Toward Optimization of the Second Aryl Substructure Common to Transthyretin Amyloidogenesis Inhibitors Using Biochemical and Structural Studies

Supporting Information

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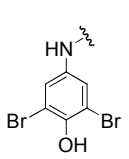
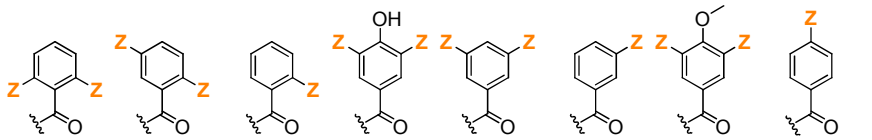
Figure S1: Inhibitor purities as determined using two distinct RP-HPLC conditions. Refer to the Experimental procedures for individual HPLC traces.





Z		2	3	4	5	6	7	8	9
OH	a		>99% *98%*	99% *>99%*		97% *97%*	>99% *>99%*		99% *>99%*
Cl	b	98% *97%*	>99% *>99%*	>99% *>99%*	97% *98%*	96% *97%*	97% *98%*	98% *95%*	99% *>99%*
Br	c		98% *>99%*	99% *98%*	>99% *>99%*	99% *>99%*	98% *>99%*	>99% *>99%*	97% *98%*
CH_3	d	>99% *>99%*	>99% *>99%*	98% *>99%*	>99% *>99%*	99% *>99%*	98% *>99%*	>99% *>99%*	>99% *>99%*
F	e	98% *>99%*	>99% *>99%*	>99% *>99%*	97% *>99%*	98% *98%*	>99% *>99%*	99% *>99%*	>99% *>99%*
NH_2	f			>99% *>99%*			98% *96%*		>99% *98%*
OCH_3	g	>99% *>99%*	99% *>99%*	98% *99%*		99% *99%*	98% *>99%*		98% *95%*
NO_2	h			99% *>99%*			97% *98%*		>99% *99%*
CO_2H	i			>99% *>99%*			>99% *>99%*		96% *98%*
CF_3	j		>99% *>99%*	96% *96%*		98% *98%*	98% *98%*		>99% *>99%*

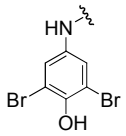
Primary RP-HPLC Conditions (Upper, black values):

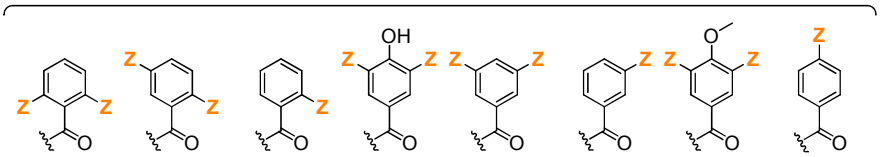
Samples were chromatographically separated using a ThermoHypersil-Keystone Betabasic-18 column (model 71503-034630, 150 Å pore size, 3 µm particle size), eluting with a H_2O:CH_3CN gradient solvent system. Linear gradients were run from either 100:0, 80:20, or 60:40 A:B to 0:100 A:B (A = 95:5 H_2O:CH_3CN, 0.25% TFA; B = 5:95 H_2O:CH_3CN, 0.25% TFA).

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

Samples were chromatographically separated using a Vydac-C_4 column (model 214TP5415, 300 Å pore size, 5 µm particle size), eluting with a H_2O:MeOH gradient solvent system. Linear gradients were run from 100:0 to 0:100 C:D (C = 99.75% H_2O, 0.25% TFA; D = 100% MeOH).

Figure S2: Phenolic pKa values calculated using the SPARC V4.0 online pKa calculator (http://ibmlc2.chem.uga.edu/sparc/). Calculations are 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. Values designated by **X** and **Z** indicate pKa's calculated for the phenolic substituents located on the aryl-**X** and aryl-**Z** rings, respectively. For compound **3a**, the pKa values for both the *ortho*- and *meta*-**Z**-phenolic substituents were calculated, as indicated respectively. For compounds **4i**, **7i**, and **9i**, pKa values for the aryl-**Z**-carboxyls were calculated, as indicated by the CO_2H.





Z		2	3	4	5	6	7	8	9
OH	a		Z=8.98-9.06 X=6.49	Z=8.87 X=6.47		Z=8.64 X=6.47	Z=8.81 X=6.45		Z=8.09 X=6.49
Cl	b	6.39	6.40	6.41	Z=8.87 X=6.52	6.41	6.42	6.46	6.42
Br	c		6.40	6.41	Z=5.41 X=6.47	6.40	6.42	6.46	6.42
CH_3	d	6.48	6.48	6.46	Z=4.97 X=6.46	6.47	6.45	6.53	6.47
F	e	6.40	6.41	6.42	Z=5.05 X=6.46	6.41	6.42	6.47	6.42
NH_2	f			6.49			6.47		6.52
OCH_3	g	6.51	6.51	6.47		6.49	6.46		6.50
NO_2	h			6.35			6.37		6.33
CO_2H	i			CO_2H=3.50 X=6.40			CO_2H=3.48 X=6.41		CO_2H=3.74 X=6.40
CF_3	j		6.42	6.42		6.42	6.42		6.44

Experimental:

Representative amide coupling procedures: Method A:

4-Amino-2,6-dibromophenol (~0.3-0.7 mmol, 1.0 eq.) was mixed with the respective substituted benzoyl chloride (~0.3-0.7 mmol, ~1-1.2 eq.) in THF (~0.5-2.0 mL) at ambient temperature. After ~1 h the reaction mixtures were diluted with H_2O (~20 mL), sonicated, and the resulting precipitates were filtered, rinsed with H_2O, collected, sonicated with sat. $NaHCO_3$ (~10 mL), filtered, rinsed with H_2O, and collected. When necessary, compounds were further purified by flash chromatography over silica, employing a hexanes:EtOAc elution system. All compounds were characterized by ^{1}H-NMR and RP-HPLC and were >95% in purity. See below for specific synthetic procedures and characterization data.

Representative amide coupling procedures: Method B:

Substituted benzoic acids (~0.3-0.7 mmol, ~1-1.2 eq.) were stirred in $SOCl_2$ (~2.0 mL) at ~70-80°C. After ~1 h the reactions were concentrated, then the resulting acid chlorides were mixed with 4-amino-2,6-dibromophenol (~0.3-0.7 mmol, 1.0 eq.) in THF (~0.5-2.0 mL) at ambient temperature. After ~1 h the reaction mixtures were diluted with H_2O (~20 mL), sonicated, and the resulting precipitates were filtered, rinsed with H_2O, collected, sonicated with sat. $NaHCO_3$ (~10 mL), filtered, rinsed with H_2O, and collected. When necessary, compounds were further purified by flash chromatography over silica, employing a hexanes:EtOAc elution system. All compounds were characterized by ^{1}H-NMR and RP-HPLC and were >95% in purity. See below for specific synthetic procedures and characterization data.

Representative anisole deprotection procedures:

Boron tribromide (0.5-3.5 mmol of 1 M BBr_3 in hexanes, 5-10 eq.) was added to a stirring mixture of the respective anisole (0.1-0.35 mmol, 1 eq.) in anhydrous CH_2Cl_2 (5-10 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 1 N HCl (25 mL), sat. $NaHCO_3$ (25 mL), and brine (25 mL). The organics were then dried over Na_2SO_4, filtered, and concentrated. Compounds were purified by flash chromatography over silica, employing a hexanes:EtOAc elution system. All compounds were characterized by ^{1}H-NMR and RP-HPLC and were >95% in purity. See below for specific synthetic procedures and characterization data.

Representative methyl ester hydrolysis procedures:

$LiOH•H_2O$ (0.5-0.85 mmol, ~4 eq.) was added to a stirring mixture of the respective methyl ester (0.13-0.2 mmol, 1 eq.) in H_2O/MeOH/THF (0.5/0.5/1.5 mL) and the reaction was stirred at room temperature. After 18 h the reaction was acidified with 1 N HCl and extracted into EtOAc (50 mL), washed with H_2O (2x25 mL) and brine (25 mL), dried over Na_2SO_4, filtered, and concentrated. Compounds were characterized by ^{1}H-NMR and RP-HPLC and were >95% in purity. See below for specific synthetic procedures and characterization data.

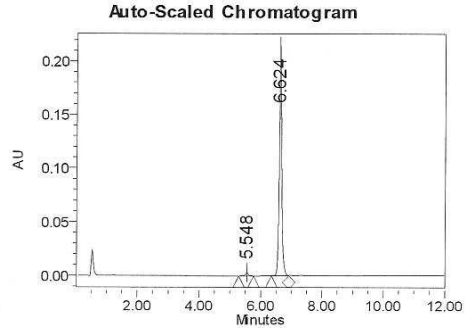
Representative NO_2 to NH_2 reduction procedures:

Tin powder (0.6-2.2 mmol, 4.0-4.7 eq.) was added to a stirring mixture of the respective nitro compound (0.13-0.55 mmol, 1 eq.) in an HCl/AcOH mixture (0.2/2.0 mL). After 18 h the reaction was diluted with H_2O (25 mL), neutralized with $NaHCO_3$, extracted into EtOAc (50 mL) and the organics were washed with H_2O (25 mL) and brine (25 mL), dried over Na_2SO_4, filtered, and concentrated. Compounds were purified by flash chromatography over silica, employing a hexanes:EtOAc elution system. All compounds were characterized by ^{1}H-NMR and RP-HPLC and were >95% in purity. See below for specific synthetic procedures and characterization data.

_N_-(3,5-Dibromo-4-hydroxyphenyl)-2,6-dichlorobenzamide (2b).

4-Amino-2,6-dibromophenol (72.3 mg, 0.258 mmol) and 2,6-dichlorobenzoyl chloride (37.0 μL, 0.258 mmol) were coupled as per procedures outlined in Method A above, affording *N*-(3,5-dibromo-4-hydroxyphenyl)-2,6-dichlorobenzamide (**2b**) as a grey powder (22.8 mg, 20%). ^{1}H-NMR (500 MHz, d_6-DMSO) δ 10.80 (s, 1H), 9.84 (s, 1H), 7.86 (s, 2H), 7.56-7.60 (m, 2H), 7.49-7.53 (m, 1H); RP-HPLC: 98% & 97% pure.

Primary RP-HPLC Conditions Chromatographic Trace:



Unknown Peak Results

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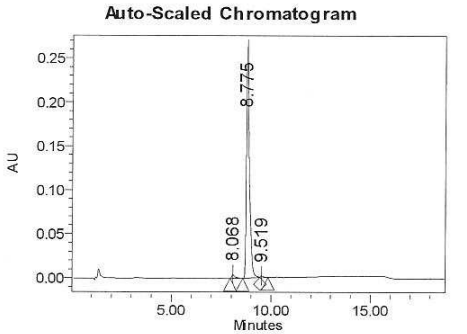
1	5.548	3129	21046	1.68
2	6.624	215448	1230112	98.32

Secondary RP-HPLC Conditions Chromatographic Trace:



Unknown Peak Results

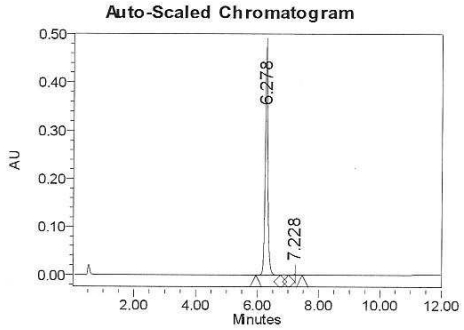
	RT	Height	Area	% Area
1	8.068	4424	45833	1.67
2	8.775	264882	2681551	97.58
3	9.519	1942	20644	0.75

_N_-(3,5-Dibromo-4-hydroxyphenyl)-2,6-dimethylbenzamide (2d).

4-Amino-2,6-dibromophenol (135 mg, 0.481 mmol) and 2,6-dimethylbenzoic acid (72.4 mg, 0.482 mmol) were coupled as per procedures outlined in Method B above. Flash chromatographic purification over silica (4:1-2:1 hexanes:EtOAc gradient elution) afforded *N*-(3,5-dibromo-4-hydroxyphenyl)-2,6-dimethylbenzamide (**2d**) as a tan solid (18.0 mg, 9%). ^{1}H-NMR (500 MHz, d_6-DMSO) δ 10.39 (s, 1H), 9.72 (s, 1H), 7.93 (s,

2H), 7.23 (t, *J*=7.6 Hz, 1H), 7.10 (d, *J*=7.4 Hz, 2H), 2.24 (s, 6H); RP-HPLC: >99% & >99% pure.

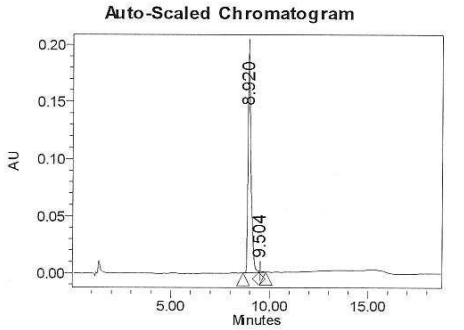
Primary RP-HPLC Conditions Chromatographic Trace:



Unknown Peak Results

	RT	Height	Area	% Area
1	6.278	474421	2831159	99.54
2	7.228	1765	13116	0.46

Secondary RP-HPLC Conditions Chromatographic Trace:



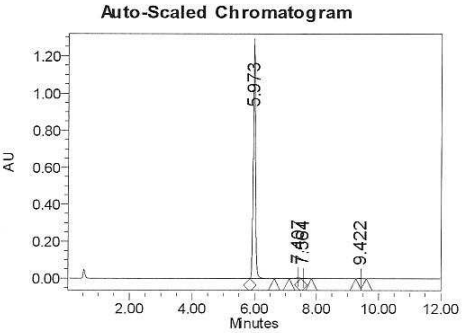
Unknown Peak Results

	RT	Height	Area	% Area
1	8.920	198394	2028702	99.31
2	9.504	1310	14188	0.69

_N_-(3,5-Dibromo-4-hydroxyphenyl)-2,6-difluorobenzamide (2e).

4-Amino-2,6-dibromophenol (96.4 mg, 0.344 mmol) and 2,6-difluorobenzoyl chloride (43.0 μL, 0.342 mmol) were coupled as per procedures outlined in Method A above, affording *N*-(3,5-dibromo-4-hydroxyphenyl)-2,6-difluorobenzamide (**2e**) as a light grey powder (100 mg, 72%). ^{1}H-NMR (500 MHz, d_6-DMSO) δ 10.82 (s, 1H), 9.84 (s, 1H), 7.88 (s, 2H), 7.56-7.64 (m, 1H), 7.23-7.29 (m, 2H); RP-HPLC: 98% & >99% pure.

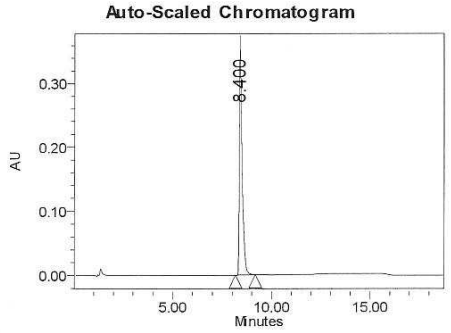
Primary RP-HPLC Conditions Chromatographic Trace:



Unknown Peak Results

	RT	Height	Area	% Area
1	5.973	1245518	6046248	98.49
2	7.407	7504	56622	0.92
3	7.564	3393	26887	0.44
4	9.422	1730	9289	0.15

Secondary RP-HPLC Conditions Chromatographic Trace:



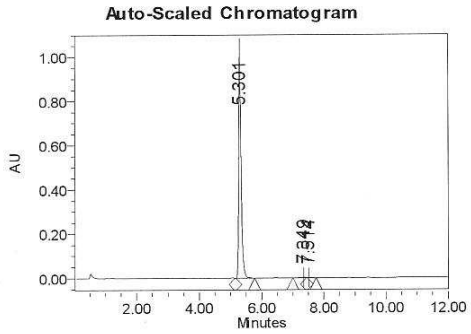
Unknown Peak Results

	RT	Height	Area	% Area
1	8.400	359336	3506624	100.00

_N_-(3,5-Dibromo-4-hydroxyphenyl)-2,6-bis-methoxybenzamide (2g).

4-Amino-2,6-dibromophenol (120 mg, 0.429 mmol) and 2,6-dimethoxybenzoyl chloride (88.5 mg, 0.441 mmol) were coupled as per procedures outlined in Method A above, affording *N*-(3,5-dibromo-4-hydroxyphenyl)-2,6-dimethoxybenzamide (**2g**) as a tan powder (71.3 mg, 39%). ^{1}H-NMR (500 MHz, d_6-DMSO) δ 10.24 (s, 1H), 9.64 (s, 1H), 7.91 (s, 2H), 7.35 (t, *J*=8.4 Hz, 1H), 6.72 (d, *J*=8.4 Hz, 2H), 3.74 (s, 6H); RP-HPLC: >99% & >99% pure.

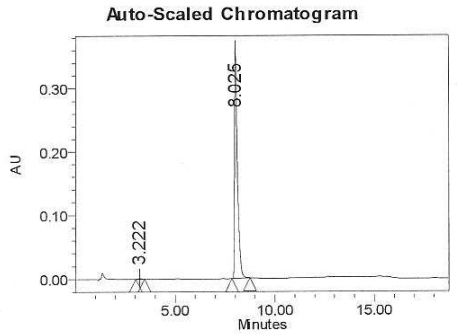
Primary RP-HPLC Conditions Chromatographic Trace:



Unknown Peak Results

	RT	Height	Area	% Area
1	5.301	1026843	5546352	99.42
2	7.349	2629	22532	0.40
3	7.514	1198	10016	0.18

Secondary RP-HPLC Conditions Chromatographic Trace:



Unknown Peak Results

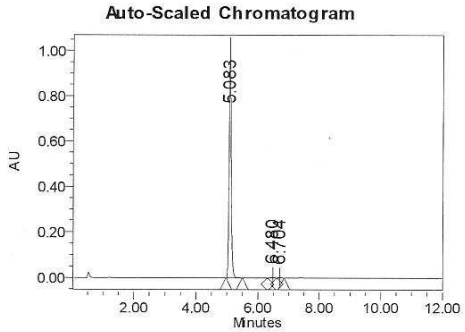
	RT	Height	Area	% Area
1	3.222	1324	14612	0.41
2	8.025	366800	3519845	99.59

_N_-(3,5-Dibromo-4-hydroxyphenyl)-2,5-bis-hydroxybenzamide (3a).

