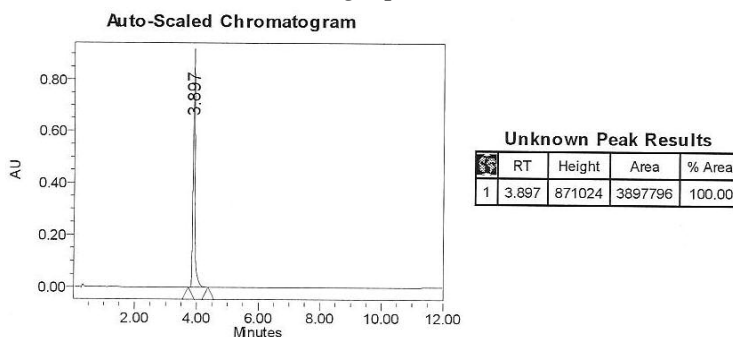
Secondary RP-HPLC Conditions Chromatographic Trace:



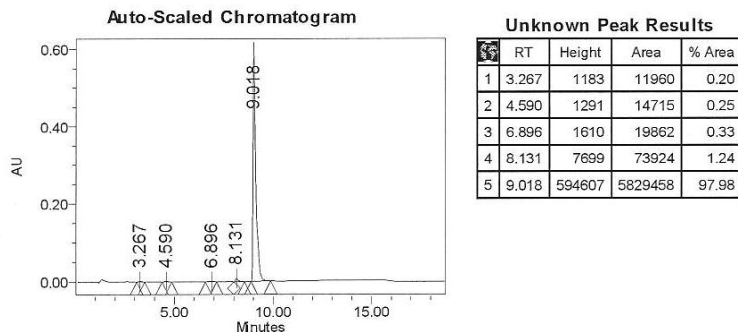
2-(3-Fluoro-4-hydroxyphenyl)benzoxazole (3b).

3-Fluoro-4-hydroxybenzoic acid (377 mg, 2.41 mmol), 2-aminophenol (220 mg, 2.02 mmol), and *p*-TsOH•H₂O (1.92 g, 10.1 mmol) were stirred in refluxing xylenes (20 mL). After 5 h the reaction was cooled, extracted into EtOAc (50 mL), and washed with saturated NaHCO₃ (2x25 mL) and brine (25 mL). The organics were then dried over Na₂SO₄, filtered, and concentrated. Flash chromatographic purification over silica (2:1-1:1 hexanes:EtOAc gradient elution) afforded 2-(3-fluoro-4-hydroxyphenyl)benzoxazole (**3b**) as a tan solid (115 mg, 25%). ¹H-NMR (500 MHz, *d*₆-DMSO) δ 10.82 (s, 1H), 7.85-7.91 (m, 2H), 7.71-7.76 (m, 2H), 7.35-7.41 (m, 2H), 7.15 (t, *J*=8.5 Hz, 1H); ¹³C-NMR (125 MHz, *d*₆-DMSO) δ 161.53 (d, *J*=2.9 Hz), 150.96 (d, *J*=243 Hz), 150.11, 148.73 (d, *J*=12.2 Hz), 141.58, 125.11, 124.77, 124.54 (d, *J*=2.9 Hz), 119.46, 118.43 (d, *J*=3.5 Hz), 117.60 (d, *J*=6.9 Hz), 115.10 (d, *J*=20.5 Hz), 110.72; ESI-TOF 230.0615 *m/z* [MH]⁺, C₁₃H₉FNO₂ requires 230.0612; RP-HPLC: >99% & 98% pure.

Primary RP-HPLC Conditions Chromatographic Trace:



Secondary RP-HPLC Conditions Chromatographic Trace:

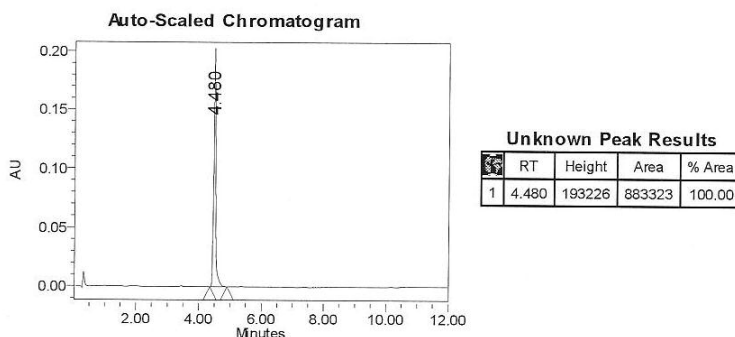


2-(3-Chloro-4-hydroxyphenyl)benzoxazole (3c).

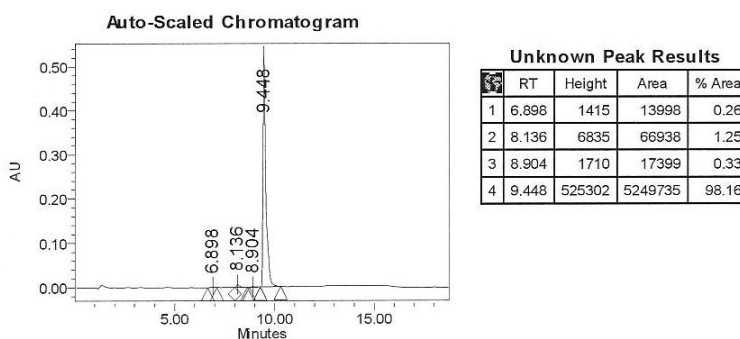
3-Chloro-4-hydroxybenzoic acid (892 mg, 5.17 mmol), 2-aminophenol (472 mg, 4.33 mmol), and *p*-TsOH•H₂O (4.09 g, 21.5 mmol) were stirred in refluxing xylenes (22 mL). After 18 h the reaction was cooled, extracted into EtOAc (100 mL), and washed with saturated NaHCO₃ (2x25 mL) and brine (25 mL). The organics were then dried over Na₂SO₄, filtered, and concentrated. Flash chromatographic purification over silica (2:1-1:1 hexanes:EtOAc gradient elution) afforded 2-(3-chloro-4-hydroxyphenyl)benzoxazole (**3c**) as a tan solid (116 mg, 11%). ¹H-NMR (500 MHz, *d*₆-DMSO) δ 11.15 (s, 1H), 8.10 (d, *J*=2.1 Hz, 1H), 7.99 (dd, *J*=2.2, 8.5 Hz, 1H), 7.72-7.77 (m, 2H), 7.36-7.41 (m, 2H), 7.16 (d, *J*=8.5 Hz, 1H); ¹³C-NMR (125 MHz, *d*₆-DMSO) δ

161.47, 156.50, 150.11, 141.56, 128.84, 127.63, 125.12, 124.78, 120.57, 119.47, 118.31, 117.25, 110.74; ESI-TOF 246.0323 m/z $[MH]^+$, $C_{13}H_9ClNO_2$ requires 246.0316; RP-HPLC: >99% & 98% pure.

Primary RP-HPLC Conditions Chromatographic Trace:



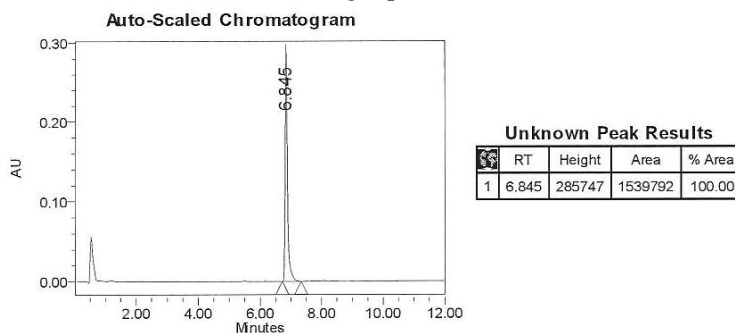
Secondary RP-HPLC Conditions Chromatographic Trace:



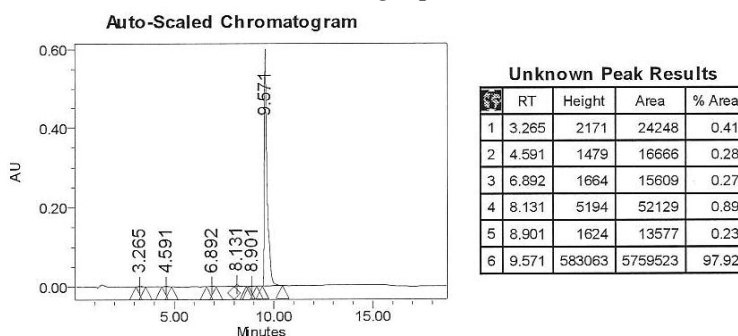
2-(3-Bromo-4-hydroxyphenyl)benzoxazole (3d).

3-Bromo-4-hydroxybenzoic acid (1.00 g, 4.63 mmol), 2-aminophenol (421 mg, 3.86 mmol), and *p*-TsOH \cdot H₂O (3.62 g, 19.0 mmol) were stirred in refluxing xylenes (20 mL). After 18 h the reaction was cooled, extracted into EtOAc (50 mL), and washed with saturated NaHCO₃ (2x25 mL) and brine (25 mL). The organics were then dried over Na₂SO₄, filtered, and concentrated. Flash chromatographic purification over silica (2:1-1:1 hexanes:EtOAc gradient elution) afforded 2-(3-bromo-4-hydroxyphenyl)benzoxazole (**3d**) as a tan solid (201 mg, 18%). ¹H-NMR (500 MHz, *d*₆-DMSO) δ 11.20 (s, 1H), 8.25 (d, *J*=2.1 Hz, 1H), 8.02 (dd, *J*=2.1, 8.5 Hz, 1H), 7.71-7.76 (m, 2H), 7.35-7.41 (m, 2H), 7.14 (d, *J*=8.5 Hz, 1H); ¹³C-NMR (125 MHz, *d*₆-DMSO) δ 161.33, 157.52, 150.11, 141.56, 131.86, 128.25, 125.10, 124.77, 119.46, 118.70, 116.89, 110.73, 109.95; ESI-TOF 289.9811 m/z $[MH]^+$, $C_{13}H_9BrNO_2$ requires 289.9811; RP-HPLC: >99% & 98% pure.

