

# **Towards optimization of the linker substructure common to transthyretin amyloidogenesis inhibitors using biochemical and structural studies**

## ***Supporting Information***

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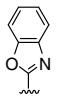
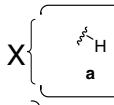
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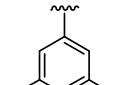
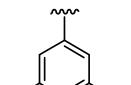
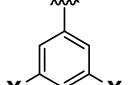
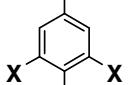
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**Figure S1:** Efficacy scoring of the compounds evaluated in the previously published aryl-X substructure optimization study. Inhibition of TTR aggregation and stoichiometry of benzoxazole bound to TTR in human blood plasma. Percent (%) values represent the extent of *in vitro* WT-TTR fibril formation in the presence of inhibitor (7.2  $\mu$ M inhibitor, 3.6  $\mu$ M TTR, pH 4.4, 37°C, 72 h) relative to aggregation in the absence of inhibitor (100%), with the best values shown in red (<20% aggregation; errors are typically less than  $\pm 5$  percentage points). The stoichiometries of the most potent aggregation inhibitors bound to TTR in human blood plasma *ex vivo* are shown in italics (10.8  $\mu$ M inhibitor, 1.8-5.4  $\mu$ M TTR; maximum binding stoichiometry 2) with those exhibiting exceptional binding selectivity to TTR boxed (errors are typically less than  $\pm 0.1$ ). The efficacies of the different substituents and substitution patterns of the aryl-X substructures were quantitatively scored by inputting the average % fibril formation (%F.F.<sub>ave</sub>) and average TTR plasma binding stoichiometry (P.S.<sub>ave</sub>) values into equation 1. Higher efficacy scores correspond to more potent and selective substructures.

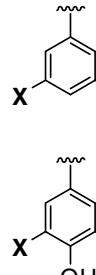
		a	b	c	d	e	f	g	h	i	%F.F. <sub>ave</sub>	P.S. <sub>ave</sub>	Efficacy Score
	X												
1		86%	83%	62%	60%	62%	70%	87%	59%	77%	71.8	0	0.094
2			88%	13% 0.06	20% 0.11		13% 0.13	87%	26%	52%	42.7	0.04	0.199
3		68%	45%	9% 0.24	4% 0.21	3% 0.26	18% 0.09	2% 0.50	61%		26.3	0.16	0.286
4			0% 0.10	0% 1.09	1% 1.41	0% 1.64	1% 0.98				0.4	1.04	0.679
5		89%	91%	96%	93%	88%	86%	83%		79%	88.1	0	0.040
6			88%	86%	93%	89%	38%				78.8	0	0.071
%F.F. <sub>ave</sub>		81.0	65.8	44.3	45.2	48.4	37.7	64.8	48.7	69.3			
P.S. <sub>ave</sub>		0	0.02	0.23	0.29	0.38	0.20	0.13	0	0			
Efficacy Score		0.063	0.116	0.229	0.235	0.237	0.249	0.132	0.171	0.102			

$$\text{Efficacy Score} = \frac{(100\% - \%F.F.\text{ ave}) \times (1 + P.S.\text{ ave})}{300\%} \dots \text{Eq. 1}$$

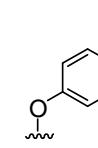
**Figure S2:** Phenolic pKa values calculated using the SPARC V4.0 online pKa calculator (<http://ibmlc2.chem.uga.edu/sparc/>). Calculations were based on unbound compounds in aqueous conditions; however, in the case of compounds bound to TTR, the local protein environment will also contribute to the phenolic pKa's and thus the values may differ.

		1	2	3	4	5
<b>X</b>						
	<b>a</b> $\text{CH}_3$					
	<b>b</b> $\text{Br}$					
	<b>c</b> $\text{CH}_3$	9.19	9.80	10.21	10.86	10.16
	<b>d</b> $\text{Br}$	5.38	5.98	6.39	7.04	6.35
<b>X</b>		6	7	8	9	10
	<b>a</b> $\text{CH}_3$					
	<b>b</b> $\text{Br}$					
	<b>c</b> $\text{CH}_3$	9.90	10.14	10.35	8.86	10.25
	<b>d</b> $\text{Br}$	6.08	6.32	6.53	5.04	6.43

**Figure S3:** Inhibitor purities as determined using two distinct RP-HPLC conditions. Refer to the Experimental procedures for individual HPLC traces.