N-(3,5-Dibromo-4-hydroxyphenyl)-2,5-bis-methoxybenzamide (**3g**, 146 mg, 0.339 mmol), boron tribromide (3.40 mL of 1 M BBr_3 in hexanes, 3.40 mmol), and anhydrous CH_2Cl_2 (10.0 mL) were subjected to the representative anisole deprotection

procedures as outlined above. Flash chromatographic purification over silica (1:1-1:2 hexanes:EtOAc gradient elution) afforded *N*-(3,5-dibromo-4-hydroxyphenyl)-2,5-bis-hydroxybenzamide (**3a**) as an off-white solid (106 mg, 77%). ^{1}H-NMR (500 MHz, d_6-DMSO) δ 10.86 (s, 1H), 10.29 (s, 1H), 9.75 (s, 1H), 9.09 (s, 1H), 7.94 (s, 2H), 7.28 (d, *J*=3.0 Hz, 1H), 6.87 (d, *J*=3.0, 8.8 Hz, 1H), 6.80 (d, *J*=8.8 Hz, 1H); RP-HPLC: >99% & 98% pure.

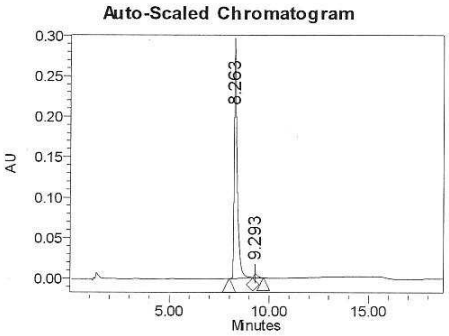
Primary RP-HPLC Conditions Chromatographic Trace:



Unknown Peak Results

	RT	Height	Area	% Area
1	5.083	995074	4750062	99.44
2	6.480	3441	15558	0.33
3	6.704	2485	10955	0.23

Secondary RP-HPLC Conditions Chromatographic Trace:



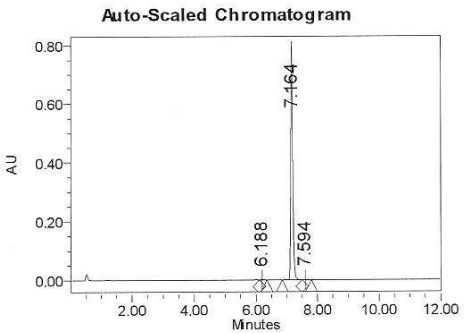
Unknown Peak Results

	RT	Height	Area	% Area
1	8.263	286407	2977980	97.88
2	9.293	5322	64448	2.12

_N_-(3,5-Dibromo-4-hydroxyphenyl)-2,5-dichlorobenzamide (3b).

4-Amino-2,6-dibromophenol (225 mg, 0.804 mmol) and 2,5-dichlorobenzoyl chloride (172 mg, 0.898 mmol) were coupled as per procedures outlined in Method A above, affording *N*-(3,5-dibromo-4-hydroxyphenyl)-2,5-dichlorobenzamide (**3b**) as a tan solid (175 mg, 50%). ^{1}H-NMR (500 MHz, d_6-DMSO) δ 10.58 (s, 1H), 9.81 (s, 1H), 7.88 (s, 2H), 7.73-7.75 (m, 1H), 7.57-7.62 (m, 2H); RP-HPLC: >99% & >99% pure.

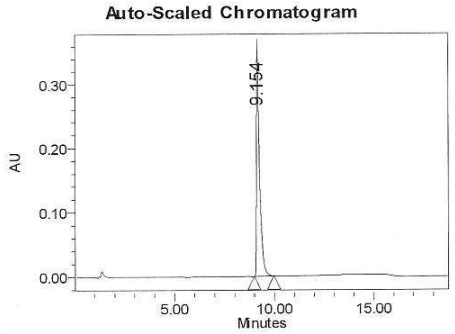
Primary RP-HPLC Conditions Chromatographic Trace:



Unknown Peak Results

	RT	Height	Area	% Area
1	6.188	1482	6945	0.19
2	7.164	773602	3555890	99.55
3	7.594	1176	9103	0.25

Secondary RP-HPLC Conditions Chromatographic Trace:



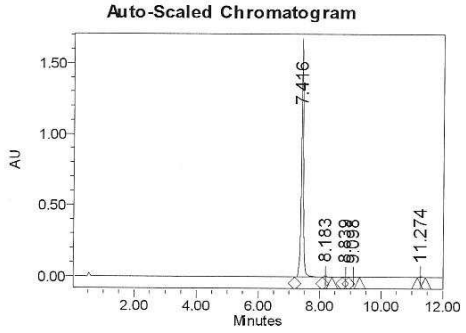
Unknown Peak Results

	RT	Height	Area	% Area
1	9.154	359757	3773369	100.00

_N_-(3,5-Dibromo-4-hydroxyphenyl)-2,5-dibromobenzamide (3c).

4-Amino-2,6-dibromophenol (111 mg, 0.395 mmol) and 2,5-dibromobenzoic acid (125 mg, 0.445 mmol) were coupled as per procedures outlined in Method B above. Flash chromatographic purification over silica (4:1-2:1 hexanes:EtOAc gradient elution) afforded *N*-(3,5-dibromo-4-hydroxyphenyl)-2,5-dibromobenzamide (**3c**) as an off-white solid (158 mg, 76%). ^{1}H-NMR (500 MHz, d_6-DMSO) δ 10.56 (s, 1H), 9.80 (s, 1H), 7.88 (s, 2H), 7.81 (d, *J*=2.4 Hz, 1H), 7.66 (d, *J*=8.5 Hz, 1H), 7.61 (dd, *J*=2.4, 8.5 Hz, 1H); RP-HPLC: 98% & >99% pure.

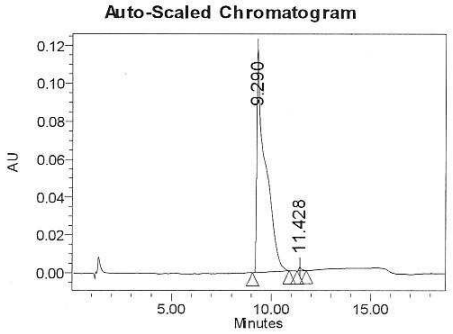
Primary RP-HPLC Conditions Chromatographic Trace:



Unknown Peak Results

	RT	Height	Area	% Area
1	7.416	1572123	7666529	98.26
2	8.183	10988	52345	0.67
3	8.839	4190	19552	0.25
4	9.098	3364	19090	0.24
5	11.274	9491	44448	0.57

Secondary RP-HPLC Conditions Chromatographic Trace:



Unknown Peak Results

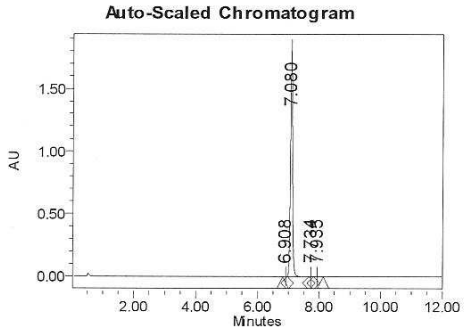
	RT	Height	Area	% Area
1	9.290	120309	3513855	99.42
2	11.428	2094	20331	0.58

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

4-Amino-2,6-dibromophenol (328 mg, 1.17 mmol) and 2,5-dimethylbenzoic acid (199 mg, 1.32 mmol) were coupled as per procedures outlined in Method B above. Flash

chromatographic purification over silica (4:1-2:1 hexanes:EtOAc gradient elution) afforded *N*-(3,5-dibromo-4-hydroxyphenyl)-2,5-dimethylbenzamide (**3d**) as a light tan solid (212 mg, 45%). ^{1}H-NMR (500 MHz, d_6-DMSO) δ 10.25 (s, 1H), 9.69 (s, 1H), 7.95 (s, 2H), 7.26 (d, *J*=1.3 Hz, 1H), 7.16-7.22 (m, 2H), 2.30 (s, 6H); RP-HPLC: >99% & >99% pure.

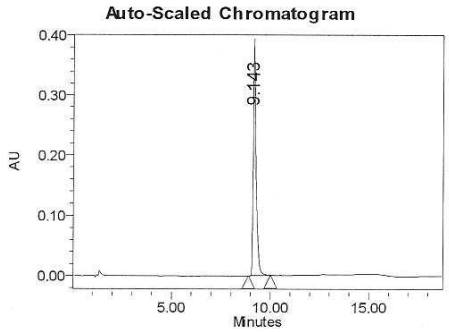
Primary RP-HPLC Conditions Chromatographic Trace:



Unknown Peak Results

	RT	Height	Area	% Area
1	6.908	1421	6221	0.07
2	7.080	1817299	8869114	99.68
3	7.734	1924	10096	0.11
4	7.935	1818	12114	0.14

Secondary RP-HPLC Conditions Chromatographic Trace:



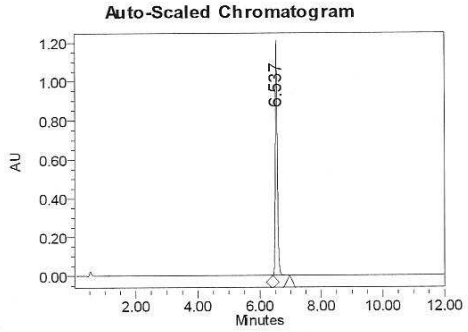
Unknown Peak Results

	RT	Height	Area	% Area
1	9.143	385548	3885210	100.00

***N*-(3,5-Dibromo-4-hydroxyphenyl)-2,5-difluorobenzamide (3e).**

4-Amino-2,6-dibromophenol (240 mg, 0.857 mmol) and 2,5-difluorobenzoyl chloride (162 mg, 0.917 mmol) were coupled as per procedures outlined in Method A above, affording *N*-(3,5-dibromo-4-hydroxyphenyl)-2,5-difluorobenzamide (**3e**) as a tan powder (331 mg, 95%). ^{1}H-NMR (500 MHz, d_6-DMSO) δ 10.48 (s, 1H), 9.80 (s, 1H), 7.91 (s, 2H), 7.52-7.57 (m, 1H), 7.40-7.48 (m, 2H); RP-HPLC: >99% & >99% pure.

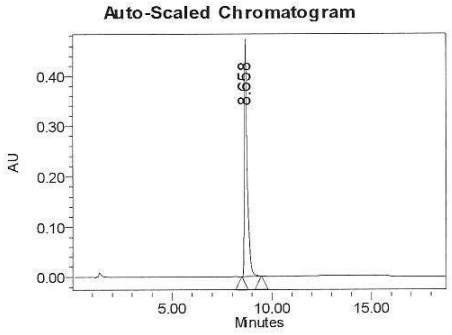
Primary RP-HPLC Conditions Chromatographic Trace:



Unknown Peak Results

	RT	Height	Area	% Area
1	6.537	1160924	5337722	100.00

Secondary RP-HPLC Conditions Chromatographic Trace:



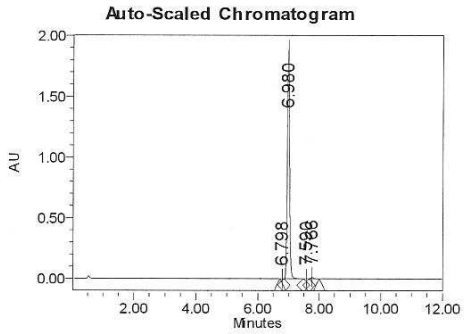
Unknown Peak Results

	RT	Height	Area	% Area
1	8.658	463837	4558381	100.00

_N_-(3,5-Dibromo-4-hydroxyphenyl)-2,5-bis-methoxybenzamide (3g).

4-Amino-2,6-dibromophenol (274 mg, 0.979 mmol) and 2,5-bis-methoxybenzoic acid (198 mg, 1.09 mmol) were coupled as per procedures outlined in Method B above, affording *N*-(3,5-dibromo-4-hydroxyphenyl)-2,5-bis-methoxybenzamide (**3g**) as a tan powder (302 mg, 72%). ^{1}H-NMR (500 MHz, d_6-DMSO) δ 10.11 (s, 1H), 9.70 (s, 1H), 7.97 (s, 2H), 7.19 (d, *J*=3.0 Hz, 1H), 7.10 (d, *J*=9.0 Hz, 1H), 7.08 (dd, *J*=3.0, 9.0 Hz, 1H), 3.84 (s, 3H), 3.74 (s, 3H); RP-HPLC: 99% & >99% pure.

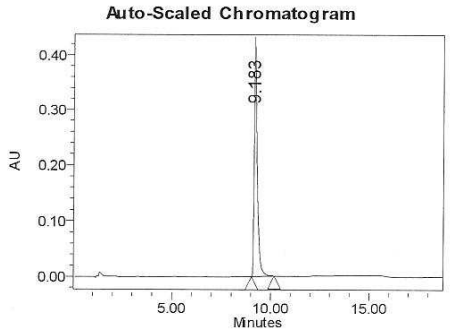
Primary RP-HPLC Conditions Chromatographic Trace:



Unknown Peak Results

	RT	Height	Area	% Area
1	6.798	1790	7321	0.08
2	6.980	1898099	9608187	99.02
3	7.590	1323	11060	0.11
4	7.766	13854	76807	0.79

Secondary RP-HPLC Conditions Chromatographic Trace:



Unknown Peak Results

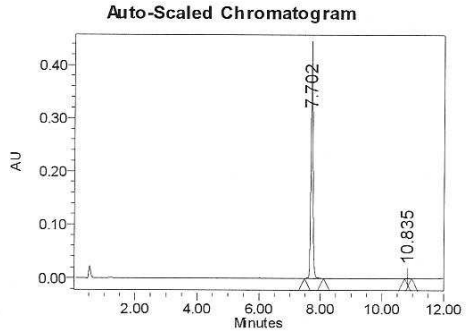
	RT	Height	Area	% Area
1	9.183	415461	4350516	100.00

_N_-(3,5-Dibromo-4-hydroxyphenyl)-2,5-bis-trifluoromethylbenzamide (3j).

4-Amino-2,6-dibromophenol (137 mg, 0.489 mmol) and 2,5-bis-trifluoromethylbenzoyl chloride (150 mg, 0.544 mmol) were coupled as per procedures outlined in Method A above, affording *N*-(3,5-dibromo-4-hydroxyphenyl)-2,5-bis-

trifluoromethylbenzamide (**3j**) as an off-white powder (228 mg, 92%). ^{1}H-NMR (500 MHz, d_6-DMSO) δ 10.71 (s, 1H), 9.84 (s, 1H), 8.21 (s, 1H), 8.11 (d, *J*=1.1 Hz, 2H), 7.85 (s, 2H); RP-HPLC: >99% & >99% pure.

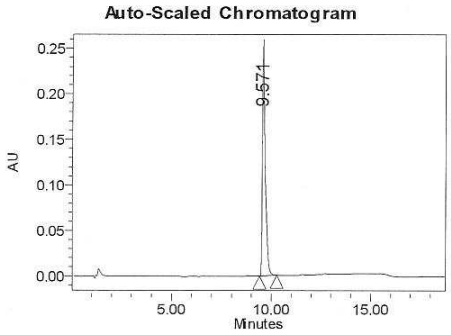
Primary RP-HPLC Conditions Chromatographic Trace:



Unknown Peak Results

	RT	Height	Area	% Area
1	7.702	422332	1903016	99.67
2	10.835	1435	6299	0.33

Secondary RP-HPLC Conditions Chromatographic Trace:



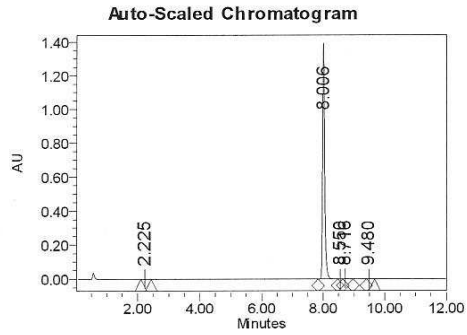
Unknown Peak Results

	RT	Height	Area	% Area
1	9.571	252461	2571416	100.00

_N_-(3,5-Dibromo-4-hydroxyphenyl)-2-hydroxybenzamide (4a).

N-(3,5-Dibromo-4-hydroxyphenyl)-2-methoxybenzamide (**4g**, 42.9 mg, 0.107 mmol), boron tribromide (0.53 mL of 1 M BBr_3 in hexanes, 0.53 mmol), and anhydrous CH_2Cl_2 (5.0 mL) were subjected to the representative anisole deprotection procedures as outlined above. Flash chromatographic purification over silica (4:1-2:1 hexanes:EtOAc gradient elution) afforded *N*-(3,5-dibromo-4-hydroxyphenyl)-2-hydroxybenzamide (**4a**) as an off-white solid (36.0 mg, 87%). ^{1}H-NMR (500 MHz, d_6-DMSO) δ 11.58 (s, 1H), 10.30 (s, 1H), 9.79 (s, 1H), 7.94 (s, 2H), 7.87 (dd, *J*=1.6, 7.9 Hz, 1H), 7.42 (ddd, *J*=1.7, 7.2, 8.3 Hz, 1H), 6.92-6.99 (m, 2H); RP-HPLC: 99% & >99% pure.