Primary RP-HPLC Conditions Chromatographic Trace:



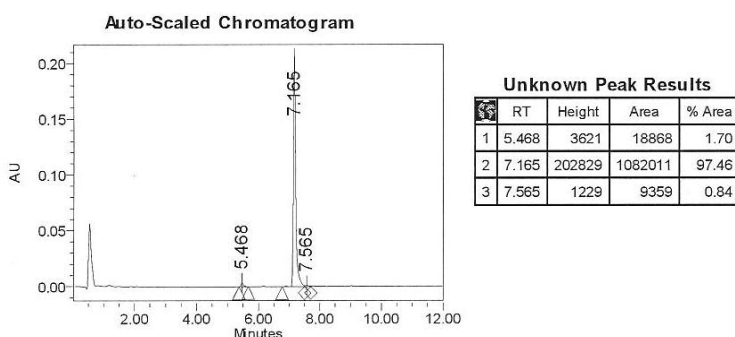
Secondary RP-HPLC Conditions Chromatographic Trace:



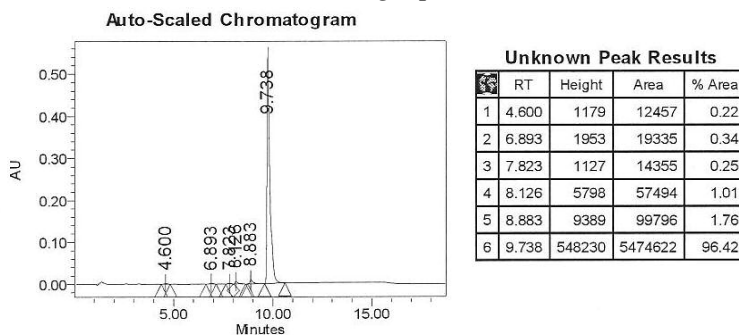
2-(3-Iodo-4-hydroxyphenyl)benzoxazole (3e).

Boron tribromide (0.88 mL of 1 M BBr₃ in hexanes, 0.88 mmol) was added to a stirring mixture of **5e** (61.5 mg, 0.175 mmol) in anhydrous CH₂Cl₂ (5.0 mL) and the reaction was stirred at room temperature under an argon atmosphere. After 18 h the reaction was quenched with MeOH (5 mL), extracted into EtOAc (50 mL), and washed with H₂O (2x25 mL) and brine (25 mL). The organics were then dried over Na₂SO₄, filtered, and concentrated. Flash chromatographic purification over silica (2:1 hexanes:EtOAc) afforded 2-(3-iodo-4-hydroxyphenyl)benzoxazole (**3e**) as an off-white solid (39.2 mg, 66%). ¹H-NMR (500 MHz, d₆-DMSO) δ 11.24 (s, 1H), 8.45 (d, *J*=2.1 Hz, 1H), 8.04 (dd, *J*=2.2, 8.5 Hz, 1H), 7.71-7.76 (m, 2H), 7.35-7.41 (m, 2H), 7.06 (d, *J*=8.5 Hz, 1H); ¹³C-NMR (125 MHz, d₆-DMSO) δ 161.21, 160.11, 150.09, 141.59, 137.88, 129.03, 125.03, 124.74, 119.42, 119.14, 115.39, 110.72, 85.17; ESI-TOF 337.9677 *m/z* [MH]⁺, C₁₃H₉INO₂ requires 337.9673; RP-HPLC: 97% & 96% pure.

Primary RP-HPLC Conditions Chromatographic Trace:



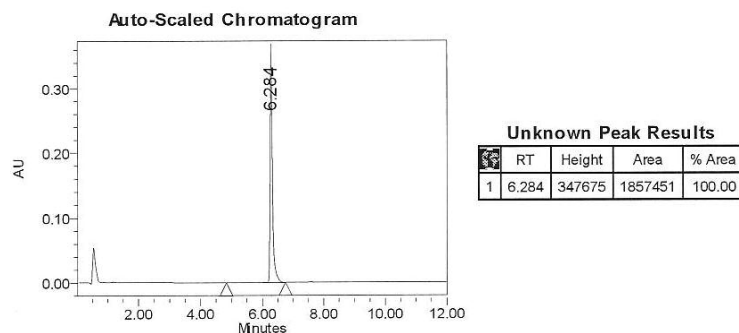
Secondary RP-HPLC Conditions Chromatographic Trace:



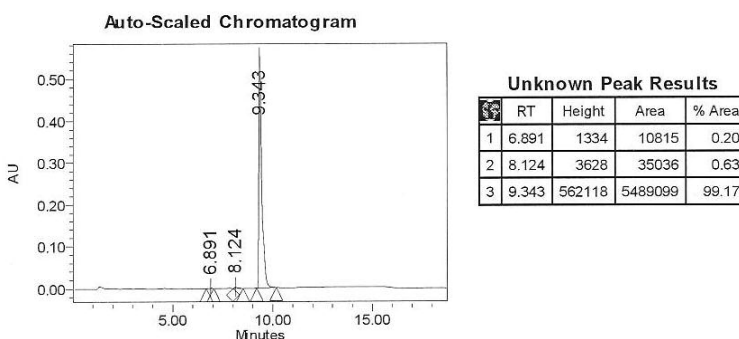
2-(3-Methyl-4-hydroxyphenyl)benzoxazole (3f).

3-Methyl-4-hydroxybenzoic acid (542 mg, 3.56 mmol), 2-aminophenol (326 mg, 2.99 mmol), and *p*-TsOH•H₂O (2.85 g, 15.0 mmol) were stirred in refluxing xylenes (30 mL). After 18 h the reaction was cooled, extracted into EtOAc (50 mL), and washed with saturated NaHCO₃ (2x25 mL) and brine (25 mL). The organics were then dried over Na₂SO₄, filtered, and concentrated. Flash chromatographic purification over silica (2:1-1:1 hexanes:EtOAc gradient elution) afforded 2-(3-methyl-4-hydroxyphenyl)benzoxazole (**3f**) as a reddish-brown crystalline solid (167 mg, 25%).
¹H-NMR (500 MHz, *d*₆-DMSO) δ 10.22 (s, 1H), 7.93 (d, *J*=1.4 Hz, 1H), 7.87 (dd, *J*=2.1, 8.4 Hz, 1H), 7.68-7.73 (m, 2H), 7.33-7.38 (m, 2H), 6.96 (d, *J*=8.4 Hz, 1H), 2.21 (s, 3H);
¹³C-NMR (125 MHz, *d*₆-DMSO) δ 161.33, 157.52, 150.11, 141.56, 131.86, 128.25, 125.10, 124.77, 119.46, 118.70, 116.89, 110.73, 109.95; ESI-TOF 226.0866 *m/z* [MH]⁺, C₁₄H₁₂NO₂ requires 226.0863; RP-HPLC: >99% & >99% pure.

Primary RP-HPLC Conditions Chromatographic Trace:



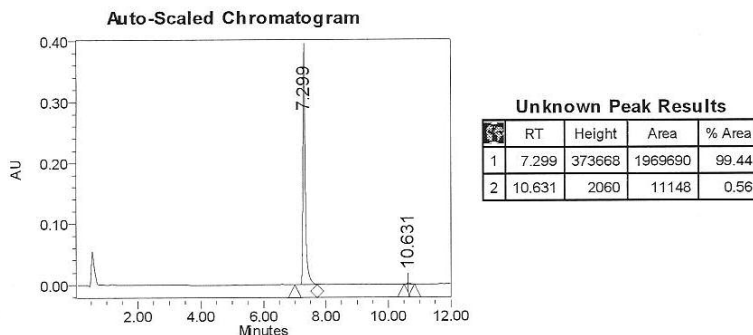
Secondary RP-HPLC Conditions Chromatographic Trace:



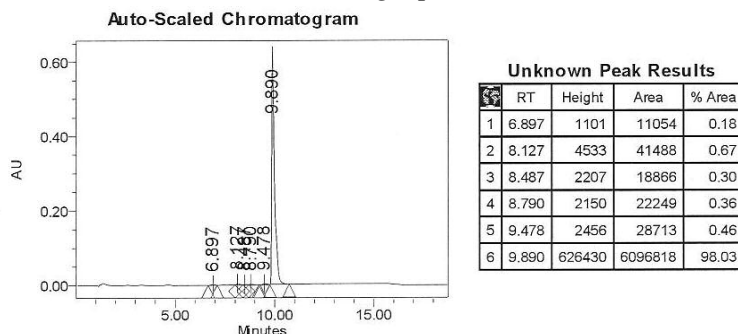
2-(3-Trifluoromethyl-4-hydroxyphenyl)benzoxazole (**3g**).

Boron tribromide (4.80 mL of 1 M BBr₃ in hexanes, 4.80 mmol) was added to a stirring mixture of **5g** (193 mg, 0.659 mmol) in anhydrous CH₂Cl₂ (7.0 mL) and the reaction was stirred at room temperature under an argon atmosphere. After 2 days the reaction was quenched with MeOH (5 mL), extracted into EtOAc (50 mL), and washed with H₂O (2x25 mL) and brine (25 mL). The organics were then dried over Na₂SO₄, filtered, and concentrated. Flash chromatographic purification over silica (2:1 hexanes:EtOAc) afforded 2-(3-trifluoromethyl-4-hydroxyphenyl)benzoxazole (**3g**) as an off-white solid (76.4 mg, 42%). ¹H-NMR (500 MHz, *d*₆-DMSO) δ 11.54 (s, 1H), 8.25-8.29 (m, 2H), 7.73-7.78 (m, 2H), 7.36-7.42 (m, 2H), 7.24 (d, *J*=8.6 Hz, 1H); ¹³C-NMR (125 MHz, *d*₆-DMSO) δ 161.47, 158.92, 150.15, 141.52, 132.85, 125.89 (q, *J*=5.6 Hz), 125.21, 124.84, 123.48 (q, *J*=272 Hz), 119.54, 118.04, 117.06, 116.24 (q, *J*=30.9 Hz), 110.82; ESI-TOF 280.0582 *m/z* [MH]⁺, C₁₄H₉F₃NO₂ requires 280.0580; RP-HPLC: >99% & 98% pure.