		1	2	3	4	5
		X				
	<b>a</b> $\text{CH}_3$	$\text{>99\%}$ $\text{>99\%}$	$\text{>99\%}$ $\text{>99\%}$	$\text{>99\%}$ $\text{>99\%}$	$\text{98\%}$ $\text{96\%}$	$\text{>99\%}$ $\text{>99\%}$
		$\text{>99\%}$ $\text{97\%}$	$\text{>99\%}$ $\text{>99\%}$	$\text{>99\%}$ $\text{>99\%}$	$\text{98\%}$ $\text{>99\%}$	$\text{>99\%}$ $\text{>99\%}$
		$\text{98\%}$ $\text{98\%}$	$\text{>99\%}$ $\text{>99\%}$	$\text{>99\%}$ $\text{>99\%}$	$\text{>99\%}$ $\text{>99\%}$	$\text{>99\%}$ $\text{98\%}$
		$\text{>99\%}$ $\text{96\%}$	$\text{>99\%}$ $\text{99\%}$	$\text{>99\%}$ $\text{>99\%}$	$\text{97\%}$ $\text{98\%}$	$\text{96\%}$ $\text{94\%}$
	<b>b</b> $\text{Br}$	$\text{>99\%}$ $\text{97\%}$	$\text{>99\%}$ $\text{>99\%}$	$\text{>99\%}$ $\text{>99\%}$	$\text{98\%}$ $\text{>99\%}$	$\text{>99\%}$ $\text{>99\%}$
		$\text{>99\%}$ $\text{96\%}$	$\text{>99\%}$ $\text{99\%}$	$\text{>99\%}$ $\text{>99\%}$	$\text{>99\%}$ $\text{97\%}$	$\text{>99\%}$ $\text{98\%}$
		$\text{>99\%}$ $\text{96\%}$	$\text{>99\%}$ $\text{99\%}$	$\text{>99\%}$ $\text{>99\%}$	$\text{>99\%}$ $\text{99\%}$	$\text{>99\%}$ $\text{98\%}$
		$\text{>99\%}$ $\text{96\%}$	$\text{>99\%}$ $\text{99\%}$	$\text{>99\%}$ $\text{>99\%}$	$\text{>99\%}$ $\text{97\%}$	$\text{>99\%}$ $\text{98\%}$
	<b>c</b> $\text{CH}_3$	$\text{98\%}$ $\text{98\%}$	$\text{>99\%}$ $\text{>99\%}$	$\text{>99\%}$ $\text{>99\%}$	$\text{>99\%}$ $\text{>99\%}$	$\text{>99\%}$ $\text{98\%}$
		$\text{>99\%}$ $\text{96\%}$	$\text{>99\%}$ $\text{99\%}$	$\text{>99\%}$ $\text{>99\%}$	$\text{>99\%}$ $\text{99\%}$	$\text{>99\%}$ $\text{98\%}$
		$\text{>99\%}$ $\text{96\%}$	$\text{>99\%}$ $\text{99\%}$	$\text{>99\%}$ $\text{>99\%}$	$\text{>99\%}$ $\text{97\%}$	$\text{>99\%}$ $\text{98\%}$
		$\text{>99\%}$ $\text{96\%}$	$\text{>99\%}$ $\text{99\%}$	$\text{>99\%}$ $\text{>99\%}$	$\text{>99\%}$ $\text{99\%}$	$\text{>99\%}$ $\text{98\%}$
	<b>d</b> $\text{Br}$	$\text{>99\%}$ $\text{96\%}$	$\text{>99\%}$ $\text{99\%}$	$\text{>99\%}$ $\text{>99\%}$	$\text{>99\%}$ $\text{97\%}$	$\text{>99\%}$ $\text{98\%}$
		$\text{>99\%}$ $\text{96\%}$	$\text{>99\%}$ $\text{99\%}$	$\text{>99\%}$ $\text{>99\%}$	$\text{>99\%}$ $\text{99\%}$	$\text{>99\%}$ $\text{98\%}$
		$\text{>99\%}$ $\text{96\%}$	$\text{>99\%}$ $\text{99\%}$	$\text{>99\%}$ $\text{>99\%}$	$\text{>99\%}$ $\text{97\%}$	$\text{>99\%}$ $\text{98\%}$
		$\text{>99\%}$ $\text{96\%}$	$\text{>99\%}$ $\text{99\%}$	$\text{>99\%}$ $\text{>99\%}$	$\text{>99\%}$ $\text{99\%}$	$\text{>99\%}$ $\text{98\%}$