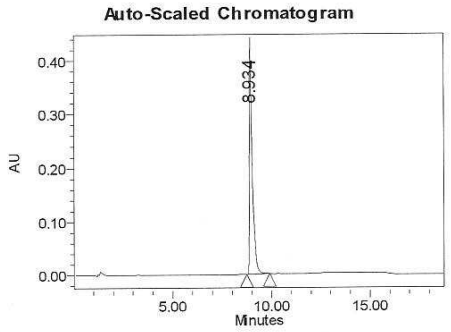
Primary RP-HPLC Conditions Chromatographic Trace:



Unknown Peak Results

	RT	Height	Area	% Area
1	2.225	1565	11259	0.18
2	8.006	1336741	6173539	99.04
3	8.550	2187	16293	0.26
4	8.716	3242	24788	0.40
5	9.480	1633	7696	0.12

Secondary RP-HPLC Conditions Chromatographic Trace:



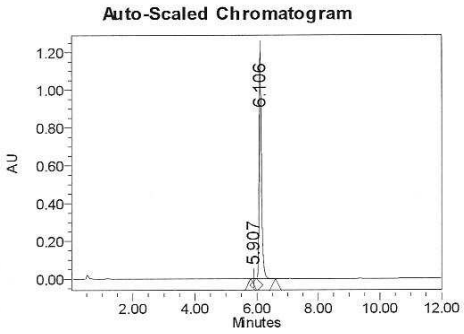
Unknown Peak Results

	RT	Height	Area	% Area
1	8.934	425443	4351185	100.00

_N_-(3,5-Dibromo-4-hydroxyphenyl)-2-chlorobenzamide (4b).

4-Amino-2,6-dibromophenol (170 mg, 0.607 mmol) and 2-chlorobenzoic acid (95.3 mg, 0.609 mmol) were coupled as per procedures outlined in Method B above. Flash chromatographic purification over silica (2:1-1:1 hexanes:EtOAc gradient elution) afforded *N*-(3,5-dibromo-4-hydroxyphenyl)-2-chlorobenzamide (**4b**) as an off-white solid (165 mg, 69%). ^{1}H-NMR (500 MHz, d_6-DMSO) δ 10.51 (s, 1H), 9.77 (s, 1H), 7.91 (s, 2H), 7.58 (dd, *J*=1.8, 7.4 Hz, 1H), 7.56 (dd, *J*=1.2, 7.9 Hz, 1H), 7.51 (dt, *J*=1.8, 7.4 Hz, 1H), 7.45 (dt, *J*=1.2, 7.4 Hz, 1H); RP-HPLC: >99% & >99% pure.

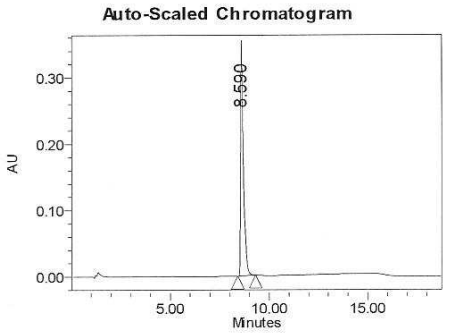
Primary RP-HPLC Conditions Chromatographic Trace:



Unknown Peak Results

	RT	Height	Area	% Area
1	5.907	1585	7661	0.12
2	6.106	1215847	6190922	99.88

Secondary RP-HPLC Conditions Chromatographic Trace:



Unknown Peak Results

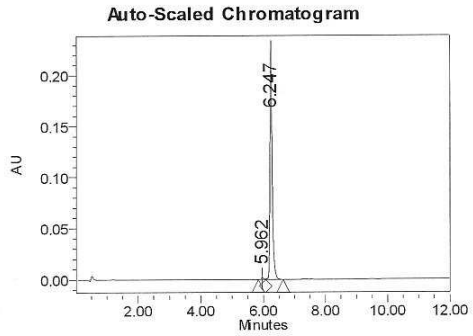
	RT	Height	Area	% Area
1	8.590	346690	3384662	100.00

_N_-(3,5-Dibromo-4-hydroxyphenyl)-2-bromobenzamide (4c).

4-Amino-2,6-dibromophenol (138 mg, 0.494 mmol) and 2-bromobenzoic acid (119 mg, 0.590 mmol) were coupled as per procedures outlined in Method B above,

affording *N*-(3,5-dibromo-4-hydroxyphenyl)-2-bromobenzamide (**4c**) as an off-white solid (148 mg, 66%). ^{1}H-NMR (500 MHz, d_6-DMSO) δ 10.50 (s, 1H), 9.77 (s, 1H), 7.90 (s, 2H), 7.71 (dd, *J*=1.0, 8.0 Hz, 1H), 7.54 (dd, *J*=1.8, 7.6 Hz, 1H), 7.49 (dt, *J*=1.1, 7.5 Hz, 1H), 7.42 (dt, *J*=1.8, 7.5 Hz, 1H); RP-HPLC: 99% & 98% pure.

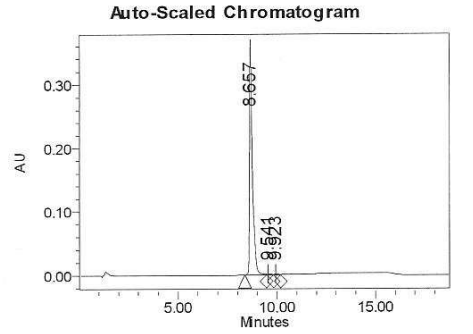
Primary RP-HPLC Conditions Chromatographic Trace:



Unknown Peak Results

	RT	Height	Area	% Area
1	5.962	2009	10621	0.93
2	6.247	223676	1133928	99.07

Secondary RP-HPLC Conditions Chromatographic Trace:



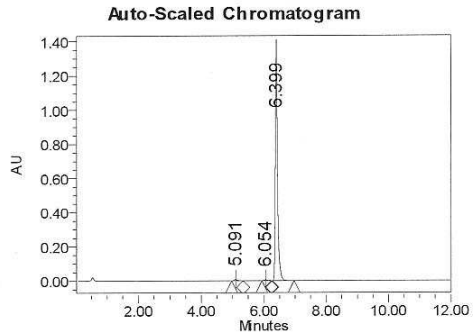
Unknown Peak Results

	RT	Height	Area	% Area
1	8.657	361470	3623466	98.41
2	9.541	1815	31041	0.84
3	9.923	1556	27390	0.74

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

4-Amino-2,6-dibromophenol (98.9 mg, 0.353 mmol) and *o*-toluoyl chloride (46.0 μL, 0.351 mmol) were coupled as per procedures outlined in Method A above, affording *N*-(3,5-dibromo-4-hydroxyphenyl)-2-methylbenzamide (**4d**) as a brownish-grey powder (73.6 mg, 54%). ^{1}H-NMR (500 MHz, d_6-DMSO) δ 10.29 (s, 1H), 9.70 (s, 1H), 7.95 (s, 2H), 7.44 (d, *J*=7.7 Hz, 1H), 7.38 (dt, *J*=1.2, 7.5 Hz, 1H), 7.26-7.32 (m, 2H); RP-HPLC: 98% & >99% pure.

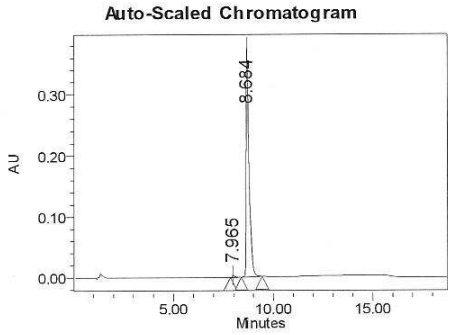
Primary RP-HPLC Conditions Chromatographic Trace:



Unknown Peak Results

	RT	Height	Area	% Area
1	5.091	10189	57067	0.84
2	6.054	7570	44545	0.65
3	6.399	1330405	6719859	98.51

Secondary RP-HPLC Conditions Chromatographic Trace:



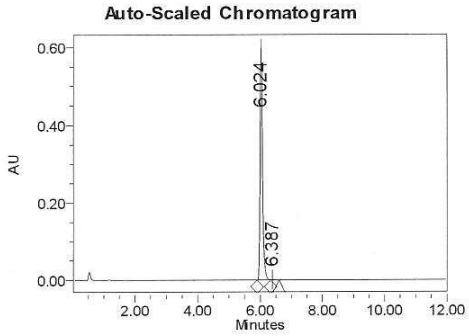
Unknown Peak Results

	RT	Height	Area	% Area
1	7.965	3276	32930	0.86
2	8.684	378181	3799154	99.14

_N_-(3,5-Dibromo-4-hydroxyphenyl)-2-fluorobenzamide (4e).

4-Amino-2,6-dibromophenol (173 mg, 0.619 mmol) and 2-fluorobenzoic acid (85.8 mg, 0.612 mmol) were coupled as per procedures outlined in Method B above. Flash chromatographic purification over silica (4:1-2:1 hexanes:EtOAc gradient elution) afforded *N*-(3,5-dibromo-4-hydroxyphenyl)-2-fluorobenzamide (**4e**) as an off-white fibrous solid (165 mg, 69%). ^{1}H-NMR (500 MHz, d_6-DMSO) δ 10.41 (s, 1H), 9.76 (s, 1H), 7.93 (s, 2H), 7.65 (dt, *J*=1.7, 7.5 Hz, 1H), 7.55-7.61 (m, 1H), 7.30-7.38 (m, 2H); RP-HPLC: >99% & >99% pure.

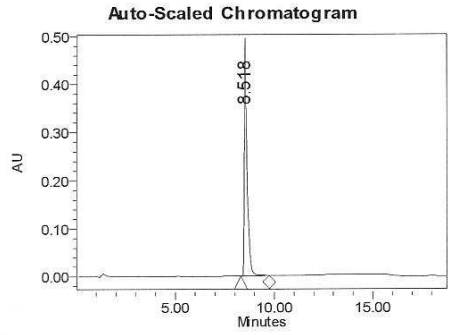
Primary RP-HPLC Conditions Chromatographic Trace:



Unknown Peak Results

	RT	Height	Area	% Area
1	6.024	600734	3117956	99.65
2	6.387	1958	11016	0.35

Secondary RP-HPLC Conditions Chromatographic Trace:



Unknown Peak Results

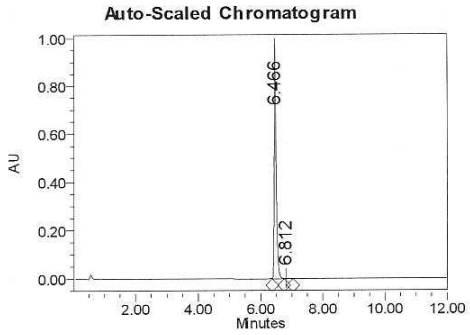
	RT	Height	Area	% Area
1	8.518	478134	4767879	100.00

_N_-(3,5-Dibromo-4-hydroxyphenyl)-2-aminobenzamide (4f).

N-(3,5-Dibromo-4-hydroxyphenyl)-2-nitrobenzamide (**4h**, 229 mg, 0.550 mmol), tin powder (263 mg, 2.22 mmol), and HCl/AcOH (0.2/2.0 mL) were subjected to the representative nitro reduction procedures as outlined above. Flash chromatographic

purification over silica (2:1-1:1 hexanes:EtOAc gradient elution) afforded *N*-(3,5-dibromo-4-hydroxyphenyl)-2-aminobenzamide (**4f**) as an off-white solid (198 mg, 93%). ^{1}H-NMR (500 MHz, d_6-DMSO) δ 9.96 (s, 1H), 9.66 (s, 1H), 7.95 (s, 2H), 7.57 (dd, *J*=1.4, 8.0 Hz, 1H), 7.19 (ddd, *J*=1.5, 7.1, 8.3 Hz, 1H), 6.73 (dd, *J*=1.0, 8.3 Hz, 1H), 6.57 (dd, *J*=1.2, 7.1 Hz, 1H), 6.57 (s, 2H); RP-HPLC: >99% & >99% pure.

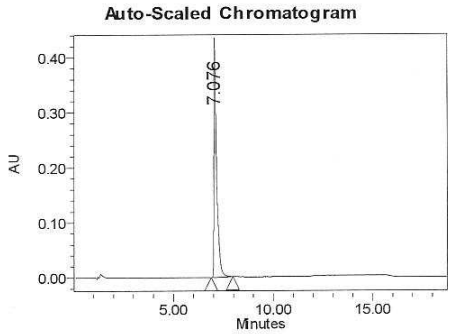
Primary RP-HPLC Conditions Chromatographic Trace:



Unknown Peak Results

	RT	Height	Area	% Area
1	6.466	929307	4099522	99.74
2	6.812	1181	10789	0.26

Secondary RP-HPLC Conditions Chromatographic Trace:



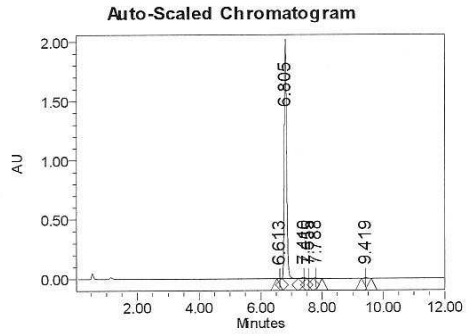
Unknown Peak Results

	RT	Height	Area	% Area
1	7.076	425286	3927478	100.00

***N*-(3,5-Dibromo-4-hydroxyphenyl)-2-methoxybenzamide (4g).**

4-Amino-2,6-dibromophenol (95.9 mg, 0.343 mmol) and *o*-anisoyl chloride (51.0 μL, 0.343 mmol) were coupled as per procedures outlined in Method A above, affording *N*-(3,5-dibromo-4-hydroxyphenyl)-2-methoxybenzamide (**4g**) as a white powder (62.1 mg, 45%). ^{1}H-NMR (500 MHz, d_6-DMSO) δ 10.09 (s, 1H), 9.69 (s, 1H), 7.97 (s, 2H), 7.61 (dd, *J*=1.8, 7.6 Hz, 1H), 7.50 (ddd, *J*=1.8, 7.4 Hz, 1H), 7.16 (d, *J*=8.3 Hz, 1H), 7.05 (dt, *J*=0.8, 7.5 Hz, 1H), 3.88 (s, 3H); RP-HPLC: 98% & 99% pure.

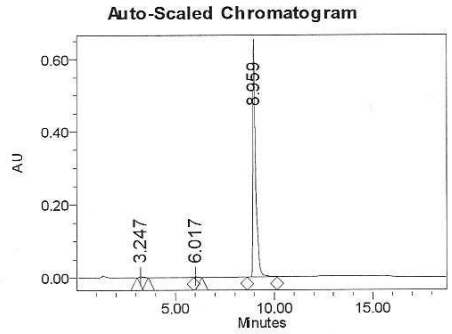
Primary RP-HPLC Conditions Chromatographic Trace:



Unknown Peak Results

	RT	Height	Area	% Area
1	6.613	2316	10451	0.10
2	6.805	1977581	10781634	98.55
3	7.410	8812	72934	0.67
4	7.555	3951	31484	0.29
5	7.788	6947	34145	0.31
6	9.419	1805	9590	0.09

Secondary RP-HPLC Conditions Chromatographic Trace:



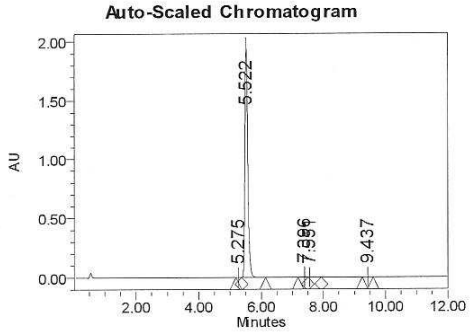
Unknown Peak Results

	RT	Height	Area	% Area
1	3.247	3702	45107	0.70
2	6.017	3551	29926	0.47
3	8.959	640916	6334214	98.83

_N_-(3,5-Dibromo-4-hydroxyphenyl)-2-nitrobenzamide (4h).

4-Amino-2,6-dibromophenol (170 mg, 0.607 mmol) and 2-nitrobenzoyl chloride (95.3 mg, 0.609 mmol) were coupled as per procedures outlined in Method A above. Flash chromatographic purification over silica (1:1-1:2 hexanes:EtOAc gradient elution) afforded *N*-(3,5-dibromo-4-hydroxyphenyl)-2-nitrobenzamide (**4h**) as an off-white solid (76.6 mg, 52%). ^{1}H-NMR (500 MHz, d_6-DMSO) δ 10.68 (s, 1H), 9.81 (s, 1H), 8.12-8.16 (m, 1H), 7.83-7.89 (m, 3H), 7.74-7.79 (m, 2H); RP-HPLC: 99% & >99% pure.

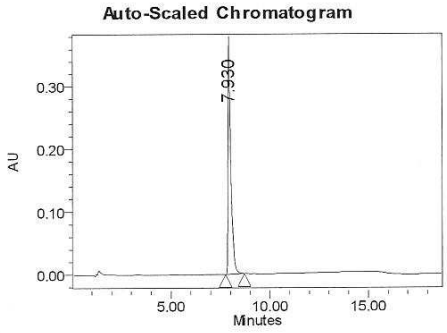
Primary RP-HPLC Conditions Chromatographic Trace:



Unknown Peak Results

	RT	Height	Area	% Area
1	5.275	2083	10393	0.08
2	5.522	1982611	12362868	99.12
3	7.396	8398	60948	0.49
4	7.551	3489	31681	0.25
5	9.437	1121	6339	0.05

Secondary RP-HPLC Conditions Chromatographic Trace:



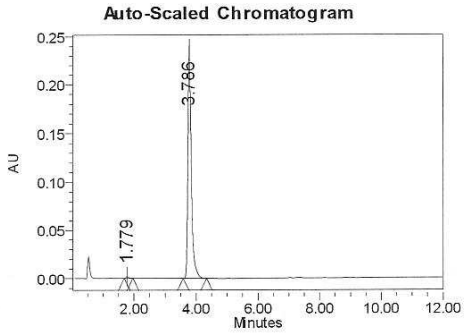
Unknown Peak Results

	RT	Height	Area	% Area
1	7.930	365174	3667080	100.00

_N_-(3,5-Dibromo-4-hydroxyphenyl)-2-carboxybenzamide (4i).