Primary RP-HPLC Conditions Chromatographic Trace:



Secondary RP-HPLC Conditions Chromatographic Trace:

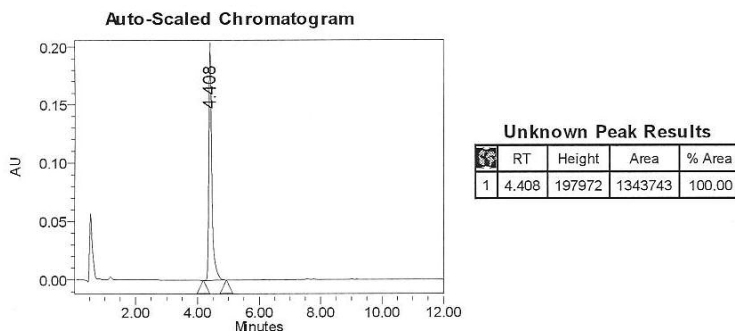


2-(3,4-Dihydroxyphenyl)benzoxazole (**3h**).

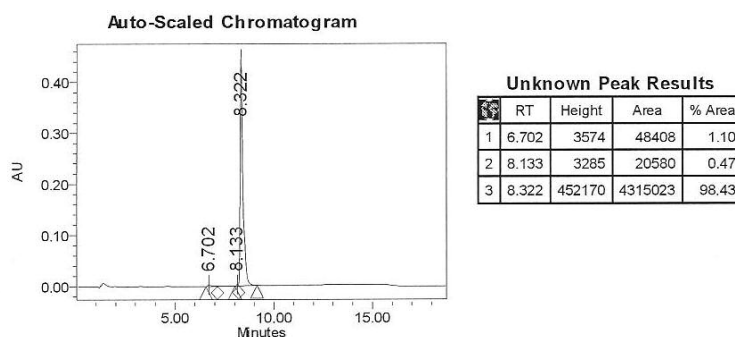
3,4-Dihydroxybenzoic acid (369 mg, 2.40 mmol), 2-aminophenol (216 mg, 1.98 mmol), and *p*-TsOH·H₂O (1.90 g, 10.0 mmol) were stirred in refluxing xylenes (20 mL). After 18 h the reaction was cooled, extracted into EtOAc (50 mL), and washed with saturated NaHCO₃ (2x25 mL) and brine (25 mL). The organics were then dried over Na₂SO₄, filtered, and concentrated. Flash chromatographic purification over silica (1:1 hexanes:EtOAc to 100% EtOAc gradient elution) afforded 2-(3,4-dihydroxyphenyl)benzoxazole (**3h**) as a brown-orange solid (185 mg, 41%). ¹H-NMR (500 MHz, *d*₆-DMSO) δ 9.78 (s, 1H), 9.50 (s, 1H), 7.68-7.73 (m, 2H), 7.58 (d, *J*=2.1 Hz,

1H), 7.52 (dd, $J=2.1, 8.3$ Hz, 1H), 7.32-7.37 (m, 2H), 6.92 (d, $J=8.3$ Hz, 1H); ^{13}C -NMR (125 MHz, d_6 -DMSO) δ 162.85, 150.04, 149.48, 145.78, 141.81, 124.64, 124.54, 119.65, 119.20, 117.37, 116.14, 114.30, 110.54; ESI-TOF 228.0657 m/z $[\text{MH}]^+$, $\text{C}_{13}\text{H}_{10}\text{NO}_3$ requires 228.0655; RP-HPLC: >99% & 98% pure.

Primary RP-HPLC Conditions Chromatographic Trace:



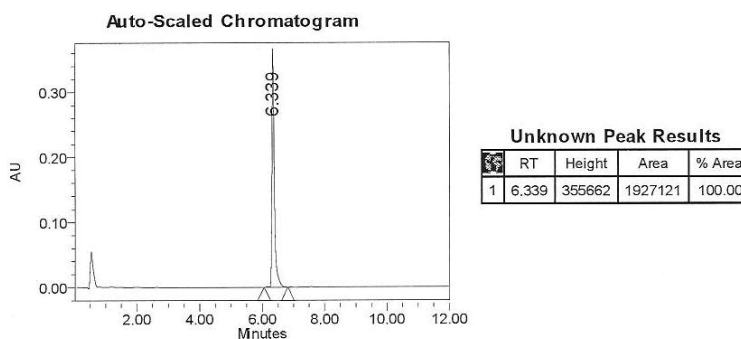
Secondary RP-HPLC Conditions Chromatographic Trace:



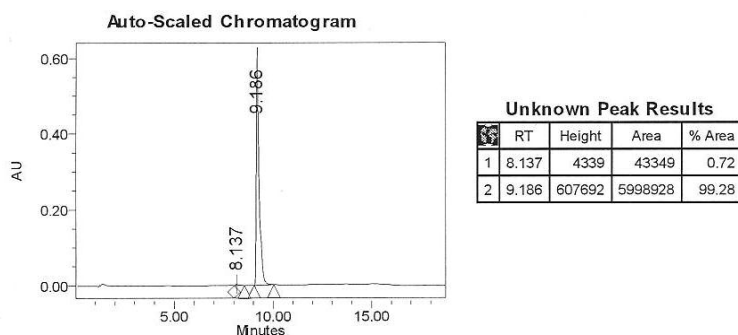
2-(3,5-Difluoro-4-hydroxyphenyl)benzoxazole (4b).

Boron tribromide (2.50 mL of 1 M BBr_3 in hexanes, 2.50 mmol) was added to a stirring mixture of **6b** (132 mg, 0.505 mmol) in anhydrous CH_2Cl_2 (5.0 mL) and the reaction was stirred at room temperature under an argon atmosphere. After 18 h the reaction was quenched with MeOH (5 mL), extracted into EtOAc (50 mL), and washed with H_2O (2x25 mL) and brine (25 mL). The organics were then dried over Na_2SO_4 , filtered, and concentrated. Flash chromatographic purification over silica (2:1 hexanes:EtOAc) afforded 2-(3,5-difluoro-4-hydroxyphenyl)benzoxazole (**4b**) as a tan solid (120 mg, 96%). ^1H -NMR (500 MHz, d_6 -DMSO) δ 11.22 (s, 1H), 7.71-7.83 (m, 4H), 7.36-7.44 (m, 2H); ^{13}C -NMR (125 MHz, d_6 -DMSO) δ 160.72 (t, $J=3.7$ Hz), 152.28 (dd, $J=7.4, 243$ Hz), 150.19, 141.42, 137.67 (t, $J=16.0$ Hz), 125.50, 124.94, 119.68, 116.43, 111.0-111.3 (m), 110.85; ESI-TOF 248.0522 m/z $[\text{MH}]^+$, $\text{C}_{13}\text{H}_8\text{F}_2\text{NO}_2$ requires 248.0518; RP-HPLC: >99% & >99% pure.

Primary RP-HPLC Conditions Chromatographic Trace:



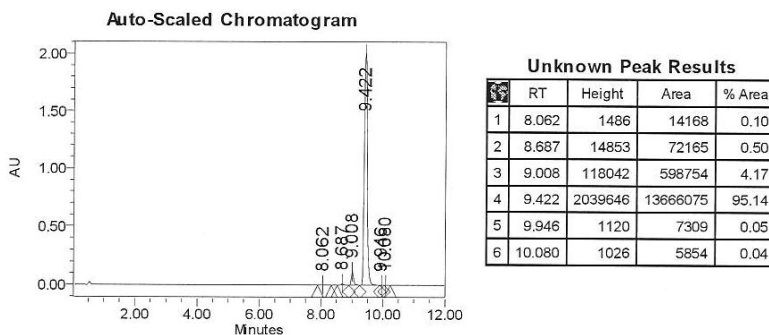
Secondary RP-HPLC Conditions Chromatographic Trace:



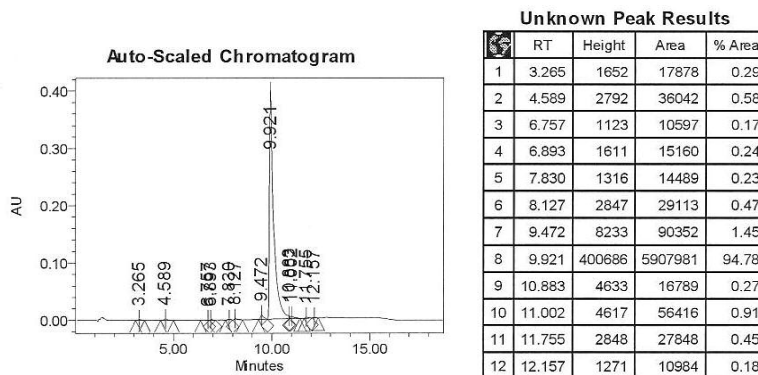
2-(3,5-Dichloro-4-hydroxyphenyl)benzoxazole (4c).

3,5-Dichloro-4-hydroxybenzoic acid (257 mg, 1.24 mmol), 2-aminophenol (112 mg, 1.03 mmol), and *p*-TsOH•H₂O (986 mg, 5.18 mmol) were stirred in refluxing xylenes (10 mL). After 18 h the reaction was cooled, extracted into EtOAc (50 mL), and washed with saturated NaHCO₃ (2x25 mL) and brine (25 mL). The organics were then dried over Na₂SO₄, filtered, and concentrated. Flash chromatographic purification over silica (2:1-1:1 hexanes:EtOAc gradient elution) afforded 2-(3,5-dichloro-4-hydroxyphenyl)benzoxazole (**4c**) as a tan solid (93.0 mg, 32%). ¹H-NMR (500 MHz, *d*₆-DMSO) δ 8.06 (s, 2H), 7.72-7.78 (m, 2H), 7.37-7.44 (m, 2H); ¹³C-NMR (125 MHz, *d*₆-DMSO) δ 160.24, 152.33, 150.22, 141.39, 127.35, 125.57, 125.00, 122.92, 119.74, 119.04, 110.92; ESI-TOF 279.9924 *m/z* [MH]⁺, C₁₃H₈Cl₂NO₂ requires 279.9927; RP-HPLC: 95% & 95% pure.