		6	7	8	9	10
		X				
	<b>a</b> $\text{CH}_3$	$\text{>99\%}$ $\text{>99\%}$	$\text{>99\%}$ $\text{>99\%}$	$\text{>99\%}$ $\text{>99\%}$	$\text{>99\%}$ $\text{>99\%}$	$\text{>99\%}$ $\text{>99\%}$
		$\text{>99\%}$ $\text{96\%}$	$\text{98\%}$ $\text{>99\%}$	$\text{97\%}$ $\text{>99\%}$	$\text{>99\%}$ $\text{>99\%}$	$\text{>99\%}$ $\text{>99\%}$
		$\text{>99\%}$ $\text{>99\%}$	$\text{>99\%}$ $\text{97\%}$	$\text{96\%}$ $\text{96\%}$	$\text{99\%}$ $\text{99\%}$	$\text{>99\%}$ $\text{>99\%}$
		$\text{>99\%}$ $\text{>99\%}$	$\text{>99\%}$ $\text{96\%}$	$\text{>99\%}$ $\text{99\%}$	$\text{98\%}$ $\text{97\%}$	$\text{98\%}$ $\text{98\%}$
	<b>b</b> $\text{Br}$	$\text{>99\%}$ $\text{96\%}$	$\text{98\%}$ $\text{>99\%}$	$\text{97\%}$ $\text{>99\%}$	$\text{>99\%}$ $\text{>99\%}$	$\text{>99\%}$ $\text{>99\%}$
		$\text{>99\%}$ $\text{96\%}$	$\text{>99\%}$ $\text{99\%}$	$\text{>99\%}$ $\text{>99\%}$	$\text{>99\%}$ $\text{99\%}$	$\text{>99\%}$ $\text{98\%}$
		$\text{>99\%}$ $\text{96\%}$	$\text{>99\%}$ $\text{97\%}$	$\text{96\%}$ $\text{96\%}$	$\text{99\%}$ $\text{99\%}$	$\text{>99\%}$ $\text{98\%}$
		$\text{>99\%}$ $\text{96\%}$	$\text{>99\%}$ $\text{96\%}$	$\text{>99\%}$ $\text{99\%}$	$\text{98\%}$ $\text{97\%}$	$\text{98\%}$ $\text{98\%}$

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

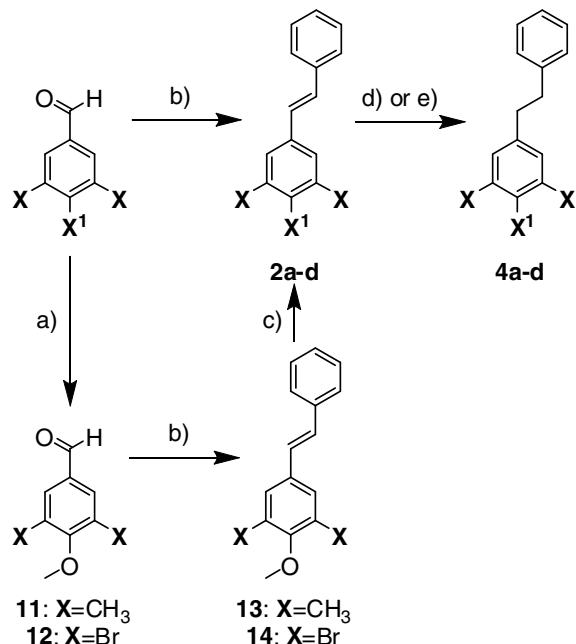
Samples were chromatographically separated using a ThermoHypersil-Keystone Betabasic-18 column (model 71503-034630, 150 Å pore size, 3 µm particle size), eluting with a  $\text{H}_2\text{O}:\text{CH}_3\text{CN}$  gradient solvent system. Linear gradients were run from either 100:0, 80:20, or 60:40 A:B to 0:100 A:B (A = 95:5  $\text{H}_2\text{O}:\text{CH}_3\text{CN}$ , 0.25% TFA; B = 5:95  $\text{H}_2\text{O}:\text{CH}_3\text{CN}$ , 0.25% TFA).

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

Samples were chromatographically separated using a Vydac-C<sub>4</sub> column (model 214TP5415, 300 Å pore size, 5 µm particle size), eluting with a  $\text{H}_2\text{O}:\text{MeOH}$  gradient solvent system. Linear gradients were run from 100:0 to 0:100 C:D (C = 99.75%  $\text{H}_2\text{O}$ , 0.25% TFA; D = 100% MeOH).