4-Amino-2,6-dibromophenol (107 mg, 0.383 mmol) and phthalic anhydride were stirred in THF (0.50 mL) for 1 h. The reaction was then diluted with H_2O (~20 mL) and sonicated, and the resulting precipitate was filtered, rinsed with H_2O, and dried to afford *N*-(3,5-dibromo-4-hydroxyphenyl)-2-carboxybenzamide (**4i**) as a light grey solid (104 mg, 66%). ^{1}H-NMR (500 MHz, d_6-DMSO) δ 13.1 (br s, 1H), 10.32 (s, 1H), 9.69 (s, 1H), 7.85-7.89 (m, 3H), 7.65 (dd, *J*=1.1, 7.5 Hz, 1H), 7.57 (dd, *J*=1.1, 7.6 Hz, 1H), 7.53 (d, *J*=7.5 Hz, 1H); RP-HPLC: >99% & >99% pure.

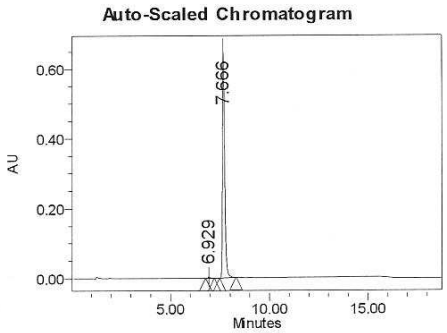
Primary RP-HPLC Conditions Chromatographic Trace:



Unknown Peak Results

	RT	Height	Area	% Area
1	1.779	1992	12069	0.65
2	3.786	239096	1849167	99.35

Secondary RP-HPLC Conditions Chromatographic Trace:



Unknown Peak Results

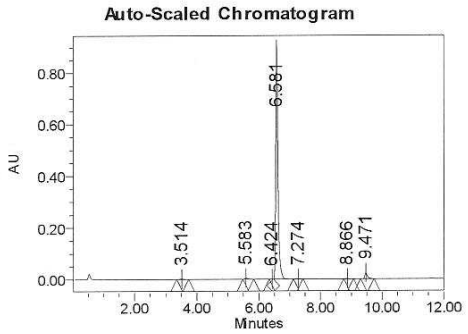
	RT	Height	Area	% Area
1	6.929	3928	32346	0.63
2	7.666	658854	5064330	99.37

_N_-(3,5-Dibromo-4-hydroxyphenyl)-2-trifluoromethylbenzamide (4j).

4-Amino-2,6-dibromophenol (87.4 mg, 0.312 mmol) and 2-trifluoromethylbenzoyl chloride (46.0 μL, 0.312 mmol) were coupled as per procedures

outlined in Method A above, affording *N*-(3,5-dibromo-4-hydroxyphenyl)-2-trifluoromethylbenzamide (**4j**) as a dark grey powder (72.7 mg, 53%). ^{1}H-NMR (500 MHz, d_6-DMSO) δ 10.58 (s, 1H), 9.78 (s, 1H), 7.87 (s, 2H), 7.83-7.86 (m, 1H), 7.76-7.82 (m, 1H), 7.68-7.74 (m, 2H); RP-HPLC: 96% & 96% pure.

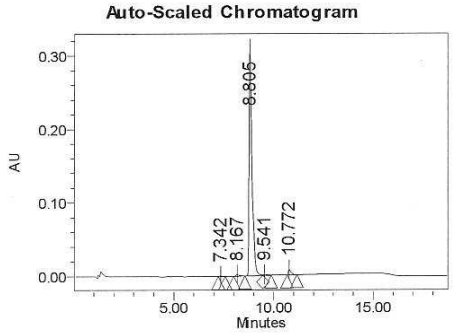
Primary RP-HPLC Conditions Chromatographic Trace:



Unknown Peak Results

	RT	Height	Area	% Area
1	3.514	1691	13187	0.29
2	5.583	5594	28815	0.63
3	6.424	1007	4152	0.09
4	6.581	880330	4412079	95.84
5	7.274	1260	7440	0.16
6	8.866	2322	11471	0.25
7	9.471	24948	126491	2.75

Secondary RP-HPLC Conditions Chromatographic Trace:



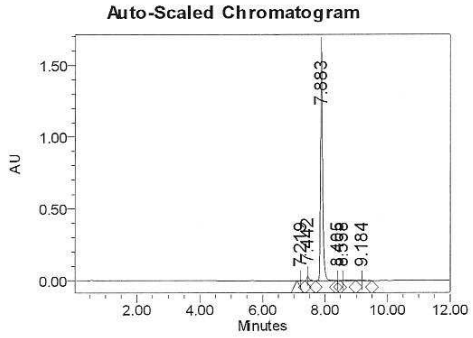
Unknown Peak Results

	RT	Height	Area	% Area
1	7.342	1137	9929	0.31
2	8.167	2294	23934	0.74
3	8.805	313743	3096968	96.08
4	9.541	1664	18561	0.58
5	10.772	7596	73821	2.29

_N_-(3,5-Dibromo-4-hydroxyphenyl)-3,5-dichloro-4-hydroxybenzamide (5b).

N-(3,5-Dibromo-4-hydroxyphenyl)-3,5-dichloro-4-methoxybenzamide (**8b**, 98.8 mg, 0.226 mmol), boron tribromide (1.06 mL of 1 M BBr_3 in hexanes, 1.06 mmol), and anhydrous CH_2Cl_2 (5.0 mL) were subjected to the representative anisole deprotection procedures as outlined above. Flash chromatographic purification over silica (2:1-1:1 hexanes:EtOAc gradient elution) afforded *N*-(3,5-dibromo-4-hydroxyphenyl)-3,5-dichloro-4-hydroxybenzamide (**5b**) as an off-white solid (41.0 mg, 42%). ^{1}H-NMR (500 MHz, d_6-DMSO) δ 10.98 (s, 1H), 10.16 (s, 1H), 9.74 (s, 1H), 7.97 (s, 2H), 7.96 (s, 2H); RP-HPLC: 97% & 98% pure.

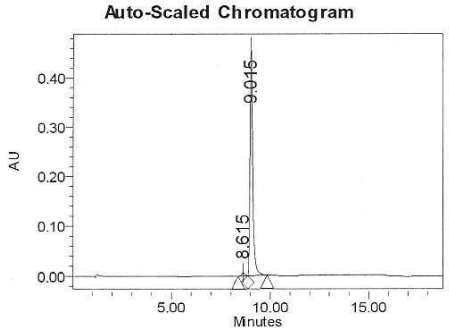
Primary RP-HPLC Conditions Chromatographic Trace:



Unknown Peak Results

	RT	Height	Area	% Area
1	7.219	2062	10548	0.14
2	7.442	31041	161168	2.09
3	7.883	1579001	7474271	97.15
4	8.405	1160	8063	0.10
5	8.558	1760	21838	0.28
6	9.184	2208	17418	0.23

Secondary RP-HPLC Conditions Chromatographic Trace:



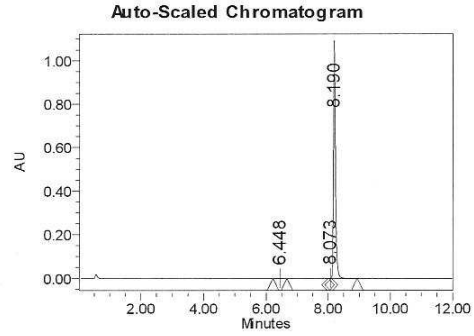
Unknown Peak Results

	RT	Height	Area	% Area
1	8.615	6528	74379	1.69
2	9.015	463123	4338977	98.31

_N_-(3,5-Dibromo-4-hydroxyphenyl)-3,5-dibromo-4-hydroxybenzamide (5c).

_N_-(3,5-Dibromo-4-hydroxyphenyl)-3,5-dibromo-4-methoxybenzamide (**8c**, 120 mg, 0.215 mmol), boron tribromide (1.10 mL of 1 M BBr_3 in hexanes, 1.10 mmol), and anhydrous CH_2Cl_2 (5.0 mL) were subjected to the representative anisole deprotection procedures as outlined above. Flash chromatographic purification over silica (2:1-1:1 hexanes:EtOAc gradient elution) afforded _N_-(3,5-dibromo-4-hydroxyphenyl)-3,5-dibromo-4-hydroxybenzamide (**5c**) as an off-white solid (68.1 mg, 58%). ^{1}H-NMR (500 MHz, d_6-DMSO) δ 10.72 (s, 1H), 10.16 (s, 1H), 9.74 (s, 1H), 8.14 (s, 2H), 7.97 (s, 2H); RP-HPLC: >99% & >99% pure.

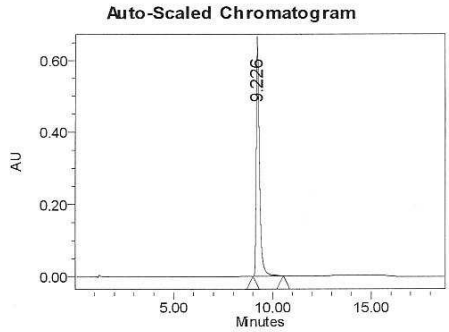
Primary RP-HPLC Conditions Chromatographic Trace:



Unknown Peak Results

	RT	Height	Area	% Area
1	6.448	2361	19531	0.40
2	8.073	2028	6809	0.14
3	8.190	1051577	4857224	99.46

Secondary RP-HPLC Conditions Chromatographic Trace:



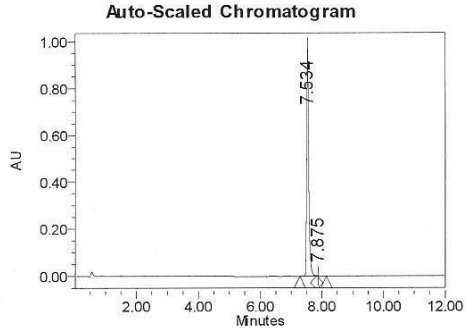
Unknown Peak Results

	RT	Height	Area	% Area
1	9.226	645156	7416893	100.00

_N_-(3,5-Dibromo-4-hydroxyphenyl)-3,5-dimethyl-4-hydroxybenzamide (5d).

N-(3,5-Dibromo-4-hydroxyphenyl)-3,5-dimethyl-4-methoxybenzamide (**8d**, 131 mg, 0.305 mmol), boron tribromide (1.50 mL of 1 M BBr_3 in hexanes, 1.50 mmol), and anhydrous CH_2Cl_2 (5.0 mL) were subjected to the representative anisole deprotection procedures as outlined above. Flash chromatographic purification over silica (2:1-1:1 hexanes:EtOAc gradient elution) afforded *N*-(3,5-dibromo-4-hydroxyphenyl)-3,5-dimethyl-4-hydroxybenzamide (**5d**) as a light-tan solid (92.0 mg, 73%). ^{1}H-NMR (500 MHz, d_6-DMSO) δ 9.91 (s, 1H), 9.63 (s, 1H), 8.92 (s, 1H), 8.00 (s, 2H), 7.56 (s, 2H); RP-HPLC: >99% & >99% pure.

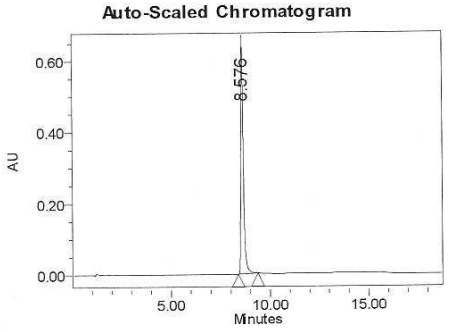
Primary RP-HPLC Conditions Chromatographic Trace:



Unknown Peak Results

	RT	Height	Area	% Area
1	7.534	948598	4250812	99.69
2	7.875	1698	13347	0.31

Secondary RP-HPLC Conditions Chromatographic Trace:



Unknown Peak Results

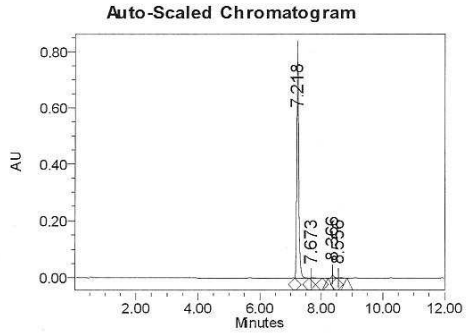
	RT	Height	Area	% Area
1	8.576	647437	5786381	100.00

_N_-(3,5-Dibromo-4-hydroxyphenyl)-3,5-difluoro-4-hydroxybenzamide (5e).

N-(3,5-Dibromo-4-hydroxyphenyl)-3,5-difluoro-4-methoxybenzamide (**8e**, 98.8 mg, 0.226 mmol), boron tribromide (1.13 mL of 1 M BBr_3 in hexanes, 1.13 mmol), and

anhydrous CH_2Cl_2 (5.0 mL) were subjected to the representative anisole deprotection procedures as outlined above. Flash chromatographic purification over silica (2:1-1:1 hexanes:EtOAc gradient elution) afforded *N*-(3,5-dibromo-4-hydroxyphenyl)-3,5-difluoro-4-hydroxybenzamide (**5e**) as a tan solid (18.3 mg, 19%). ^{1}H-NMR (500 MHz, d_6-DMSO) δ 11.05 (s, 1H), 10.10 (s, 1H), 9.74 (s, 1H), 7.97 (s, 2H), 7.64-7.71 (m, 2H); RP-HPLC: 97% & >99% pure.

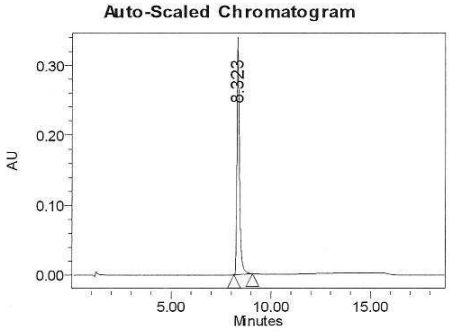
Primary RP-HPLC Conditions Chromatographic Trace:



Unknown Peak Results

	RT	Height	Area	% Area
1	7.218	788530	3489897	97.62
2	7.673	2242	16298	0.46
3	8.366	12636	56942	1.59
4	8.556	1272	12016	0.34

Secondary RP-HPLC Conditions Chromatographic Trace:



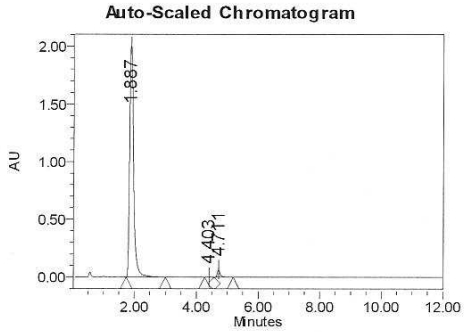
Unknown Peak Results

	RT	Height	Area	% Area
1	8.323	330143	2939368	100.00

***N*-(3,5-Dibromo-4-hydroxyphenyl)-3,5-bis-hydroxybenzamide (6a).**

N-(3,5-Dibromo-4-hydroxyphenyl)-3,5-bis-methoxybenzamide (**6g**, 71.7 mg, 0.166 mmol), boron tribromide (1.66 mL of 1 M BBr_3 in hexanes, 1.66 mmol), and anhydrous CH_2Cl_2 (5.0 mL) were subjected to the representative anisole deprotection procedures as outlined above. Flash chromatographic purification over silica (1:1-1:4 hexanes:EtOAc gradient elution) afforded *N*-(3,5-dibromo-4-hydroxyphenyl)-3,5-bis-hydroxybenzamide (**6a**) as a tan solid (44.2 mg, 66%). ^{1}H-NMR (500 MHz, d_6-DMSO) δ 10.06 (s, 1H), 9.67 (s, 1H), 9.55 (s, 1H), 7.99 (s, 2H), 6.74 (d, *J*=2.2 Hz, 2H), 6.40 (t, *J*=2.2 Hz, 1H); RP-HPLC: 97% & 97% pure.

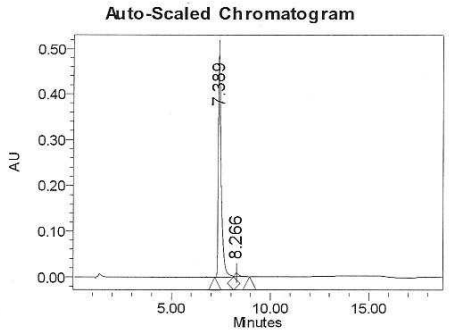
Primary RP-HPLC Conditions Chromatographic Trace:



Unknown Peak Results

	RT	Height	Area	% Area
1	1.887	2023692	18316878	97.69
2	4.403	1450	11935	0.06
3	4.711	66909	420454	2.24

Secondary RP-HPLC Conditions Chromatographic Trace:



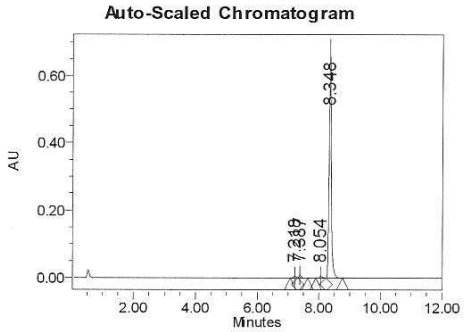
Unknown Peak Results

	RT	Height	Area	% Area
1	7.389	506240	4926223	97.45
2	8.266	8917	128794	2.55

***N*-(3,5-Dibromo-4-hydroxyphenyl)-3,5-dichlorobenzamide (6b).**

4-Amino-2,6-dibromophenol (89.4 mg, 0.319 mmol) and 3,5-dichlorobenzoyl chloride (67.7 mg, 0.323 mmol) were coupled as per procedures outlined in Method A above, affording *N*-(3,5-dibromo-4-hydroxyphenyl)-3,5-dichlorobenzamide (**6b**) as a grey solid (102 mg, 72%). ^{1}H-NMR (500 MHz, d_6-DMSO) δ 10.38 (s, 1H), 9.81 (s, 1H), 7.98 (s, 2H), 7.95 (s, 2H), 7.87 (s, 1H); RP-HPLC: 96% & 97% pure.