Primary RP-HPLC Conditions Chromatographic Trace:



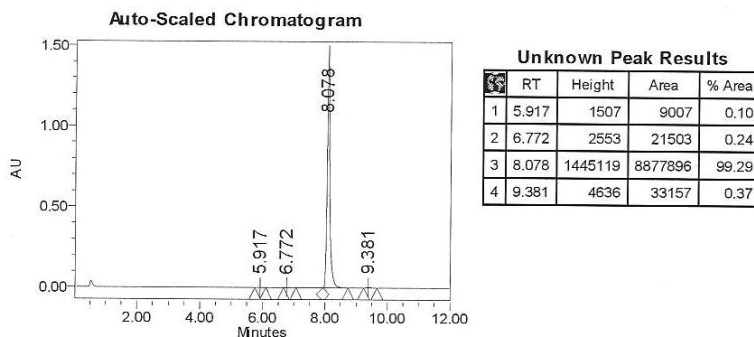
Secondary RP-HPLC Conditions Chromatographic Trace:



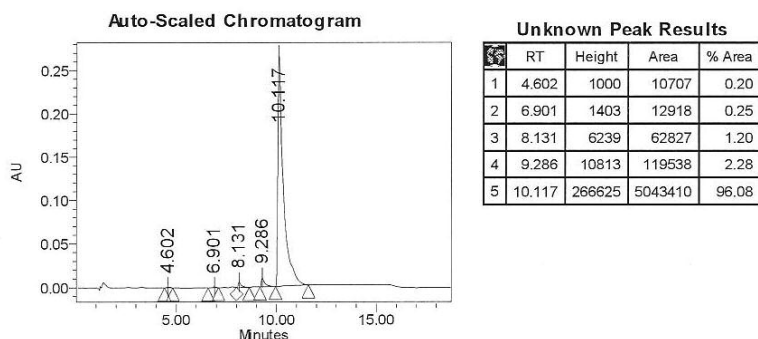
2-(3,5-Dibromo-4-hydroxyphenyl)benzoxazole (4d).

3,5-Dibromo-4-hydroxybenzoic acid (385 mg, 1.30 mmol), 2-aminophenol (117 mg, 1.08 mmol), and *p*-TsOH·H₂O (1.04 g, 5.48 mmol) were stirred in refluxing xylenes (10 mL). After 18 h the reaction was cooled, extracted into EtOAc (50 mL), and washed with saturated NaHCO₃ (2x25 mL) and brine (25 mL). The organics were then dried over Na₂SO₄, filtered, and concentrated. Flash chromatographic purification over silica (4:1-1:1 hexanes:EtOAc gradient elution) afforded 2-(3,5-dichloro-4-hydroxyphenyl)benzoxazole (**4c**) as a tan solid (67.2 mg, 17%). ¹H-NMR (500 MHz, *d*₆-DMSO) δ 10.76 (br s, 1H), 8.24 (s, 2H), 7.72-7.78 (m, 2H), 7.37-7.44 (m, 2H); ¹³C-NMR (125 MHz, *d*₆-DMSO) δ 159.95, 154.11, 150.22, 141.38, 130.99, 125.54, 124.98, 120.34, 119.72, 112.31, 110.92; ESI-TOF 367.8916 *m/z* [MH]⁺, C₁₃H₈Br₂NO₂ requires 367.8916; RP-HPLC: >99% & 96% pure.

Primary RP-HPLC Conditions Chromatographic Trace:



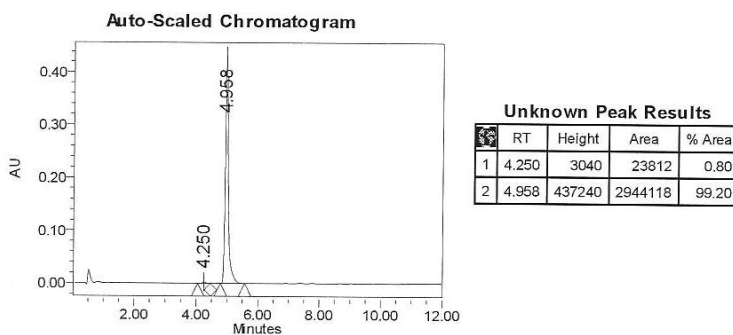
Secondary RP-HPLC Conditions Chromatographic Trace:



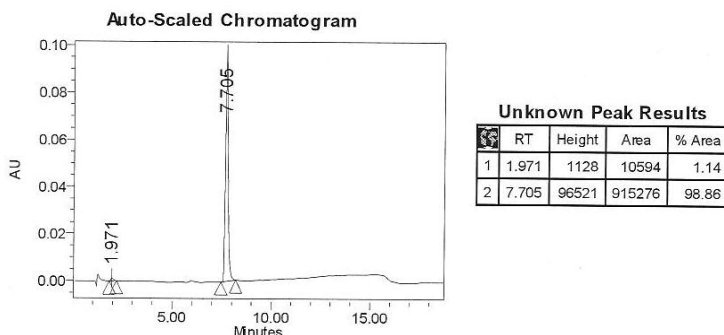
2-(3,5-Diiodo-4-hydroxyphenyl)benzoxazole (4e).

Boron tribromide (3.00 mL of 1 M BBr₃ in hexanes, 3.00 mmol) was added to a stirring mixture of **6e** (146 mg, 0.307 mmol) in anhydrous CH₂Cl₂ (3.0 mL) and the reaction was stirred at room temperature under an argon atmosphere. After 2 days the reaction was quenched with MeOH (5 mL), extracted into EtOAc (50 mL), and washed with H₂O (2x25 mL) and brine (25 mL). The organics were then dried over Na₂SO₄, filtered, and concentrated. Flash chromatographic purification over silica (2:1-1:1 hexanes:EtOAc gradient elution) afforded 2-(3,5-diiodo-4-hydroxyphenyl)benzoxazole (**4b**) as an off-white solid (122 mg, 86%). ¹H-NMR (500 MHz, *d*₆-DMSO) δ 10.40 (br, s, 1H), 8.45 (s, 2H), 7.73-7.78 (m, 2H), 7.36-7.43 (m, 2H); ¹³C-NMR (125 MHz, *d*₆-DMSO) δ 159.57, 158.83, 150.19, 141.41, 137.83, 125.44, 124.92, 121.90, 119.66, 110.91, 87.00; ESI-TOF 463.8634 *m/z* [MH]⁺, C₁₃H₈I₂NO₂ requires 463.8639; RP-HPLC: >99% & 99% pure.

Primary RP-HPLC Conditions Chromatographic Trace:



Secondary RP-HPLC Conditions Chromatographic Trace:

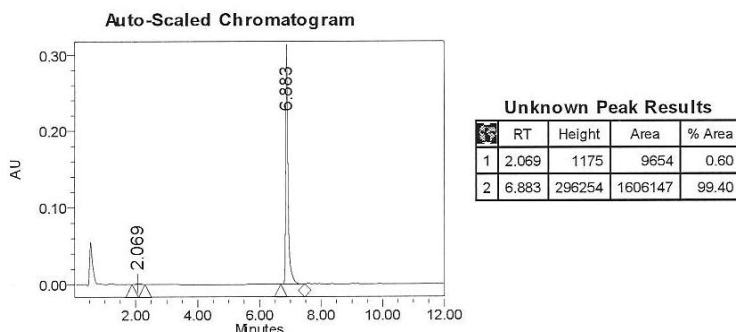


2-(3,5-Dimethyl-4-hydroxyphenyl)benzoxazole (4f).

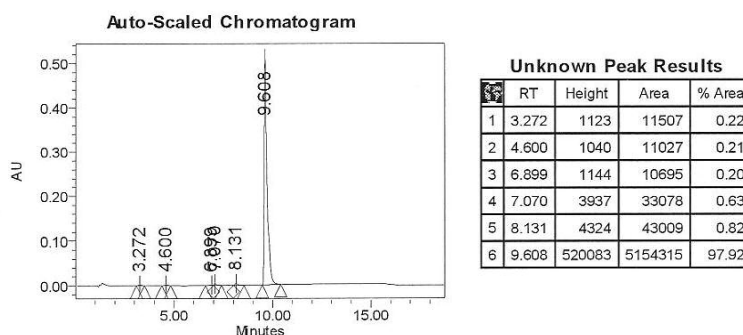
3,5-Methyl-4-hydroxybenzoic acid (394 mg, 2.37 mmol), 2-aminophenol (215 mg, 1.97 mmol), and *p*-TsOH·H₂O (1.87 g, 9.83 mmol) were stirred in refluxing xylenes (20 mL). After 18 h the reaction was cooled, extracted into EtOAc (100 mL), and washed with saturated NaHCO₃ (2x25 mL) and brine (25 mL). The organics were then dried over Na₂SO₄, filtered, and concentrated. Flash chromatographic purification over silica (2:1 hexanes:EtOAc) afforded 2-(3,5-dimethyl-4-hydroxyphenyl)benzoxazole (**4f**) as a pale-orange solid (366 mg, 78%). ¹H-NMR (500 MHz, *d*₆-DMSO) δ 9.11 (s, 1H), 7.79 (s, 2H), 7.67-7.72 (m, 2H), 7.33-7.38 (m, 2H), 2.26 (s, 6H); ¹³C-NMR (125 MHz, *d*₆-DMSO) δ 162.93, 157.02, 150.04, 141.83, 127.70, 125.03, 124.63, 124.53, 119.17,

117.03, 110.51, 16.57; ESI-TOF 240.1027 m/z $[MH]^+$, $C_{15}H_{14}NO_2$ requires 240.1019; RP-HPLC: >99% & 98% pure.

Primary RP-HPLC Conditions Chromatographic Trace:



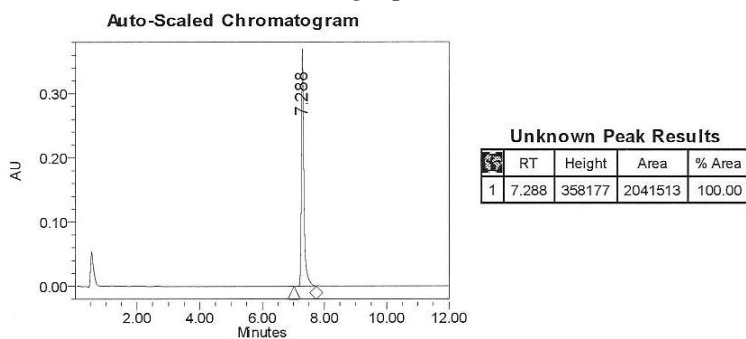
Secondary RP-HPLC Conditions Chromatographic Trace:



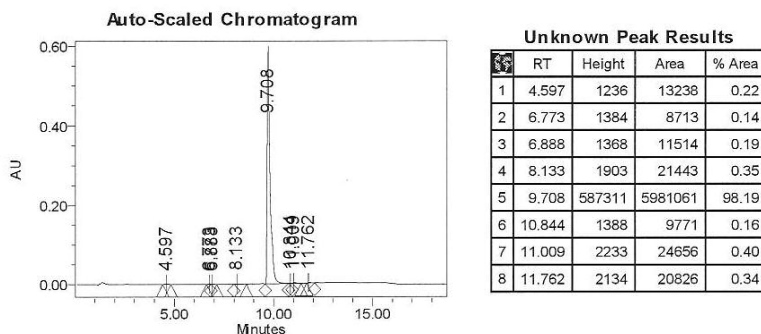
2-(4-Methoxyphenyl) benzoxazole (5a).

p-Anisoyl chloride (199 mg, 1.16 mmol) and 2-aminophenol (101 mg, 0.925 mmol) were stirred in xylenes (10 mL) at room temperature for 5 minutes, then *p*-TsOH•H₂O (890 mg, 4.68 mmol) was added and the reaction was stirred at reflux. After 4 h the reaction was cooled, extracted into EtOAc (50 mL), and washed with saturated NaHCO₃ (2x25 mL) and brine (25 mL). The organics were then dried over Na₂SO₄, filtered, and concentrated. Flash chromatographic purification over silica (4:1-1:1 hexanes:EtOAc gradient elution) afforded 2-(4-methoxyphenyl)benzoxazole (**5a**) as a pale-yellow solid (164 mg, 79%). ¹H-NMR (500 MHz, *d*₆-DMSO) δ 8.11-8.15 (m, 2H), 7.72-7.76 (m, 2H), 7.35-7.39 (m, 2H), 7.13-7.17 (m, 2H), 3.85 (s, 3H); ¹³C-NMR (125 MHz, *d*₆-DMSO) δ 162.37, 162.16, 150.11, 141.68, 129.14, 124.97, 124.71, 119.43, 118.76, 114.79, 110.71, 55.53; ESI-TOF 226.0862 m/z $[MH]^+$, $C_{14}H_{12}NO_2$ requires 226.0863; RP-HPLC: >99% & 98% pure.

Primary RP-HPLC Conditions Chromatographic Trace:



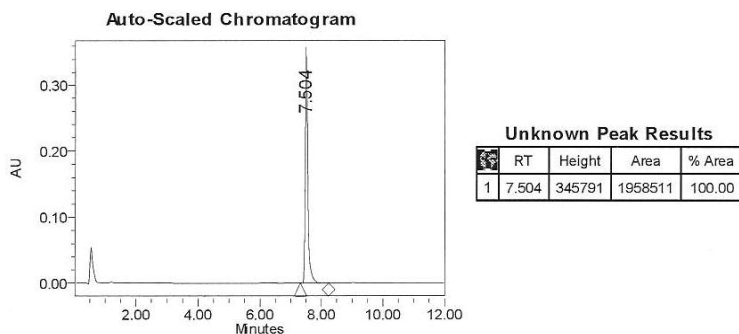
Secondary RP-HPLC Conditions Chromatographic Trace:



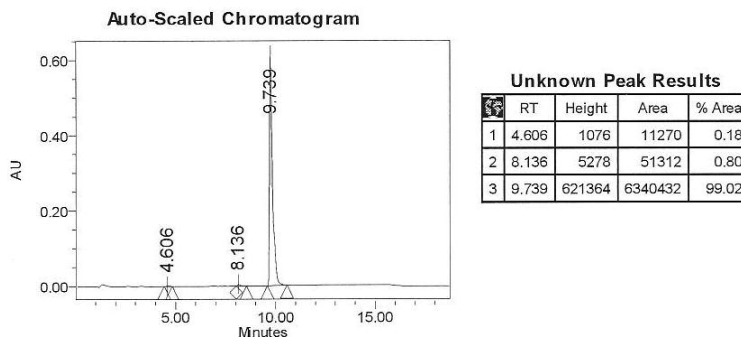
2-(3-Fluoro-4-methoxyphenyl)benzoxazole (5b).

2-(3-Fluoro-4-hydroxyphenyl)benzoxazole (**3b**, 57.7 mg, 0.252 mmol), iodomethane (31.5 μ L, 0.506 mmol), and K_2CO_3 (69.0 mg, 0.499 mmol) were stirred in DMF (3 mL) at room temperature. After 18 h the reaction was concentrated with silica to a powder. Flash chromatographic purification over silica (4:1 hexanes:EtOAc) afforded 2-(3-fluoro-4-methoxyphenyl)benzoxazole (**5b**) as a tan solid (37.1 mg, 61%). 1H -NMR (500 MHz, $CDCl_3$) δ 8.01 (ddd, $J=1.3, 2.1, 8.5$ Hz, 1H), 7.97 (dd, $J=2.1, 11.7$ Hz, 1H), 7.72-7.77 (m, 1H), 7.54-7.59 (m, 1H), 7.32-7.38 (m, 2H), 7.08 (t, $J=8.4$ Hz, 1H), 3.98 (s, 3H); ^{13}C -NMR (125 MHz, $CDCl_3$) δ 162.05 (d, $J=2.9$ Hz), 152.31 (d, $J=247$ Hz), 150.75, 150.58 (d, $J=10.6$ Hz), 142.15, 125.00, 124.63, 124.31 (d, $J=3.6$ Hz), 120.12 (d, $J=7.2$ Hz), 119.85, 115.40 (d, $J=20.7$ Hz), 113.30 (d, $J=2.1$ Hz), 110.51, 56.32; ESI-TOF 244.0767 m/z $[MH]^+$, $C_{14}H_{11}FNO_2$ requires 244.0768; RP-HPLC: >99% & 99% pure.

Primary RP-HPLC Conditions Chromatographic Trace:



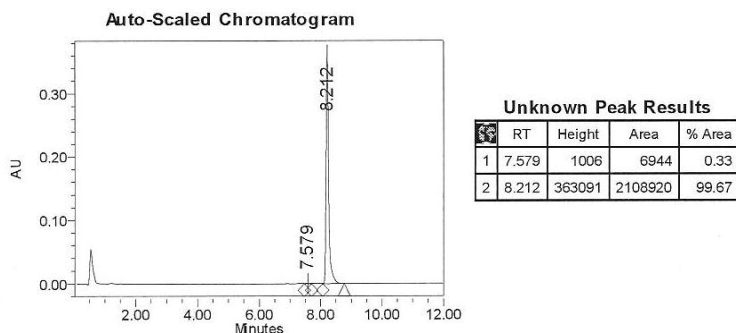
Secondary RP-HPLC Conditions Chromatographic Trace:



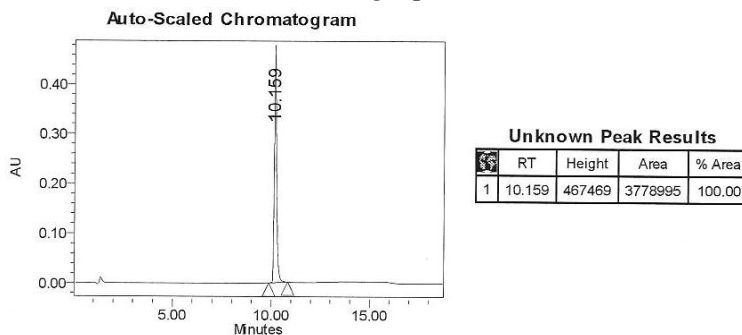
2-(3-Chloro-4-methoxyphenyl)benzoxazole (5c).

2-(3-Chloro-4-hydroxyphenyl)benzoxazole (**3c**, 46.3 mg, 0.188 mmol), iodomethane (23.5 μ L, 0.377 mmol), and K_2CO_3 (53.3 mg, 0.386 mmol) were stirred in DMF (3 mL) at room temperature. After 18 h the reaction was concentrated with silica to a powder. Flash chromatographic purification over silica (4:1-2:1 hexanes:EtOAc gradient elution) afforded 2-(3-chloro-4-methoxyphenyl)benzoxazole (**5c**) as an off-white solid (41.1 mg, 84%). 1H -NMR (500 MHz, $CDCl_3$) δ 8.29 (d, $J=2.1$ Hz, 1H), 8.14 (dd, $J=2.1, 8.6$ Hz, 1H), 7.73-7.76 (m, 1H), 7.54-7.58 (m, 1H), 7.32-7.37 (m, 2H), 7.05 (d, $J=8.6$ Hz, 1H), 3.99 (s, 3H); ^{13}C -NMR (125 MHz, $CDCl_3$) δ 161.91, 157.61, 150.74, 142.12, 129.55, 127.52, 125.01, 124.64, 123.30, 120.54, 119.84, 112.02, 110.51, 56.36; ESI-TOF 260.0472 m/z $[MH]^+$, $C_{14}H_{11}ClNO_2$ requires 260.0473; RP-HPLC: >99% & >99% pure.

Primary RP-HPLC Conditions Chromatographic Trace:



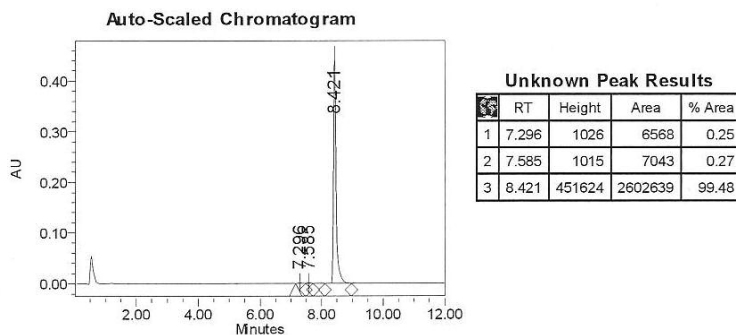
Secondary RP-HPLC Conditions Chromatographic Trace:



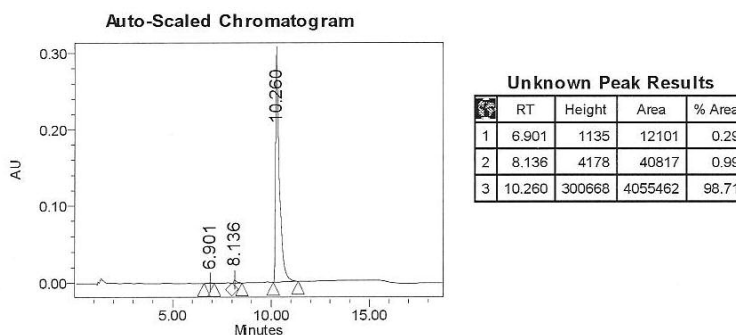
2-(3-Bromo-4-methoxyphenyl)benzoxazole (5d).