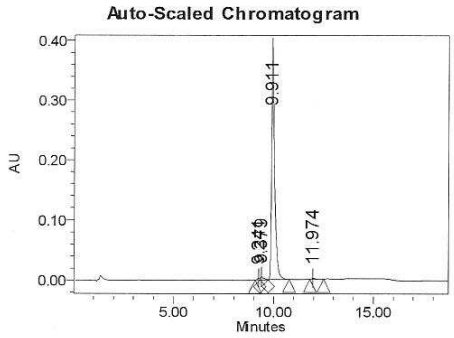
Primary RP-HPLC Conditions Chromatographic Trace:



Unknown Peak Results

	RT	Height	Area	% Area
1	7.218	6113	40175	1.14
2	7.387	8413	43148	1.23
3	8.054	6016	35821	1.02
4	8.348	675397	3394077	96.61

Secondary RP-HPLC Conditions Chromatographic Trace:



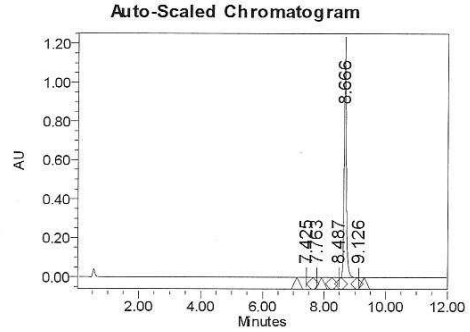
Unknown Peak Results

	RT	Height	Area	% Area
1	9.241	3469	26653	0.63
2	9.379	5091	63013	1.50
3	9.911	394548	4094717	97.39
4	11.974	1860	19902	0.47

_N_-(3,5-Dibromo-4-hydroxyphenyl)-3,5-dibromobenzamide (6c).

4-Amino-2,6-dibromophenol (93.4 mg, 0.334 mmol) and 3,5-dibromobenzoic acid (90.9 mg, 0.325 mmol) were coupled as per procedures outlined in Method B above, affording *N*-(3,5-dibromo-4-hydroxyphenyl)-3,5-dibromobenzamide (**6c**) as a tan powder (80.8 mg, 47%). ^{1}H-NMR (500 MHz, d_6-DMSO) δ 10.37 (s, 1H), 9.81 (s, 1H), 8.07-8.14 (m, 3H), 7.97 (s, 2H); RP-HPLC: 99% & >99% pure.

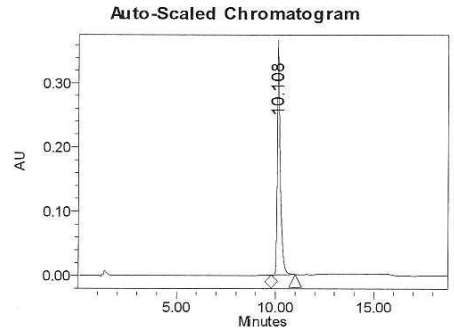
Primary RP-HPLC Conditions Chromatographic Trace:



Unknown Peak Results

	RT	Height	Area	% Area
1	7.425	2243	27707	0.47
2	7.763	1158	9778	0.17
3	8.487	1805	18502	0.31
4	8.666	1161043	5860771	98.94
5	9.126	1064	6879	0.12

Secondary RP-HPLC Conditions Chromatographic Trace:



Unknown Peak Results

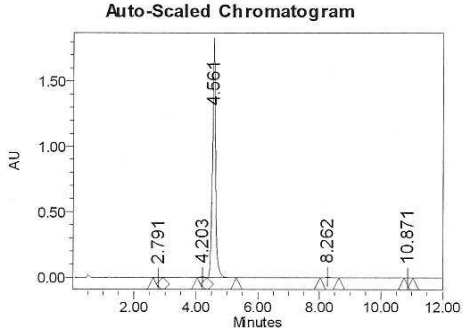
	RT	Height	Area	% Area
1	10.108	358838	3800020	100.00

_N_-(3,5-Dibromo-4-hydroxyphenyl)-3,5-dimethylbenzamide (6d).

4-Amino-2,6-dibromophenol (189 mg, 0.675 mmol) and 3,5-dimethylbenzoic acid (96.9 mg, 0.645 mmol) were coupled as per procedures outlined in Method B above, affording *N*-(3,5-dibromo-4-hydroxyphenyl)-3,5-dimethylbenzamide (**6d**) as a tan

powder (138 mg, 54%). ^{1}H-NMR (500 MHz, d_6-DMSO) δ 10.14 (s, 1H), 9.70 (s, 1H), 8.01 (s, 2H), 7.52 (s, 2H), 7.21 (s, 1H), 2.34 (s, 6H); RP-HPLC: 99% & >99% pure.

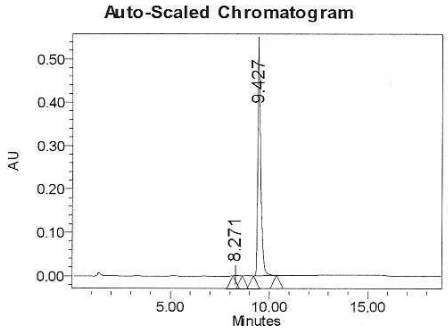
Primary RP-HPLC Conditions Chromatographic Trace:



Unknown Peak Results

	RT	Height	Area	% Area
1	2.791	1218	9132	0.07
2	4.203	8728	64648	0.51
3	4.561	1770593	12496264	98.94
4	8.262	8496	52736	0.42
5	10.871	1449	7530	0.06

Secondary RP-HPLC Conditions Chromatographic Trace:



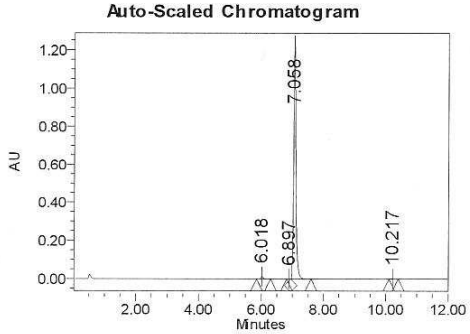
Unknown Peak Results

	RT	Height	Area	% Area
1	8.271	2240	20570	0.37
2	9.427	539307	5488374	99.63

_N_-(3,5-Dibromo-4-hydroxyphenyl)-3,5-difluorobenzamide (6e).

4-Amino-2,6-dibromophenol (90.5 mg, 0.323 mmol) and 3,5-difluorobenzoyl chloride (41.0 μL, 0.325 mmol) were coupled as per procedures outlined in Method A above, affording *N*-(3,5-dibromo-4-hydroxyphenyl)-3,5-difluorobenzamide (**6e**) as a grey powder (91.6 mg, 70%). ^{1}H-NMR (500 MHz, d_6-DMSO) δ 10.33 (s, 1H), 9.81 (s, 1H), 7.98 (s, 2H), 7.61-7.67 (m, 2H), 7.53 (tt, *J*=2.3, 9.1 Hz, 1H); RP-HPLC: 98% & 98% pure.

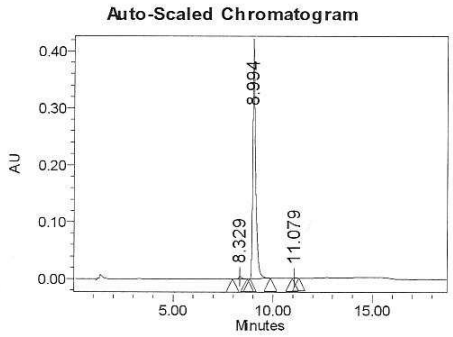
Primary RP-HPLC Conditions Chromatographic Trace:



Unknown Peak Results

	RT	Height	Area	% Area
1	6.018	13916	70186	1.12
2	6.897	1321	5742	0.09
3	7.058	1225737	6154542	98.62
4	10.217	1999	10085	0.16

Secondary RP-HPLC Conditions Chromatographic Trace:



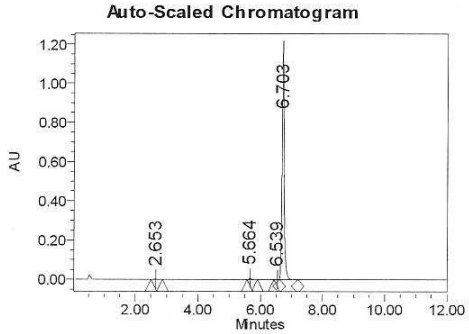
Unknown Peak Results

	RT	Height	Area	% Area
1	8.329	4318	43475	1.03
2	8.994	413236	4151403	98.73
3	11.079	1158	9798	0.23

_N_-(3,5-Dibromo-4-hydroxyphenyl)-3,5-bis-methoxybenzamide (6g).

4-Amino-2,6-dibromophenol (96.2 mg, 0.344 mmol) and 3,5-bis-methoxybenzoyl chloride (72.5 mg, 0.361 mmol) were coupled as per procedures outlined in Method A above, affording *N*-(3,5-dibromo-4-hydroxyphenyl)-3,5-bis-methoxybenzamide (**6g**) as a grey powder (87.1 mg, 59%). ^{1}H-NMR (500 MHz, d_6-DMSO) δ 10.15 (s, 1H), 9.73 (s, 1H), 8.00 (s, 2H), 7.07 (d, *J*=2.2 Hz, 2H), 6.71 (d *J*=2.1 Hz, 1H), 3.81 (s, 6H); RP-HPLC: 99% & 99% pure.

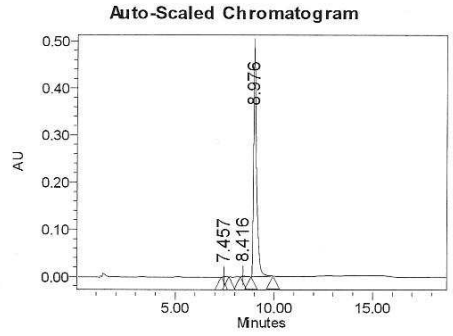
Primary RP-HPLC Conditions Chromatographic Trace:



Unknown Peak Results

	RT	Height	Area	% Area
1	2.653	2031	14723	0.26
2	5.664	8564	42449	0.74
3	6.539	1236	5667	0.10
4	6.703	1166152	5682064	98.91

Secondary RP-HPLC Conditions Chromatographic Trace:



Unknown Peak Results

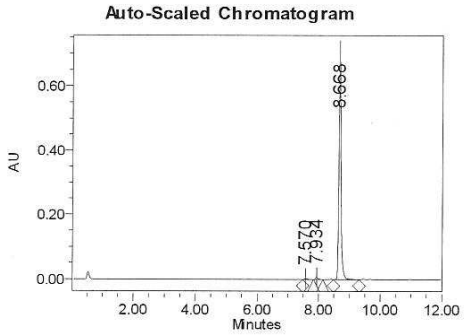
	RT	Height	Area	% Area
1	7.457	1797	14770	0.29
2	8.416	2880	30816	0.61
3	8.976	494611	5018403	99.10

_N_-(3,5-Dibromo-4-hydroxyphenyl)-3,5-bis-trifluoromethylbenzamide (6j).

4-Amino-2,6-dibromophenol (98.8 mg, 0.353 mmol) and 3,5-bis-trifluoromethylbenzoyl chloride (64.0 μL, 0.353 mmol) were coupled as per procedures outlined in Method A above, affording *N*-(3,5-dibromo-4-hydroxyphenyl)-3,5-bis-

trifluoromethylbenzamide (**6j**) as a grey powder (145 mg, 81%). ^{1}H-NMR (500 MHz, d_6-DMSO) δ 10.61 (s, 1H), 9.86 (s, 1H), 8.58 (s, 2H), 8.38 (s, 1H), 7.99 (s, 2H); RP-HPLC: 98% & 98% pure.

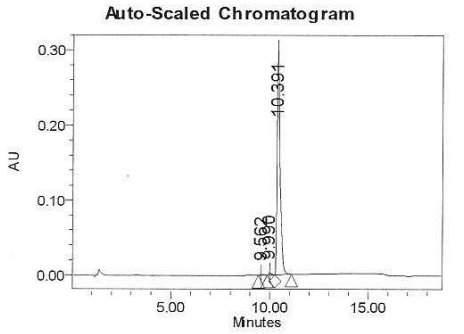
Primary RP-HPLC Conditions Chromatographic Trace:



Unknown Peak Results

	RT	Height	Area	% Area
1	7.570	3483	16858	0.48
2	7.934	7621	35738	1.01
3	8.668	703883	3480434	98.51

Secondary RP-HPLC Conditions Chromatographic Trace:



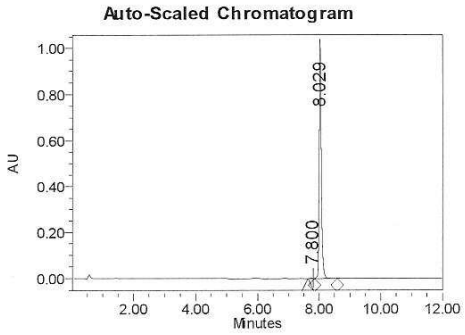
Unknown Peak Results

	RT	Height	Area	% Area
1	9.562	1582	15689	0.50
2	9.990	3173	29217	0.93
3	10.391	305758	3095704	98.57

_N_-(3,5-Dibromo-4-hydroxyphenyl)-3-hydroxybenzamide (7a).

_N_-(3,5-Dibromo-4-hydroxyphenyl)-3-methoxybenzamide (**7g**, 75.1 mg, 0.187 mmol), boron tribromide (0.94 mL of 1 M BBr_3 in hexanes, 0.94 mmol), and anhydrous CH_2Cl_2 (5.0 mL) were subjected to the representative anisole deprotection procedures as outlined above. Flash chromatographic purification over silica (1:1-1:2 hexanes:EtOAc gradient elution) afforded _N_-(3,5-dibromo-4-hydroxyphenyl)-3-hydroxybenzamide (**7a**) as a brownish-white solid (56.2 mg, 78%). ^{1}H-NMR (500 MHz, d_6-DMSO) δ 10.14 (s, 1H), 9.74 (s, 1H), 9.70 (s, 1H), 8.00 (s, 2H), 7.28-7.36 (m, 3H), 6.96 (ddd, J=1.3, 2.5, 7.8 Hz, 1H); RP-HPLC: >99% & >99% pure.

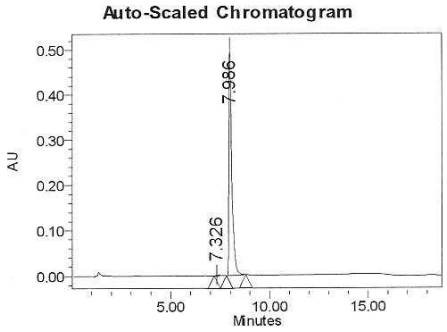
Primary RP-HPLC Conditions Chromatographic Trace:



Unknown Peak Results

	RT	Height	Area	% Area
1	7.800	2624	11783	0.25
2	8.029	986505	4630367	99.75

Secondary RP-HPLC Conditions Chromatographic Trace:



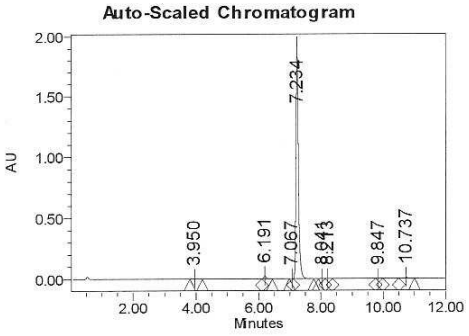
Unknown Peak Results

	RT	Height	Area	% Area
1	7.326	2277	24928	0.50
2	7.986	508560	4988567	99.50

_N_-(3,5-Dibromo-4-hydroxyphenyl)-3-chlorobenzamide (7b).

4-Amino-2,6-dibromophenol (96.9 mg, 0.346 mmol) and 3-chlorobenzoyl chloride (44.0 μL, 0.344 mmol) were coupled as per procedures outlined in Method A above, affording *N*-(3,5-dibromo-4-hydroxyphenyl)-3-chlorobenzamide (**7b**) as a brownish-grey powder (93.1 mg, 67%). ^{1}H-NMR (500 MHz, d_6-DMSO) δ 10.32 (s, 1H), 9.77 (s, 1H), 8.00 (s, 2H), 7.98 (t, *J*=1.8 Hz, 1H), 7.88 (dt, *J*=1.2, 7.8 Hz, 1H), 7.66 (ddd, *J*=0.9, 2.0, 8.0 Hz, 1H), 7.56 (t, *J*=7.9 Hz, 1H); RP-HPLC: 97% & 98% pure.