2-(3-Bromo-4-hydroxyphenyl)benzoxazole (**3d**, 95.9 mg, 0.331 mmol), iodomethane (41.0 μ L, 0.659 mmol), and K_2CO_3 (93.6 mg, 0.677 mmol) were stirred in DMF (3 mL) at room temperature. After 18 h the reaction was concentrated with silica to a powder. Flash chromatographic purification over silica (4:1-1:1 hexanes:EtOAc gradient elution) afforded 2-(3-bromo-4-methoxyphenyl)benzoxazole (**5d**) as an off-white solid (67.0 mg, 67%). 1H -NMR (500 MHz, $CDCl_3$) δ 8.46 (d, $J=2.1$ Hz, 1H), 8.18 (dd, $J=2.1, 8.6$ Hz, 1H), 7.73-7.78 (m, 1H), 7.54-7.59 (m, 1H), 7.33-7.38 (m, 2H), 7.02 (d, $J=8.6$ Hz, 1H), 3.99 (s, 3H); ^{13}C -NMR (125 MHz, $CDCl_3$) δ 161.76, 158.44, 150.71, 142.09, 132.64, 128.26, 125.01, 124.64, 120.95, 119.82, 112.25, 111.81, 110.51, 56.46; ESI-TOF 303.9965 m/z $[MH]^+$, $C_{14}H_{11}BrNO_2$ requires 303.9968; RP-HPLC: >99% & 99% pure.

Primary RP-HPLC Conditions Chromatographic Trace:



Secondary RP-HPLC Conditions Chromatographic Trace:

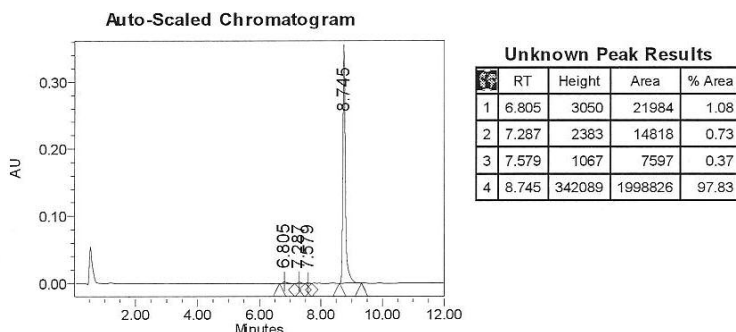


2-(3-Iodo-4-methoxyphenyl)benzoxazole (5e).

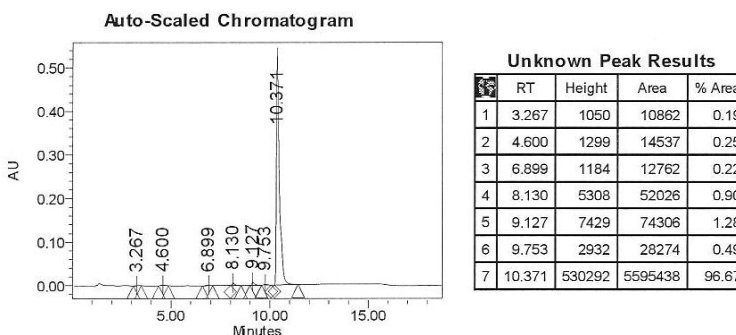
3-Iodo-4-methoxybenzoic acid (683 mg, 2.46 mmol), 2-aminophenol (223 mg, 2.04 mmol), and p -TsOH \cdot H $_2$ O (1.94 g, 10.2 mmol) were stirred in refluxing xylenes (20 mL). After 5 h the reaction was cooled, extracted into EtOAc (50 mL), and washed with saturated $NaHCO_3$ (2x25 mL) and brine (25 mL). The organics were then dried over Na_2SO_4 , filtered, and concentrated. Flash chromatographic purification over silica (4:1 hexanes:EtOAc) afforded 2-(3-iodo-4-methoxyphenyl)benzoxazole (**5e**) as an orange-red solid (75.3 mg, 11%). 1H -NMR (500 MHz, $CDCl_3$) δ 8.69 (d, $J=2.1$ Hz, 1H), 8.21 (dd, $J=2.1, 8.6$ Hz, 1H), 7.72-7.76 (m, 1H), 7.54-7.58 (m, 1H), 7.32-7.37 (m, 2H), 6.93 (d, $J=8.6$ Hz, 1H), 3.97 (s, 3H); ^{13}C -NMR (125 MHz, $CDCl_3$) δ 161.57, 160.64, 150.69, 142.08, 138.73, 129.27, 124.96, 124.62, 121.50, 119.79, 110.69, 110.49, 86.16, 56.60;

ESI-TOF 351.9825 m/z $[MH]^+$, $C_{14}H_{11}NO_2$ requires 351.9829; RP-HPLC: 98% & 97% pure.

Primary RP-HPLC Conditions Chromatographic Trace:



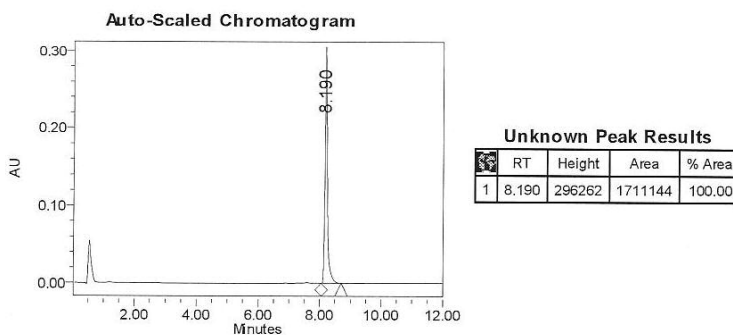
Secondary RP-HPLC Conditions Chromatographic Trace:



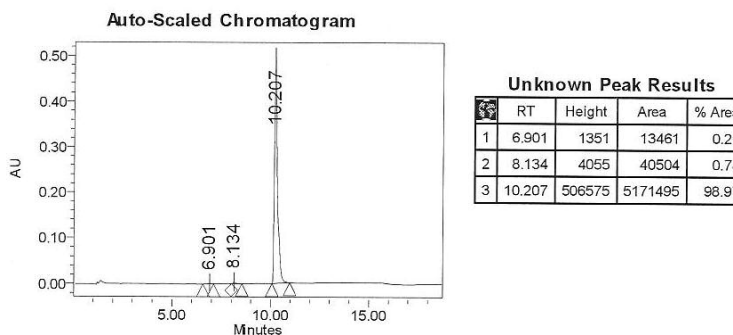
2-(3-Methyl-4-methoxyphenyl)benzoxazole (5f).

2-(3-Methyl-4-hydroxyphenyl)benzoxazole (**3f**, 47.1 mg, 0.209 mmol), iodomethane (26.0 μ L, 0.418 mmol), and K_2CO_3 (59.8 mg, 0.433 mmol) were stirred in DMF (3 mL) at room temperature. After 18 h the reaction was concentrated with silica to a powder. Flash chromatographic purification over silica (4:1 hexanes:EtOAc) afforded 2-(3-methyl-4-methoxyphenyl)benzoxazole (**5f**) as a pale-orange solid (44.0 mg, 88%). 1H -NMR (500 MHz, 1:1 d_6 -DMSO:CD₃OD) δ 7.98 (ddd, $J=0.4, 2.2, 8.5$ Hz, 1H), 7.93 (dd, $J=0.8, 2.2$ Hz, 1H), 7.58-7.65 (m, 2H), 7.28-7.32 (m, 2H), 7.05 (d, $J=8.5$ Hz, 1H), 3.84 (s, 3H); ^{13}C -NMR (125 MHz, 1:1 d_6 -DMSO:CD₃OD) δ 163.82, 161.50, 151.18, 142.64, 130.11, 127.83, 127.81, 125.58, 125.35, 119.94, 119.23, 111.24, 111.20, 55.97, 16.27; ESI-TOF 240.1020 m/z $[MH]^+$, $C_{15}H_{14}NO_2$ requires 240.1019; RP-HPLC: >99% & 99% pure.

Primary RP-HPLC Conditions Chromatographic Trace:



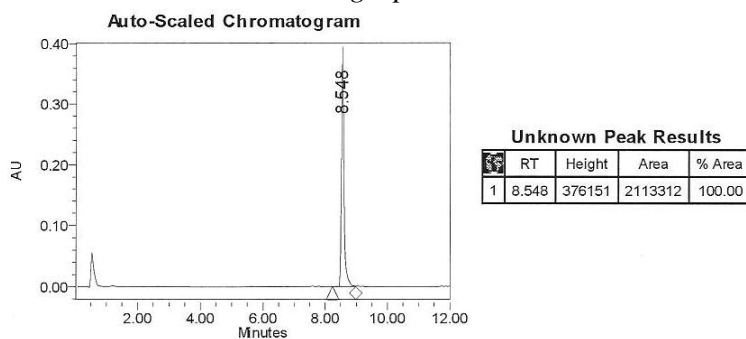
Secondary RP-HPLC Conditions Chromatographic Trace:



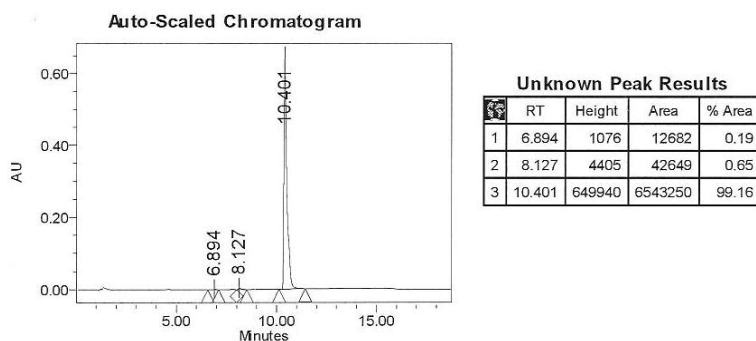
2-(3-Trifluoromethyl-4-methoxyphenyl)benzoxazole (5g).