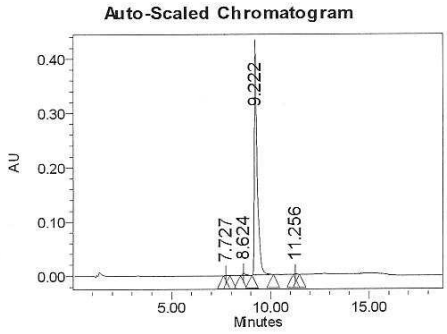
Primary RP-HPLC Conditions Chromatographic Trace:



Unknown Peak Results

	RT	Height	Area	% Area
1	3.950	3740	27432	0.26
2	6.191	25376	134026	1.27
3	7.067	2767	10732	0.10
4	7.234	1904307	10337703	97.58
5	8.041	1523	7556	0.07
6	8.213	1405	9665	0.09
7	9.847	1487	8185	0.08
8	10.737	10900	58481	0.55

Secondary RP-HPLC Conditions Chromatographic Trace:



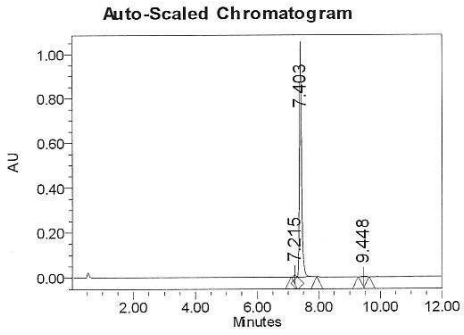
Unknown Peak Results

	RT	Height	Area	% Area
1	7.727	1093	8705	0.20
2	8.624	4263	44983	1.04
3	9.222	422517	4262041	98.53
4	11.256	1215	9983	0.23

***N*-(3,5-Dibromo-4-hydroxyphenyl)-3-bromobenzamide (7c).**

4-Amino-2,6-dibromophenol (106 mg, 0.378 mmol) and 3-bromobenzoyl chloride (50.0 μL, 0.379 mmol) were coupled as per procedures outlined in Method A above, affording *N*-(3,5-dibromo-4-hydroxyphenyl)-3-bromobenzamide (**7c**) as a light grey powder (118 mg, 69%). ^{1}H-NMR (500 MHz, d_6-DMSO) δ 10.32 (s, 1H), 9.76 (s, 1H), 8.11 (t, *J*=1.8 Hz, 1H), 7.99 (s, 2H), 7.91 (ddd, *J*=1.0, 1.6, 7.8 Hz, 1H), 7.79 (ddd, *J*=1.0, 2.0, 8.0 Hz, 1H), 7.50 (t, *J*=7.9 Hz, 1H); RP-HPLC: 98% & >99% pure.

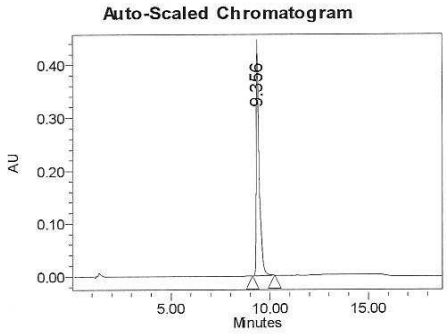
Primary RP-HPLC Conditions Chromatographic Trace:



Unknown Peak Results

	RT	Height	Area	% Area
1	7.215	9862	49269	0.98
2	7.403	1009178	4945065	98.81
3	9.448	1809	10184	0.20

Secondary RP-HPLC Conditions Chromatographic Trace:



Unknown Peak Results

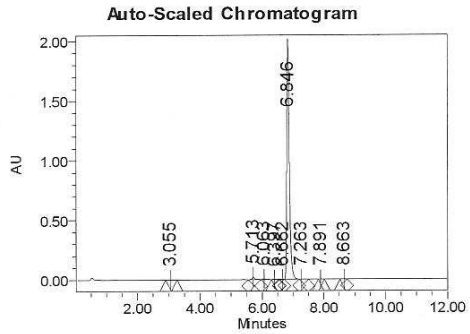
	RT	Height	Area	% Area
1	9.356	434958	4479287	100.00

***N*-(3,5-Dibromo-4-hydroxyphenyl)-3-methylbenzamide (7d).**

4-Amino-2,6-dibromophenol (93.6 mg, 0.334 mmol) and *m*-toluoyl chloride (44.0 μL, 0.333 mmol) were coupled as per procedures outlined in Method A above, affording *N*-(3,5-dibromo-4-hydroxyphenyl)-3-methylbenzamide (**7d**) as a grey powder (51.3 mg,

40%). ^{1}H-NMR (500 MHz, d_6-DMSO) δ 10.19 (s, 1H), 9.71 (s, 1H), 8.01 (s, 2H), 7.68-7.76 (m, 2H), 7.38-7.44 (m, 2H), 2.38 (s, 3H); RP-HPLC: 98% & >99% pure.

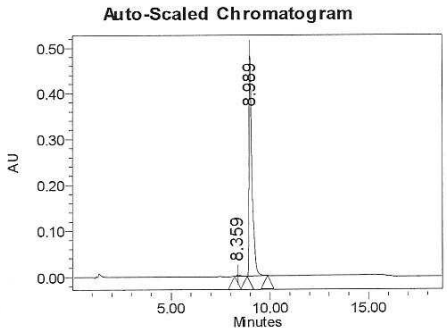
Primary RP-HPLC Conditions Chromatographic Trace:



Unknown Peak Results

	RT	Height	Area	% Area
1	3.055	1565	11965	0.10
2	5.713	21632	112167	0.96
3	6.063	8061	41258	0.35
4	6.397	1102	7925	0.07
5	6.662	3441	15805	0.13
6	6.846	1956564	11481941	98.06
7	7.263	3467	26614	0.23
8	7.891	1028	4400	0.04
9	8.663	1460	6879	0.06

Secondary RP-HPLC Conditions Chromatographic Trace:



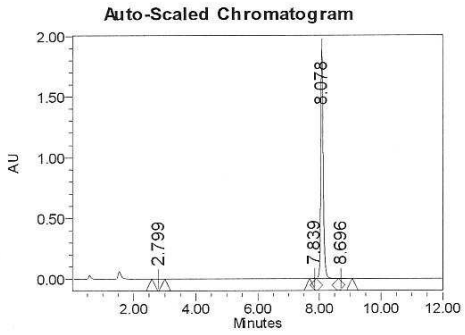
Unknown Peak Results

	RT	Height	Area	% Area
1	8.359	3863	45934	0.90
2	8.989	501714	5061916	99.10

_N_-(3,5-Dibromo-4-hydroxyphenyl)-3-fluorobenzamide (7e).

4-Amino-2,6-dibromophenol (181 mg, 0.646 mmol) and 3-fluorobenzoic acid (90.0 mg, 0.642 mmol) were coupled as per procedures outlined in Method B above. Flash chromatographic purification over silica (4:1-1:1 hexanes:EtOAc gradient elution) afforded *N*-(3,5-dibromo-4-hydroxyphenyl)-3-fluorobenzamide (**7e**) as an off-white solid (154 mg, 62%). ^{1}H-NMR (500 MHz, d_6-DMSO) δ 10.29 (s, 1H), 9.76 (s, 1H), 8.00 (s, 2H), 7.78 (dt, *J*=1.2, 7.9 Hz, 1H), 7.73 (ddd, *J*=1.6, 2.5, 9.9 Hz, 1H), 7.56-7.62 (m, 1H), 7.44 (ddt, *J*=0.8, 2.6, 8.9 Hz, 1H), 7.45 (dt, *J*=1.2, 7.4 Hz, 1H); RP-HPLC: >99% & >99% pure.

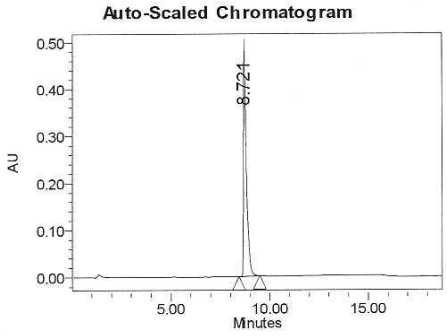
Primary RP-HPLC Conditions Chromatographic Trace:



Unknown Peak Results

	RT	Height	Area	% Area
1	2.799	1121	10636	0.10
2	7.839	8799	36922	0.34
3	8.078	1918108	10663333	99.10
4	8.696	4573	49379	0.46

Secondary RP-HPLC Conditions Chromatographic Trace:



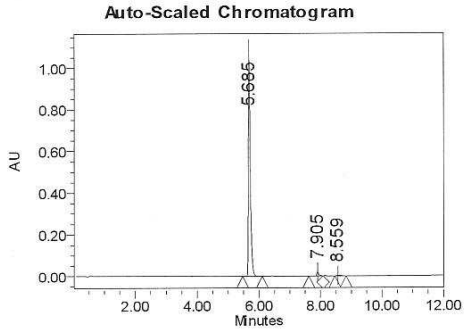
Unknown Peak Results

	RT	Height	Area	% Area
1	8.721	491809	4890778	100.00

_N_-(3,5-Dibromo-4-hydroxyphenyl)-3-aminobenzamide (7f).

N-(3,5-Dibromo-4-hydroxyphenyl)-3-nitrobenzamide (**7h**, 72.2 mg, 0.174 mmol), tin powder (94.3 mg, 0.795 mmol), and HCl/AcOH (0.2/2.0 mL) were subjected to the representative nitro reduction procedures as outlined above. Flash chromatographic purification over silica (1:1-1:4 hexanes:EtOAc gradient elution) afforded *N*-(3,5-dibromo-4-hydroxyphenyl)-3-aminobenzamide (**7f**) as a tan solid (27.5 mg, 41%). ^{1}H-NMR (500 MHz, d_6-DMSO) δ 10.06 (s, 1H), 9.66 (s, 1H), 7.99 (s, 2H), 7.13 (t, *J*=7.8 Hz, 1H), 7.05 (t, *J*=2.0 Hz, 1H), 7.02 (dt, *J*=1.2, 7.6 Hz, 1H), 6.74 (ddd, *J*=0.9, 2.3, 8.0 Hz, 1H), 5.31 (s, 2H); RP-HPLC: 98% & 96% pure.

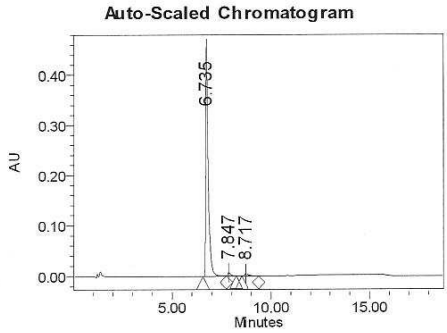
Primary RP-HPLC Conditions Chromatographic Trace:



Unknown Peak Results

	RT	Height	Area	% Area
1	5.685	1068702	4693626	97.79
2	7.905	19682	94710	1.97
3	8.559	1181	11153	0.23

Secondary RP-HPLC Conditions Chromatographic Trace:



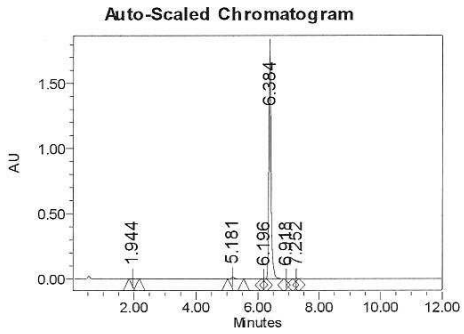
Unknown Peak Results

	RT	Height	Area	% Area
1	6.735	455756	3889398	96.72
2	7.847	6829	63321	1.57
3	8.717	4824	68378	1.70

_N_-(3,5-Dibromo-4-hydroxyphenyl)-3-methoxybenzamide (7g).

4-Amino-2,6-dibromophenol (104 mg, 0.370 mmol) and *m*-anisoyl chloride (52.0 μL, 0.370 mmol) were coupled as per procedures outlined in Method A above, affording *N*-(3,5-dibromo-4-hydroxyphenyl)-3-methoxybenzamide (**7g**) as a brown powder (97.2 mg, 66%). ^{1}H-NMR (500 MHz, d_6-DMSO) δ 10.19 (s, 1H), 9.73 (s, 1H), 8.01 (s, 2H), 7.50 (d, *J*=7.7 Hz, 1H), 7.42-7.47 (m, 2H), 7.15 (dd, *J*=2.5, 8.1 Hz, 1H), 3.82 (s, 3H); RP-HPLC: 98% & >99% pure.

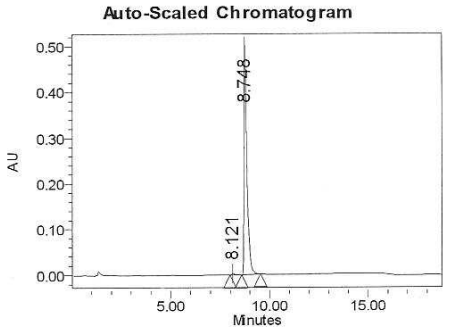
Primary RP-HPLC Conditions Chromatographic Trace:



Unknown Peak Results

	RT	Height	Area	% Area
1	1.944	2017	12565	0.14
2	5.181	13693	74370	0.84
3	6.196	2024	9219	0.10
4	6.384	1736476	8707446	98.72
5	6.918	1190	8829	0.10
6	7.252	1173	7833	0.09

Secondary RP-HPLC Conditions Chromatographic Trace:



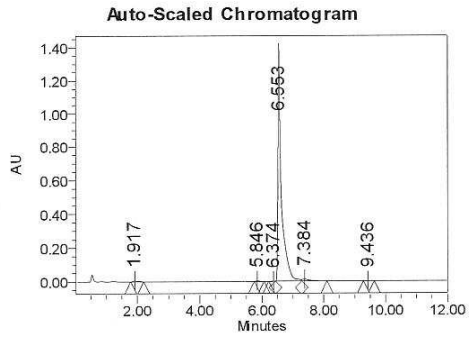
Unknown Peak Results

	RT	Height	Area	% Area
1	8.121	3765	41986	0.83
2	8.748	500923	5044675	99.17

_N_-(3,5-Dibromo-4-hydroxyphenyl)-3-nitrobenzamide (7h).

4-Amino-2,6-dibromophenol (102 mg, 0.365 mmol) and 3-nitrobenzoyl chloride (66.3 mg, 0.357 mmol) were coupled as per procedures outlined in Method A above, affording *N*-(3,5-dibromo-4-hydroxyphenyl)-3-nitrobenzamide (**7h**) as a pale yellow solid (93.0 mg, 63%). ^{1}H-NMR (500 MHz, d_6-DMSO) δ 10.56 (s, 1H), 9.81 (s, 1H), 8.78 (t, *J*=1.9 Hz, 1H), 8.44 (ddd, *J*=1.0, 2.3, 8.2 Hz, 1H), 8.37 (ddd, *J*=1.0, 1.5, 7.8 Hz, 1H), 8.02 (s, 2H), 7.85 (t, *J*=8.0 Hz, 1H); RP-HPLC: 97% & 98% pure.

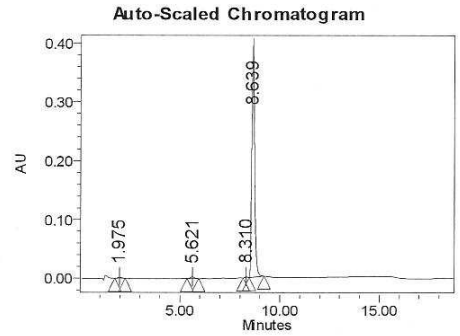
Primary RP-HPLC Conditions Chromatographic Trace:



Unknown Peak Results

	RT	Height	Area	% Area
1	1.917	7853	52313	0.47
2	5.846	5403	27527	0.25
3	6.374	1146	5571	0.05
4	6.553	1367744	10904609	97.13
5	7.384	13500	228355	2.03
6	9.436	1577	8837	0.08

Secondary RP-HPLC Conditions Chromatographic Trace:



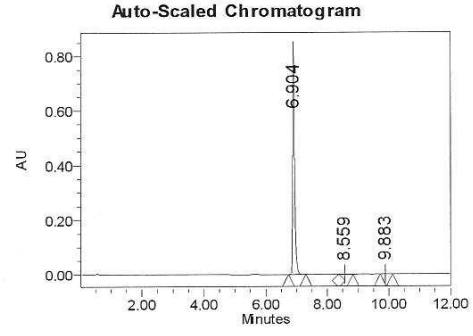
Unknown Peak Results

	RT	Height	Area	% Area
1	1.975	2180	23992	0.61
2	5.621	3060	38588	0.98
3	8.310	2450	19668	0.50
4	8.639	391370	3863120	97.92

_N_-(3,5-Dibromo-4-hydroxyphenyl)-3-carboxybenzamide (7i).

4-Amino-2,6-dibromophenol (220 mg, 0.786 mmol) and mono-methyl isophthalate (140 mg, 0.774 mmol) were coupled as per procedures outlined in Method B above. Flash chromatographic purification over silica (2:1-1:1 hexanes:EtOAc gradient elution) afforded the intermediate methyl ester (150 mg, 45%), from which 82.3 mg (0.192 mmol) was hydrolyzed with $LiOH•H_2O$ (35.5 mg, 0.846 mmol) in H_2O/MeOH/THF (0.5/0.5/1.5 mL) as per the representative methyl ester hydrolysis procedures as outlined above, affording *N*-(3,5-dibromo-4-hydroxyphenyl)-3-carboxybenzamide (**7i**) as a pale yellow solid (55.8 mg, 70%). ^{1}H-NMR (500 MHz, d_6-DMSO) δ 13.25 (s, 1H), 10.43 (s, 1H), 9.75 (s, 1H), 8.51 (t, *J*=1.4 Hz, 1H), 8.16 (dt, *J*=1.4, 7.7 Hz, 1H), 8.13 (dt, *J*=1.4, 7.7 Hz, 1H), 8.02 (s, 2H), 7.66 (t, *J*=7.7 Hz, 1H); RP-HPLC: >99% & >99% pure.

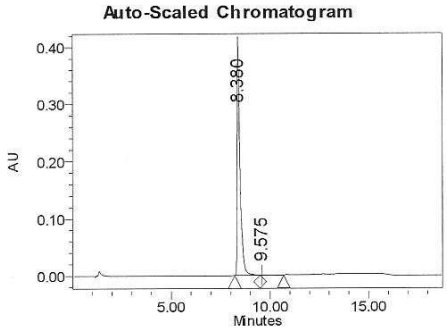
Primary RP-HPLC Conditions Chromatographic Trace:



Unknown Peak Results

	RT	Height	Area	% Area
1	6.904	811079	3495666	99.38
2	8.559	1230	12036	0.34
3	9.883	1926	9732	0.28

Secondary RP-HPLC Conditions Chromatographic Trace:



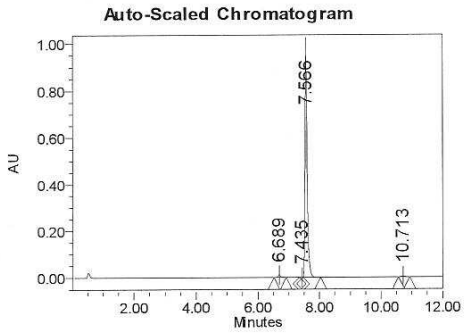
Unknown Peak Results

	RT	Height	Area	% Area
1	8.380	403784	4123014	99.41
2	9.575	1001	24303	0.59

_N_-(3,5-Dibromo-4-hydroxyphenyl)-3-trifluoromethylbenzamide (7j).

4-Amino-2,6-dibromophenol (95.5 mg, 0.341 mmol) and 3-trifluoromethylbenzoyl chloride (52.0 μL, 0.345 mmol) were coupled as per procedures outlined in Method A above, affording *N*-(3,5-dibromo-4-hydroxyphenyl)-3-trifluoromethylbenzamide (**7j**) as a grey powder (115 mg, 77%). ^{1}H-NMR (500 MHz, d_6-DMSO) δ 10.44 (s, 1H), 9.83 (s, 1H), 8.26 (s, 1H), 8.22 (d, *J*=7.7 Hz, 1H), 8.00 (s, 2H), 7.96 (d, *J*=7.9 Hz, 1H), 7.78 (t, *J*=7.8 Hz, 1H); RP-HPLC: 98% & 98% pure.

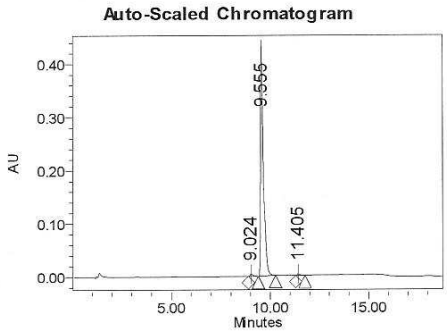
Primary RP-HPLC Conditions Chromatographic Trace:



Unknown Peak Results

	RT	Height	Area	% Area
1	6.689	10034	48623	1.02
2	7.435	1118	5295	0.11
3	7.566	960830	4707894	98.37
4	10.713	4669	24157	0.50

Secondary RP-HPLC Conditions Chromatographic Trace:



Unknown Peak Results

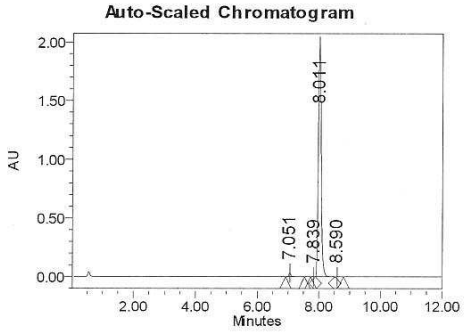
	RT	Height	Area	% Area
1	9.024	4397	42289	0.97
2	9.555	431486	4286262	98.43
3	11.405	2671	26180	0.60

_N_-(3,5-Dibromo-4-hydroxyphenyl)-3,5-dichloro-4-methoxybenzamide (8b).

4-Amino-2,6-dibromophenol (174 mg, 0.621 mmol) and 3,5-dichloro-4-methoxybenzoic acid (137 mg, 0.620 mmol) were coupled as per procedures outlined in Method B above. Flash chromatographic purification over silica (4:1-2:1 hexanes:EtOAc

gradient elution) afforded *N*-(3,5-dibromo-4-hydroxyphenyl)-3,5-dichloro-4-methoxybenzamide (**8b**) as an off-white solid (151 mg, 52%). ^{1}H-NMR (500 MHz, d_6-DMSO) δ 10.31 (s, 1H), 9.79 (s, 1H), 8.04 (s, 2H), 7.97 (s, 2H), 3.89 (s, 3H); RP-HPLC: 98% & 95% pure.

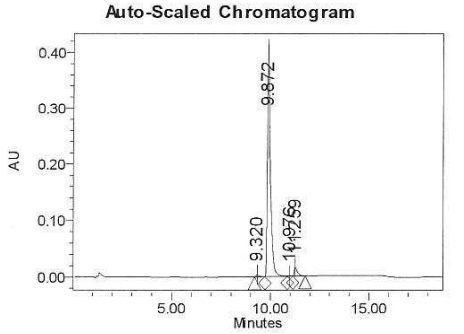
Primary RP-HPLC Conditions Chromatographic Trace:



Unknown Peak Results

	RT	Height	Area	% Area
1	7.051	33758	174228	1.36
2	7.839	2818	12362	0.10
3	8.011	2000100	12602861	98.45
4	8.590	1820	11317	0.09

Secondary RP-HPLC Conditions Chromatographic Trace:



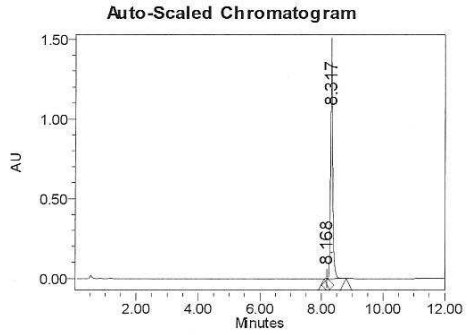
Unknown Peak Results

	RT	Height	Area	% Area
1	9.320	3493	38813	0.86
2	9.872	412537	4267337	95.01
3	10.976	1402	14706	0.33
4	11.259	15609	170759	3.80

***N*-(3,5-Dibromo-4-hydroxyphenyl)-3,5-dibromo-4-methoxybenzamide (8c).**

4-Amino-2,6-dibromophenol (125 mg, 0.448 mmol) and 3,5-dibromo-4-methoxybenzoic acid (140 mg, 0.452 mmol) were coupled as per procedures outlined in Method B above. Flash chromatographic purification over silica (4:1-2:1 hexanes:EtOAc gradient elution) afforded *N*-(3,5-dibromo-4-hydroxyphenyl)-3,5-dibromo-4-methoxybenzamide (**8c**) as a white solid (185 mg, 74%). ^{1}H-NMR (500 MHz, d_6-DMSO) δ 10.31 (s, 1H), 9.79 (s, 1H), 8.21 (s, 2H), 7.97 (s, 2H), 3.86 (s, 3H); RP-HPLC: >99% & >99% pure.

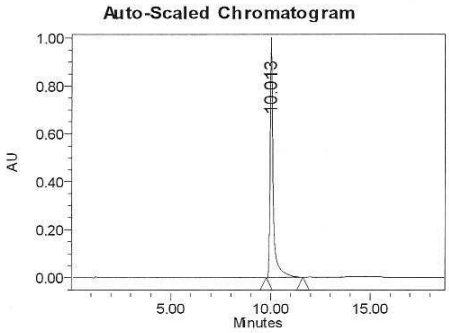
Primary RP-HPLC Conditions Chromatographic Trace:



Unknown Peak Results

	RT	Height	Area	% Area
1	8.168	2467	9421	0.14
2	8.317	1414139	6963168	99.86

Secondary RP-HPLC Conditions Chromatographic Trace:



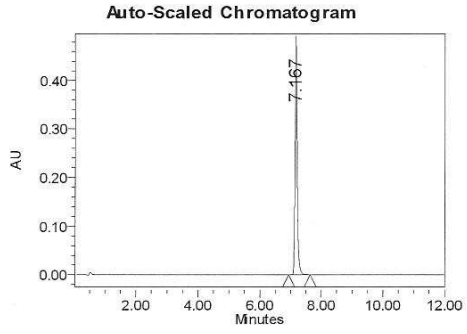
Unknown Peak Results

	RT	Height	Area	% Area
1	10.013	966482	10817700	100.00

_N_-(3,5-Dibromo-4-hydroxyphenyl)-3,5-dimethyl-4-methoxybenzamide (8d).

4-Amino-2,6-dibromophenol (123 mg, 0.438 mmol) and 3,5-dimethyl-4-methoxybenzoic acid (87.5 mg, 0.486 mmol) were coupled as per procedures outlined in Method B above. Flash chromatographic purification over silica (4:1-2:1 hexanes:EtOAc gradient elution) afforded *N*-(3,5-dibromo-4-hydroxyphenyl)-3,5-dimethyl-4-methoxybenzamide (**8d**) as an off-white solid (139 mg, 74%). ^{1}H-NMR (500 MHz, d_6-DMSO) δ 10.07 (s, 1H), 9.69 (s, 1H), 7.99 (s, 2H), 7.62 (s, 2H), 3.69 (s, 3H), 2.28 (s, 6H); RP-HPLC: >99% & >99% pure.

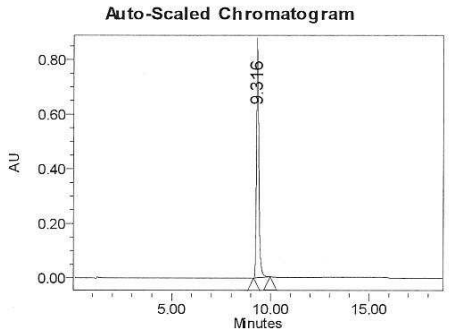
Primary RP-HPLC Conditions Chromatographic Trace:



Unknown Peak Results

	RT	Height	Area	% Area
1	7.167	461013	2272812	100.00

Secondary RP-HPLC Conditions Chromatographic Trace:



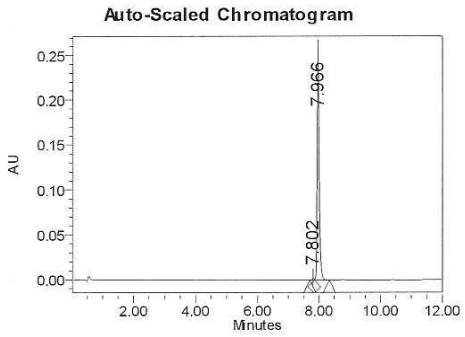
Unknown Peak Results

	RT	Height	Area	% Area
1	9.316	843621	7154925	100.00

_N_-(3,5-Dibromo-4-hydroxyphenyl)-3,5-difluoro-4-methoxybenzamide (8e).

4-Amino-2,6-dibromophenol (119 mg, 0.427 mmol) and 3,5-difluoro-4-methoxybenzoyl chloride (122 mg, 0.590 mmol) were coupled as per procedures outlined in Method A above. Flash chromatographic purification over silica (4:1-2:1 hexanes:EtOAc gradient elution) afforded *N*-(3,5-dibromo-4-hydroxyphenyl)-3,5-difluoro-4-methoxybenzamide (**8e**) as a light grey solid (140 mg, 75%). ^{1}H-NMR (500 MHz, d_6-DMSO) δ 10.22 (s, 1H), 9.78 (s, 1H), 7.97 (s, 2H), 7.70-7.77 (m, 2H), 4.02 (s, 3H); RP-HPLC: 99% & >99% pure.

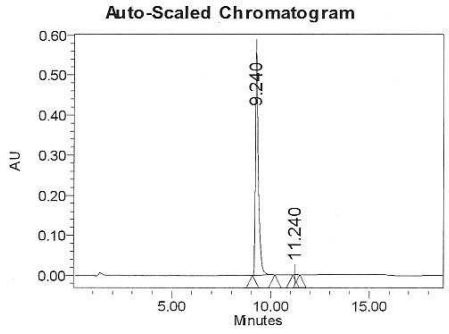
Primary RP-HPLC Conditions Chromatographic Trace:



Unknown Peak Results

	RT	Height	Area	% Area
1	7.802	2587	10640	0.92
2	7.966	251020	1147980	99.08

Secondary RP-HPLC Conditions Chromatographic Trace:



Unknown Peak Results

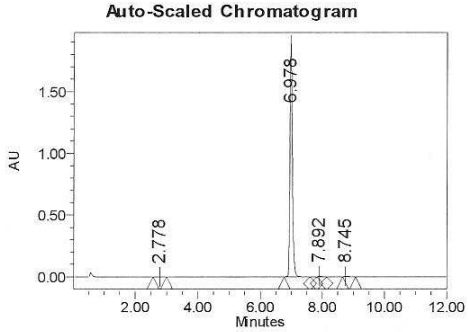
	RT	Height	Area	% Area
1	9.240	575049	5797213	99.73
2	11.240	1810	15496	0.27

_N_-(3,5-Dibromo-4-hydroxyphenyl)-4-hydroxybenzamide (9a).

N-(3,5-Dibromo-4-hydroxyphenyl)-4-methoxybenzamide (**9g**, 58.9 mg, 0.147 mmol), boron tribromide (0.73 mL of 1 M BBr_3 in hexanes, 0.73 mmol), and anhydrous CH_2Cl_2 (5.0 mL) were subjected to the representative anisole deprotection procedures as

outlined above. Flash chromatographic purification over silica (1:1-1:2 hexanes:EtOAc gradient elution) afforded *N*-(3,5-dibromo-4-hydroxyphenyl)-4-hydroxybenzamide (**9a**) as a white solid (40.3 mg, 71%). ^{1}H-NMR (500 MHz, d_6-DMSO) δ 10.11 (s, 1H), 9.97 (s, 1H), 9.65 (s, 1H), 7.99 (s, 2H), 7.79-7.83 (m, 2H), 6.83-6.87 (m, 2H); RP-HPLC: 99% & >99% pure.

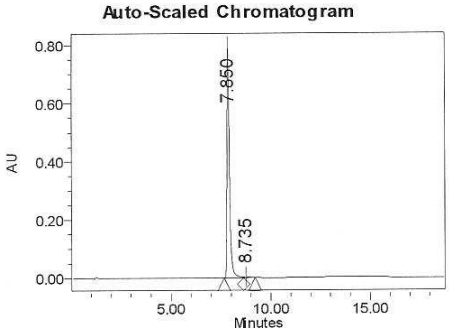
Primary RP-HPLC Conditions Chromatographic Trace:



Unknown Peak Results

	RT	Height	Area	% Area
1	2.778	1148	10978	0.11
2	6.978	1887836	10219661	99.01
3	7.892	10583	56236	0.54
4	8.745	3620	34720	0.34

Secondary RP-HPLC Conditions Chromatographic Trace:



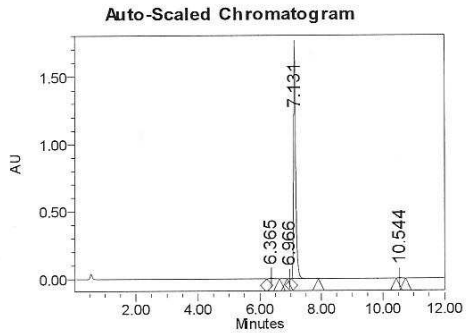
Unknown Peak Results

	RT	Height	Area	% Area
1	7.850	796799	6912570	99.15
2	8.735	3383	59422	0.85

***N*-(3,5-Dibromo-4-hydroxyphenyl)-4-chlorobenzamide (9b).**

4-Amino-2,6-dibromophenol (180 mg, 0.641 mmol) and 4-chlorobenzoic acid (101 mg, 0.642 mmol) were coupled as per procedures outlined in Method B above, affording *N*-(3,5-dibromo-4-hydroxyphenyl)-4-chlorobenzamide (**9b**) as an off-white solid (191 mg, 74%). ^{1}H-NMR (500 MHz, d_6-DMSO) δ 10.29 (s, 1H), 9.75 (s, 1H), 7.99 (s, 2H), 7.94-7.97 (m, 2H), 7.59-7.63 (m, 2H); RP-HPLC: 99% & >99% pure.

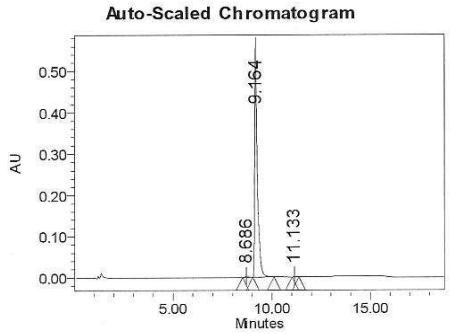
Primary RP-HPLC Conditions Chromatographic Trace:



Unknown Peak Results

	RT	Height	Area	% Area
1	6.365	9677	50441	0.61
2	6.966	1353	5742	0.07
3	7.131	1669989	8214715	99.04
4	10.544	4783	23557	0.28

Secondary RP-HPLC Conditions Chromatographic Trace:



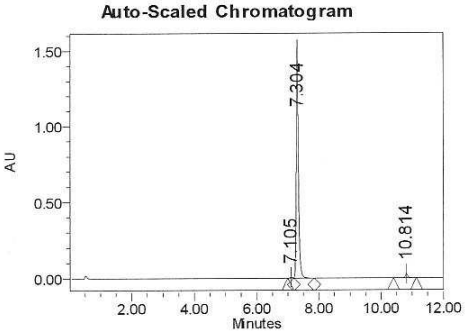
Unknown Peak Results

	RT	Height	Area	% Area
1	8.686	2478	26747	0.51
2	9.164	558545	5219907	99.27
3	11.133	1385	11764	0.22

_N_-(3,5-Dibromo-4-hydroxyphenyl)-4-bromobenzamide (9c).