3-Trifluoromethylbenzoyl chloride (282 mg, 1.18 mmol), 2-aminophenol (105 mg, 0.958 mmol), and pyridine (78.5 μ L, 0.963 mmol) were stirred in xylenes (10 mL) at room temperature for 1 hour, then *p*-TsOH \cdot H₂O (912 mg, 4.79 mmol) was added and the reaction was stirred at reflux. After 18 h the reaction was cooled, extracted into EtOAc (50 mL), and washed with saturated NaHCO₃ (2x25 mL) and brine (25 mL). The organics were then dried over Na₂SO₄, filtered, and concentrated. Flash chromatographic purification over silica (4:1 hexanes:EtOAc) afforded 2-(3-trifluoromethyl-4-methoxyphenyl)benzoxazole (**5g**) as an orange solid (168 mg, 60%). ¹H-NMR (500 MHz, CDCl₃) δ 8.47 (d, *J*=2.1 Hz, 1H), 8.38 (dd, *J*=2.2, 8.7 Hz, 1H), 7.72-7.77 (m, 1H), 7.54-7.59 (m, 1H), 7.32-7.37 (m, 2H), 7.13 (d, *J*=8.7 Hz, 1H), 3.99 (s, 3H); ¹³C-NMR (125 MHz, CDCl₃) δ 161.82, 159.84, 150.72, 142.05, 132.69, 126.88 (q, *J*=5.3 Hz), 125.14, 124.72, 123.16 (q, *J*=272 Hz), 119.88, 119.50 (q, *J*=31.5 Hz), 119.12, 112.30, 110.57, 56.24; ESI-TOF 294.0736 *m/z* [MH]⁺, C₁₅H₁₁F₃NO₃ requires 294.0736; RP-HPLC: >99% & >99% pure.

Primary RP-HPLC Conditions Chromatographic Trace:



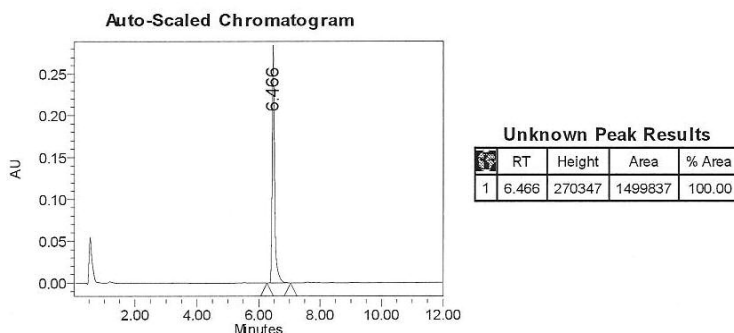
Secondary RP-HPLC Conditions Chromatographic Trace:



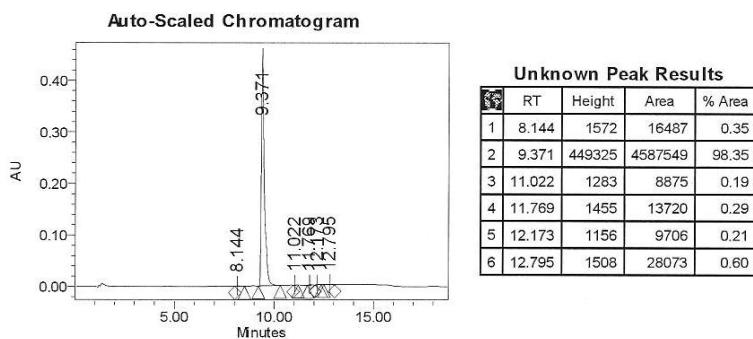
2-(3,4-Dimethoxyphenyl)benzoxazole (5i).

2-(3,4-Dihydroxyphenyl)benzoxazole (**3h**, 79.9 mg, 0.351 mmol), iodomethane (66.0 μ L, 1.06 mmol), and K_2CO_3 (148 mg, 1.07 mmol) were stirred in DMF (3 mL) at room temperature. After 18 h the reaction was concentrated with silica to a powder. Flash chromatographic purification over silica (2:1 hexanes:EtOAc) afforded 2-(3,4-dimethoxyphenyl)benzoxazole (**5i**) as a pale-orange solid (68.3 mg, 76%). 1H -NMR (500 MHz, $CDCl_3$) δ 7.86 (dd, $J=2.0, 8.4$ Hz, 1H), 7.73-7.78 (m, 2H), 7.54-7.58 (m, 1H), 7.30-7.36 (m, 2H), 6.99 (d, $J=8.4$ Hz, 1H), 4.02 (s, 3H), 3.97 (s, 3H); ^{13}C -NMR (125 MHz, $CDCl_3$) δ 163.15, 152.01, 150.72, 149.27, 142.25, 124.71, 124.49, 121.21, 119.82, 119.64, 111.05, 110.39, 110.09, 56.15, 56.05; ESI-TOF 256.0969 m/z $[MH]^+$, $C_{15}H_{14}NO_3$ requires 256.0968; RP-HPLC: >99% & 98% pure.

Primary RP-HPLC Conditions Chromatographic Trace:



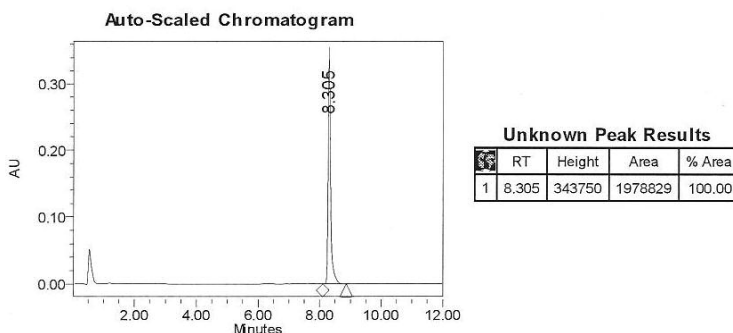
Secondary RP-HPLC Conditions Chromatographic Trace:



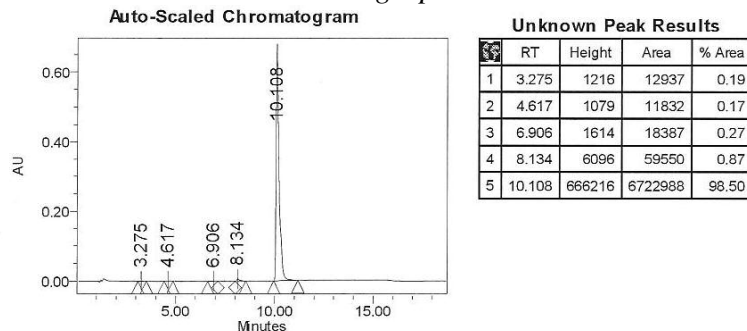
2-(3,5-Difluoro-4-methoxyphenyl)benzoxazole (6b).

3,5-Difluoro-4-methoxybenzoyl chloride (534 mg, 2.59 mmol), 2-aminophenol (234 mg, 2.14 mmol), and pyridine (0.18 mL, 2.21 mmol) were stirred in xylenes (22 mL) at room temperature for 1 hour, then *p*-TsOH•H₂O (2.03 g, 10.7 mmol) was added and the reaction was stirred at reflux. After 3 h the reaction was cooled, extracted into EtOAc (100 mL), and washed with saturated NaHCO₃ (2x50 mL) and brine (50 mL). The organics were then dried over Na₂SO₄, filtered, and concentrated. Flash chromatographic purification over silica (4:1 hexanes:EtOAc) afforded 2-(3,5-difluoro-4-methoxyphenyl)benzoxazole (**6b**) as an off-white solid (307 mg, 55%). ¹H-NMR (500 MHz, *d*₆-DMSO) δ 7.84-7.90 (m, 2H), 7.75-7.82 (m, 2H), 7.39-7.47 (m, 2H), 4.05 (t, *J*=1.4 Hz, 3H); ¹³C-NMR (125 MHz, *d*₆-DMSO) δ 160.17 (t, *J*=3.6 Hz), 154.89 (dd, *J*=6.2, 248 Hz), 150.31, 141.30, 138.79 (t, *J*=13.6 Hz), 125.97, 125.16, 120.96 (t, *J*=10.1 Hz), 119.99, 111.60-111.90 (m), 111.05, 61.86 (t, *J*=3.4 Hz); ESI-TOF 262.0676 *m/z* [MH]⁺, C₁₄H₁₀F₂NO₂ requires 262.0674; RP-HPLC: >99% & 98% pure.

Primary RP-HPLC Conditions Chromatographic Trace:



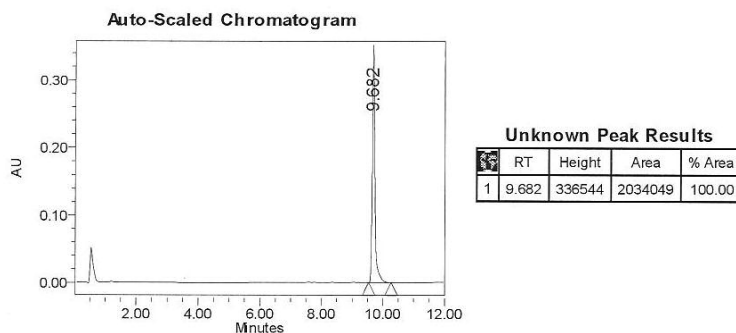
Secondary RP-HPLC Conditions Chromatographic Trace:



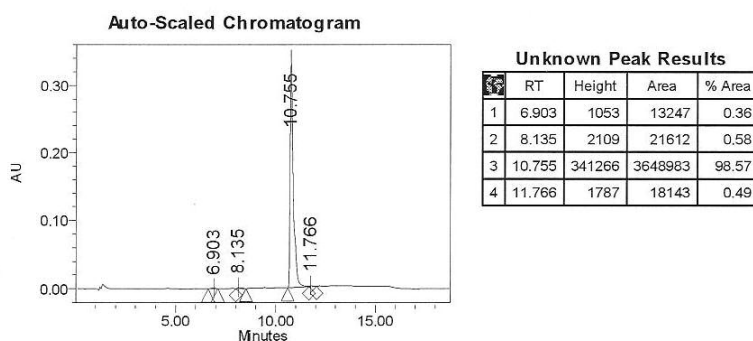
2-(3,5-Dichloro-4-methoxyphenyl)benzoxazole (6c).

2-(3,5-Dichloro-4-hydroxyphenyl)benzoxazole (**4c**, 28.8 mg, 0.103 mmol), iodomethane (13.0 μ L, 0.209 mmol), and K_2CO_3 (28.5 mg, 0.206 mmol) were stirred in DMF (3 mL) at room temperature. After 18 h the reaction was concentrated with silica to a powder. Flash chromatographic purification over silica (4:1 hexanes:EtOAc) afforded 2-(3,5-dichloro-4-methoxyphenyl)benzoxazole (**6c**) as a white solid (27.0 mg, 89%). 1H -NMR (500 MHz, $CDCl_3$) δ 8.20 (s, 2H), 7.75-7.79 (m, 1H), 7.56-7.61 (m, 1H), 7.35-7.41 (m, 2H), 3.98 (s, 3H); ^{13}C -NMR (125 MHz, $CDCl_3$) δ 160.38, 154.90, 150.86, 141.88, 130.27, 127.98, 125.70, 124.97, 124.43, 120.27, 110.74, 60.99; ESI-TOF 294.0079 m/z $[MH]^+$, $C_{14}H_{10}Cl_2NO_2$ requires 294.0083; RP-HPLC: >99% & 98% pure.