4-Amino-2,6-dibromophenol (94.0 mg, 0.336 mmol) and 4-bromobenzoyl chloride (74.8 mg, 0.341 mmol) were coupled as per procedures outlined in Method A above, affording *N*-(3,5-dibromo-4-hydroxyphenyl)-4-bromobenzamide (**9c**) as a light-grey powder (107 mg, 71%). ^{1}H-NMR (500 MHz, d_6-DMSO) δ 10.29 (s, 1H), 9.75 (s, 1H), 7.99 (s, 2H), 7.86-7.90 (m, 2H), 7.73-7.77 (m, 2H); RP-HPLC: 97% & 98% pure.

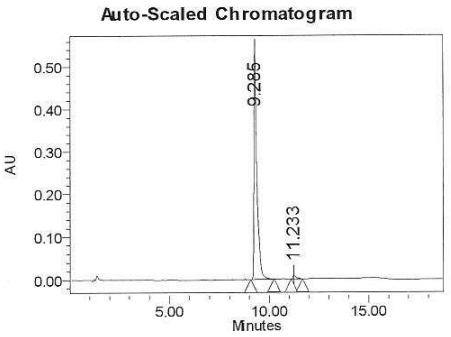
Primary RP-HPLC Conditions Chromatographic Trace:



Unknown Peak Results

	RT	Height	Area	% Area
1	7.105	8025	40077	0.53
2	7.304	1504553	7338119	97.74
3	10.814	25614	129322	1.72

Secondary RP-HPLC Conditions Chromatographic Trace:



Unknown Peak Results

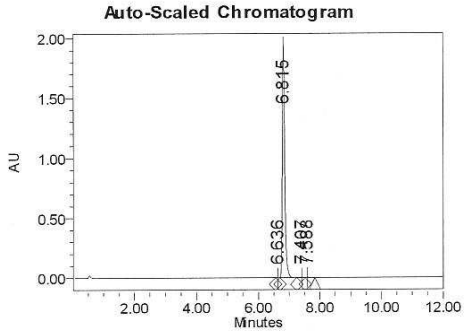
	RT	Height	Area	% Area
1	9.285	542345	5305740	98.10
2	11.233	9963	102499	1.90

_N_-(3,5-Dibromo-4-hydroxyphenyl)-4-methylbenzamide (9d).

4-Amino-2,6-dibromophenol (93.2 mg, 0.333 mmol) and *p*-toluoyl chloride (44.0 μL, 0.333 mmol) were coupled as per procedures outlined in Method A above. Flash chromatographic purification over silica (4:1-2:1 hexanes:EtOAc gradient elution) afforded *N*-(3,5-dibromo-4-hydroxyphenyl)-4-methylbenzamide (**9d**) as a white solid

(54.0 mg, 42%). ^{1}H-NMR (500 MHz, d_6-DMSO) δ 10.14 (s, 1H), 9.69 (s, 1H), 8.01 (s, 2H), 7.82-7.86 (m, 2H), 7.30-7.35 (m, 2H), 2.37 (s, 3H); RP-HPLC: >99% & >99% pure.

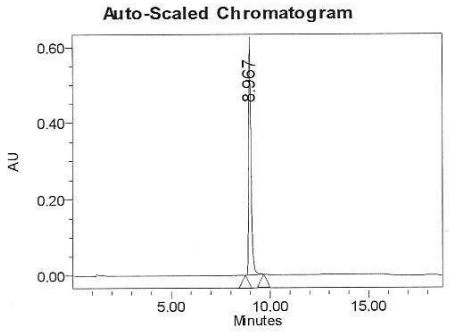
Primary RP-HPLC Conditions Chromatographic Trace:



Unknown Peak Results

	RT	Height	Area	% Area
1	6.636	2997	13173	0.12
2	6.815	1930223	10681710	99.30
3	7.407	3486	38230	0.36
4	7.588	3385	23626	0.22

Secondary RP-HPLC Conditions Chromatographic Trace:



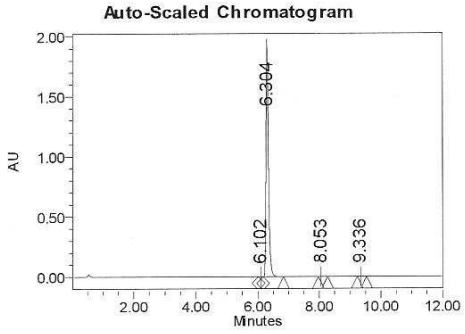
Unknown Peak Results

	RT	Height	Area	% Area
1	8.967	601637	5140334	100.00

_N_-(3,5-Dibromo-4-hydroxyphenyl)-4-fluorobenzamide (9e).

4-Amino-2,6-dibromophenol (189 mg, 0.675 mmol) and 4-fluorobenzoic acid (93.8 mg, 0.669 mmol) were coupled as per procedures outlined in Method B above. Flash chromatographic purification over silica (4:1-1:1 hexanes:EtOAc gradient elution) afforded *N*-(3,5-dibromo-4-hydroxyphenyl)-4-fluorobenzamide (**9e**) as an off-white solid (150 mg, 58%). ^{1}H-NMR (500 MHz, d_6-DMSO) δ 10.24 (s, 1H), 9.73 (s, 1H), 7.98-8.03 (m, 4H), 7.34-7.39 (m, 2H); RP-HPLC: >99% & >99% pure.

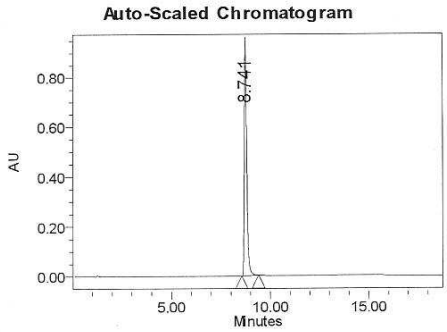
Primary RP-HPLC Conditions Chromatographic Trace:



Unknown Peak Results

	RT	Height	Area	% Area
1	6.102	1829	8206	0.08
2	6.304	1921456	10631563	99.70
3	8.053	2268	10899	0.10
4	9.336	2372	12378	0.12

Secondary RP-HPLC Conditions Chromatographic Trace:



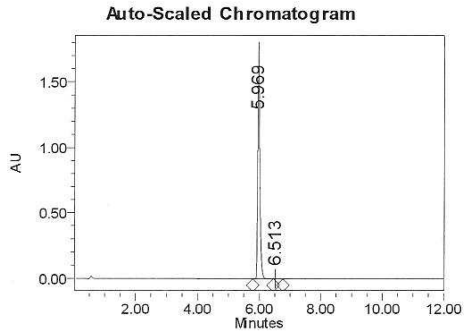
Unknown Peak Results

	RT	Height	Area	% Area
1	8.741	933013	7911438	100.00

_N_-(3,5-Dibromo-4-hydroxyphenyl)-4-aminobenzamide (9f).

N-(3,5-Dibromo-4-hydroxyphenyl)-4-nitrobenzamide (**9h**, 56.3 mg, 0.135 mmol), tin powder (74.7 mg, 0.629 mmol), and HCl/AcOH (0.2/2.0 mL) were subjected to the representative nitro reduction procedures as outlined above. Flash chromatographic purification over silica (1:1-1:2 hexanes:EtOAc gradient elution) afforded *N*-(3,5-dibromo-4-hydroxyphenyl)-4-aminobenzamide (**9f**) as an off-white solid (45.0 mg, 86%). ^{1}H-NMR (500 MHz, d_6-DMSO) δ 9;74 (s, 1H), 9.58 (s, 1H), 7.99 (s, 2H), 7.65-7.70 (m, 2H), 6.55-6.60 (m, 2H), 5.77 (s, 2H); RP-HPLC: >99% & 98% pure.

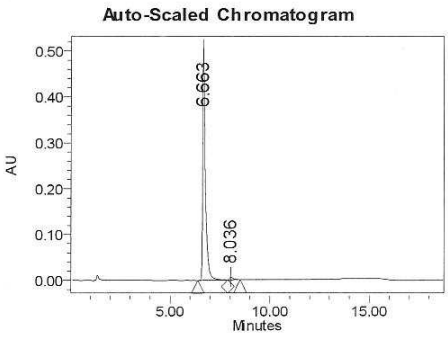
Primary RP-HPLC Conditions Chromatographic Trace:



Unknown Peak Results

	RT	Height	Area	% Area
1	5.969	1712835	7926812	99.89
2	6.513	1224	8930	0.11

Secondary RP-HPLC Conditions Chromatographic Trace:



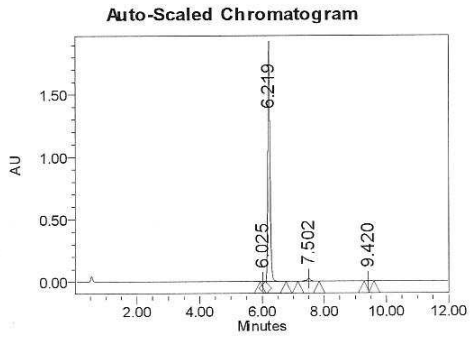
Unknown Peak Results

	RT	Height	Area	% Area
1	6.663	505825	4641244	98.43
2	8.036	6020	74242	1.57

***N*-(3,5-Dibromo-4-hydroxyphenyl)-4-methoxybenzamide (9g).**

4-Amino-2,6-dibromophenol (104 mg, 0.372 mmol) and *p*-anisoyl chloride (51.0 μL, 0.370 mmol) were coupled as per procedures outlined in Method A above, affording *N*-(3,5-dibromo-4-hydroxyphenyl)-4-methoxybenzamide (**9g**) as a light grey solid (77.8 mg, 52%). ^{1}H-NMR (500 MHz, d_6-DMSO) δ 10.07 (s, 1H), 9.67 (s, 1H), 8.00 (s, 2H), 7.90-7.95 (m, 2H), 7.03-7.08 (m, 2H); RP-HPLC: 98% & 95% pure.

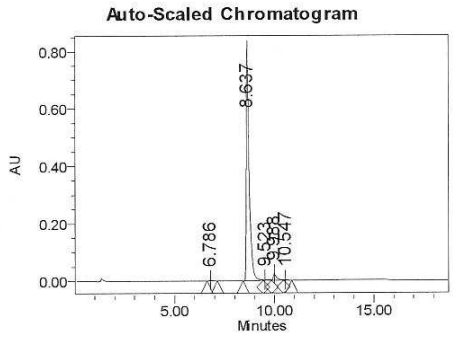
Primary RP-HPLC Conditions Chromatographic Trace:



Unknown Peak Results

	RT	Height	Area	% Area
1	6.025	1613	7507	0.08
2	6.219	1850549	9063013	97.84
3	7.502	24092	183388	1.98
4	9.420	1787	9602	0.10

Secondary RP-HPLC Conditions Chromatographic Trace:



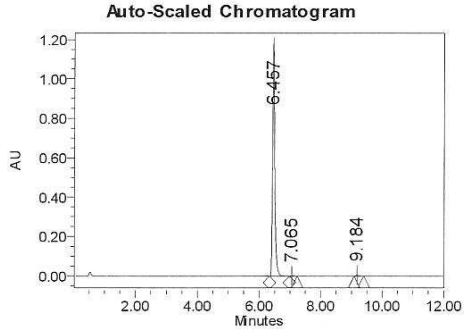
Unknown Peak Results

	RT	Height	Area	% Area
1	6.786	3972	33402	0.39
2	8.637	813023	8087511	95.27
3	9.523	3280	60849	0.72
4	9.988	22556	286734	3.38
5	10.547	1610	20620	0.24

***N*-(3,5-Dibromo-4-hydroxyphenyl)-4-nitrobenzamide (9h).**

4-Amino-2,6-dibromophenol (281 mg, 0.789 mmol) and 4-nitrobenzoic acid (168 mg, 1.01 mmol) were coupled as per procedures outlined in Method B above. Flash chromatographic purification over silica (1:1-1:2 hexanes:EtOAc gradient elution) afforded *N*-(3,5-dibromo-4-hydroxyphenyl)-4-nitrobenzamide (**9h**) as a yellow solid (99.0 mg, 27%). ^{1}H-NMR (500 MHz, d_6-DMSO) δ 10.54 (s, 1H), 9.82 (s, 1H), 8.35-8.39 (m, 2H), 8.14-8.18 (m, 2H), 8.00 (s, 2H); RP-HPLC: >99% & 99% pure.

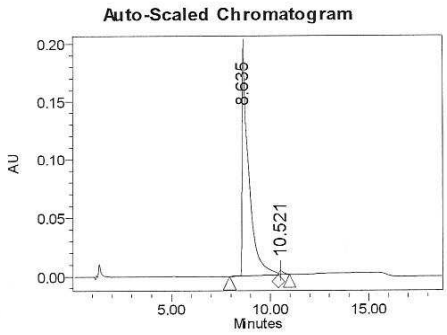
Primary RP-HPLC Conditions Chromatographic Trace:



Unknown Peak Results

	RT	Height	Area	% Area
1	6.457	1165398	5807935	99.25
2	7.065	1408	7350	0.13
3	9.184	7736	36254	0.62

Secondary RP-HPLC Conditions Chromatographic Trace:



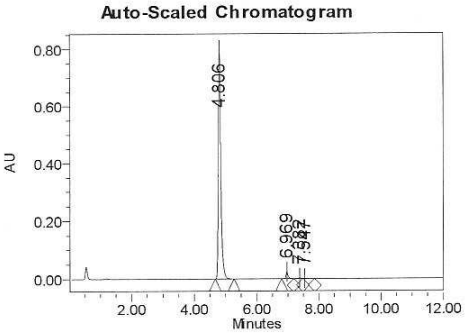
Unknown Peak Results

	RT	Height	Area	% Area
1	8.635	196361	4500038	98.88
2	10.521	3481	50951	1.12

_N_-(3,5-Dibromo-4-hydroxyphenyl)-4-carboxybenzamide (9i).

4-Amino-2,6-dibromophenol (94.9 mg, 0.339 mmol) and terephthalic acid mono-methyl ester chloride (66.3 mg, 0.334 mmol) were coupled as per procedures outlined in Method A above, affording the intermediate methyl ester (84.5 mg, 59%). 57.3 mg (0.134 mmol) of this intermediate was hydrolyzed with LiOH•H_2O (22.1 mg, 0.527 mmol) in H_2O/MeOH/THF (0.5/0.5/1.5 mL) as per the representative methyl ester hydrolysis procedures as outlined above, affording *N*-(3,5-dibromo-4-hydroxyphenyl)-4-carboxybenzamide (**9i**) as a white solid (35.7 mg, 64%). ^{1}H-NMR (500 MHz, d_6-DMSO) δ 13.24 (s, 1H), 10.39 (s, 1H), 9.77 (s, 1H), 8.00-8.08 (m, 6H); RP-HPLC: 96% & 98% pure.

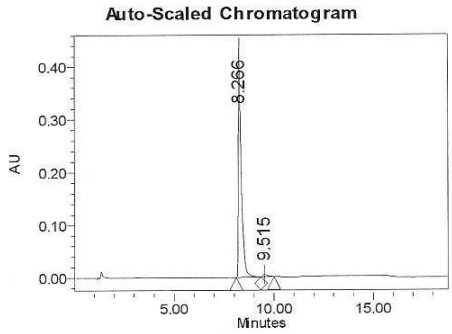
Primary RP-HPLC Conditions Chromatographic Trace:



Unknown Peak Results

	RT	Height	Area	% Area
1	4.806	803803	4320284	96.74
2	6.969	23333	109906	2.46
3	7.382	2777	22928	0.51
4	7.547	1372	12929	0.29

Secondary RP-HPLC Conditions Chromatographic Trace:



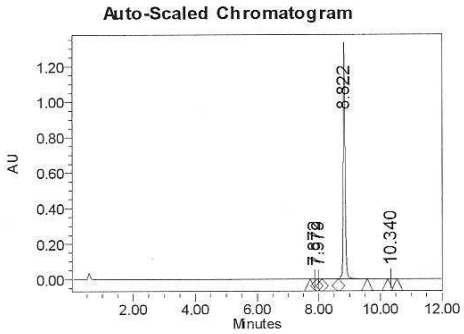
Unknown Peak Results

	RT	Height	Area	% Area
1	8.266	437540	4395827	98.38
2	9.515	4646	72210	1.62

_N_-(3,5-Dibromo-4-hydroxyphenyl)-4-trifluoromethylbenzamide (9j).

4-Amino-2,6-dibromophenol (104 mg, 0.371 mmol) and 4-trifluoromethylbenzoyl chloride (55.0 μL, 0.370 mmol) were coupled as per procedures outlined in Method A above, affording *N*-(3,5-dibromo-4-hydroxyphenyl)-4-trifluoromethylbenzamide (**9j**) as a light-grey powder (133 mg, 82%). ^{1}H-NMR (500 MHz, d_6-DMSO) δ 10.45 (s, 1H), 9.79 (s, 1H), 8.12 (d, *J*=8.1 Hz, 2H), 8.01 (s, 2H), 7.92 (d, *J*=8.3 Hz, 2H); RP-HPLC: >99% & >99% pure.

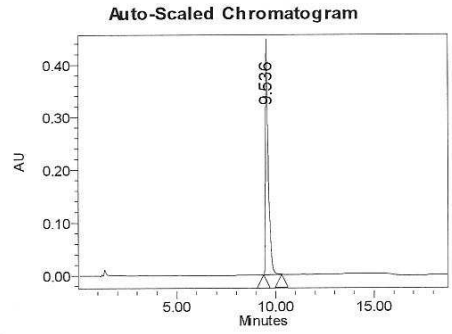
Primary RP-HPLC Conditions Chromatographic Trace:



Unknown Peak Results

	RT	Height	Area	% Area
1	7.872	1826	8129	0.14
2	7.979	1195	6118	0.11
3	8.822	1279839	5666139	99.52
4	10.340	2705	13197	0.23

Secondary RP-HPLC Conditions Chromatographic Trace:



Unknown Peak Results

	RT	Height	Area	% Area
1	9.536	433269	4273374	100.00