Primary RP-HPLC Conditions Chromatographic Trace:



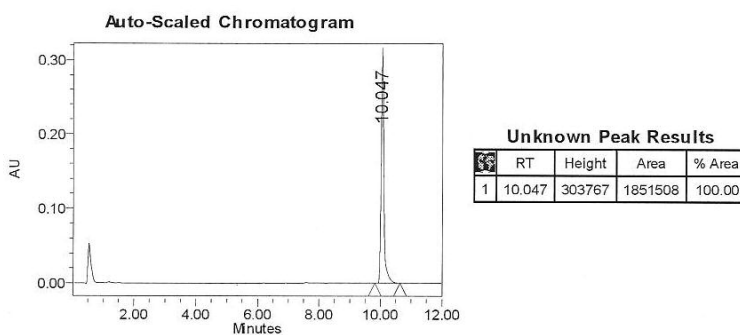
Secondary RP-HPLC Conditions Chromatographic Trace:



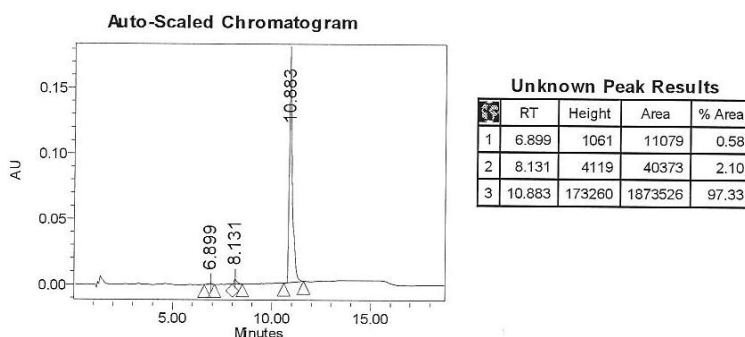
2-(3,5-Dibromo-4-methoxyphenyl)benzoxazole (6d).

2-(3,5-Dibromo-4-hydroxyphenyl)benzoxazole (**4d**, 34.2 mg, 0.0927 mmol), iodomethane (11.5 μ L, 0.185 mmol), and K_2CO_3 (25.8 mg, 0.187 mmol) were stirred in DMF (3 mL) at room temperature. After 18 h the reaction was concentrated with silica to a powder. Flash chromatographic purification over silica (4:1 hexanes:EtOAc) afforded 2-(3,5-dibromo-4-methoxyphenyl)benzoxazole (**6d**) as a white solid (30.1 mg, 85%). 1H -NMR (500 MHz, $CDCl_3$) δ 8.41 (s, 2H), 7.74-7.79 (m, 1H), 7.56-7.61 (m, 1H), 7.36-7.41 (m, 2H), 3.97 (s, 3H); ^{13}C -NMR (125 MHz, $CDCl_3$) δ 160.02, 156.76, 150.84, 141.85, 131.72, 125.70, 125.54, 124.96, 120.26, 118.87, 110.73, 60.86; ESI-TOF 381.9062 m/z $[MH]^+$, $C_{14}H_{10}Br_2NO_2$ requires 381.9073; RP-HPLC: >99% & 97% pure.

Primary RP-HPLC Conditions Chromatographic Trace:



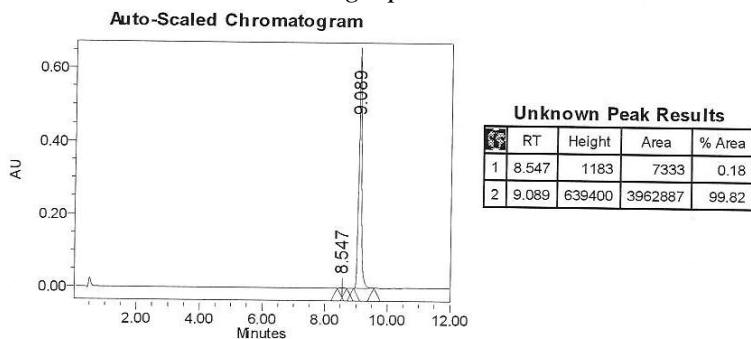
Secondary RP-HPLC Conditions Chromatographic Trace:



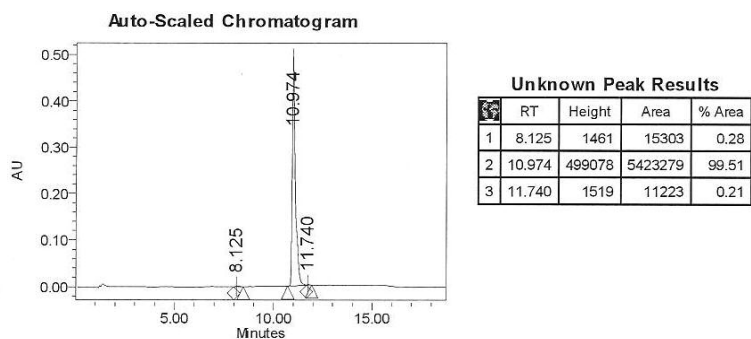
2-(3,5-Diiodo-4-methoxyphenyl)benzoxazole (6e).

Modified procedures from Kumar *et al.* were employed.⁵⁰ 3,5-Diiodo-4-methoxybenzoic acid (1.08 g, 2.67 mmol, obtained in 81% yield from dimethylation of commercially available 3,5-Diiodo-4-hydroxybenzoic acid and subsequent ester hydrolysis) was added to a stirring solution of N,N'-carbonyldiimidazole (432 mg, 2.66 mmol) in anhydrous THF (27 mL) at room temperature under an argon atmosphere. After 15 minutes the 2-aminophenol was added (243 mg, 2.23 mmol) and the reaction was stirred at reflux. After 2 h the reaction was concentrated, then refluxed with *p*-TsOH•H₂O (2.10 g, 11.0 mmol) in *p*-xylene (22 mL). After 2 h the reaction was cooled, extracted into EtOAc (100 mL), and washed with saturated NaHCO₃ (2x25 mL) and brine (25 mL). The organics were then dried over Na₂SO₄, filtered, and concentrated. Flash chromatographic purification over silica (9:1-4:1 hexanes:EtOAc gradient elution) afforded 2-(3,5-diiodo-4-methoxyphenyl)benzoxazole (**6e**) as a pale yellow solid (264.2 mg, 25%). ¹H-NMR (500 MHz, CDCl₃) δ 8.65 (s, 2H), 7.74-7.79 (m, 1H), 7.56-7.60 (m, 1H), 7.35-7.40 (m, 2H), 3.93 (s, 3H); ¹³C-NMR (125 MHz, CDCl₃) δ 161.45, 159.47, 150.80, 141.82, 138.79, 126.54, 125.65, 124.93, 120.19, 110.71, 90.78, 60.87; ESI-TOF 477.8796 *m/z* [MH]⁺, C₁₄H₁₀I₂NO₂ requires 477.8796; RP-HPLC: >99% & >99% pure.

Primary RP-HPLC Conditions Chromatographic Trace:



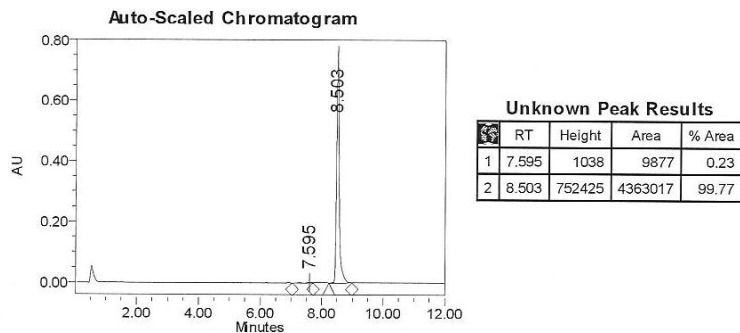
Secondary RP-HPLC Conditions Chromatographic Trace:



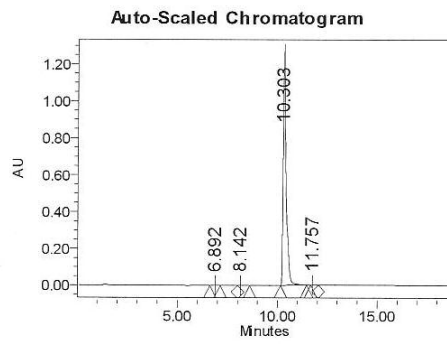
2-(3,5-Dimethyl-4-methoxyphenyl)benzoxazole (6f).

2-(3,5-Dimethyl-4-hydroxyphenyl)benzoxazole (**4f**, 88.5 mg, 0.370 mmol), iodomethane (46.0 μ L, 0.739 mmol), and K_2CO_3 (109 mg, 0.787 mmol) were stirred in DMF (4 mL) at room temperature. After 18 h the reaction was concentrated with silica to a powder. Flash chromatographic purification over silica (4:1 hexanes:EtOAc) afforded 2-(3,5-dimethyl-4-methoxyphenyl)benzoxazole (**6f**) as a white solid (75.1 mg, 80%). 1H -NMR (500 MHz, $CDCl_3$) δ 7.88 (s, 2H), 7.72-7.78 (m, 2H), 7.36-7.43 (m, 2H), 3.72 (s, 3H), 2.31 (s, 6H); ^{13}C -NMR (125 MHz, $CDCl_3$) δ 162.24, 159.80, 150.18, 141.62, 131.70, 127.91, 125.22, 124.77, 121.69, 119.59, 110.78, 59.48, 15.89; ESI-TOF 254.1173 m/z $[MH]^+$, $C_{16}H_{16}NO_2$ requires 254.1175; RP-HPLC: >99% & >99% pure.

Primary RP-HPLC Conditions Chromatographic Trace:



Secondary RP-HPLC Conditions Chromatographic Trace:



Unknown Peak Results

	RT	Height	Area	% Area
1	6.892	1616	20708	0.16
2	8.142	1629	20807	0.16
3	10.303	1268728	13166769	99.58
4	11.757	1222	14146	0.11