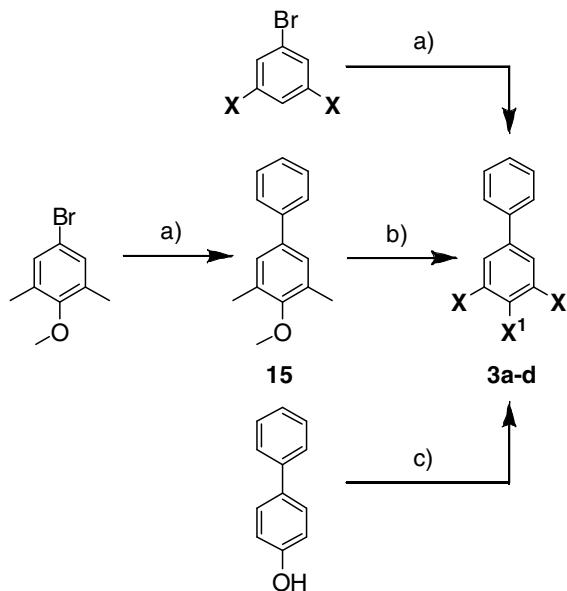
### Synthetic Schemes:

Synthesis of the *trans*-stilbenes (**Scheme S1**) was accomplished using procedures published by Yang *et al.* (Yang, J. S.; Chiou, S. Y.; Liau, K. L. Fluorescence enhancement of trans-4-aminostilbene by N-phenyl substitutions: the "amino conjugation effect". *J. Am. Chem. Soc.* **2002**, 124, 2518-2527). Stilbenes **2a** & **c** were hydrogenated to afford their dihydrostilbene counterparts (**4a** & **c**) using standard procedures employing 10% Pd/C. Hydrogenation procedures adapted from Wu *et al.* (Wu, G.; Huang, M.; Richards, M.; Poirier, M.; Wen, X.; Draper, R. W. Novel  $ZnX_2$ -modulated Pd/C and Pt/C catalysts for chemoselective hydrogenation and hydrogenolysis of halogen-substituted nitroarenes, alkenes, benzyl ethers, and aromatic ketones. *Synthesis* **2003**, 1657-1600), using stoichiometric amounts of  $ZnBr_2$ , were employed to prevent loss of the bromine substituents in **4b** & **4d**.



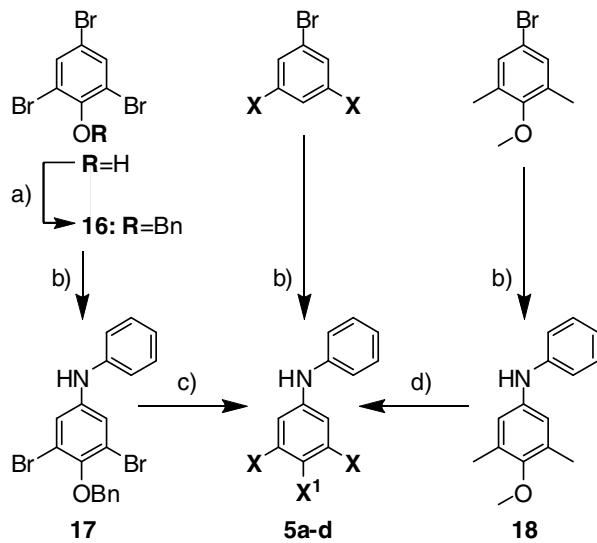
**Scheme S1:** Synthesis of stilbenes **2a-d** and dihydrostilbenes **4a-d**. a)  $X^1=OH$ : Iodomethane,  $K_2CO_3$ , DMF (**11**, 95%; **12**, 87%); b) Benzyl bromide, triethylphosphite, sodium hydride, DMF, then Ar-CHO in DMF (**2a**, 94%; **2b**, 14%; **13**, 94%; **14**, 83%); c) **13** or **14**,  $BBr_3$ ,  $CH_2Cl_2$  (**2c**, 87%; **2d**, 56%); d) **2a** or **2c**, 10% Pd/C,  $H_2$ , MeOH (**4a**, 93%; **4c**, 91%); e) **2b** or **2d**,  $ZnBr_2$ , 10% Pd/C,  $H_2$ , EtOAc (**4b**, 46%; **4d**, 82%).

Biphenyls **3a** & **b** and **15** (**Scheme S2**) were synthesized using Suzuki coupling procedures as described by Adamski-Werner *et al.* (Adamski-Werner, S. L.; Palaninathan, S. K.; Sacchettini, J. C.; Kelly, J. W. Diflunisal analogues stabilize the native state of transthyretin. *J. Med. Chem.* **2004**, 47, 355-374), with subsequent hydroxyl deprotection of **15** using  $\text{BBr}_3$  to afford **3c** in high yield. Alternate procedures were adopted for the synthesis of **3d**, namely selective bromination of 4-phenylphenol, as regioselective Suzuki coupling was envisioned to be problematic, especially considering the relatively poor yield obtained for **3b**.



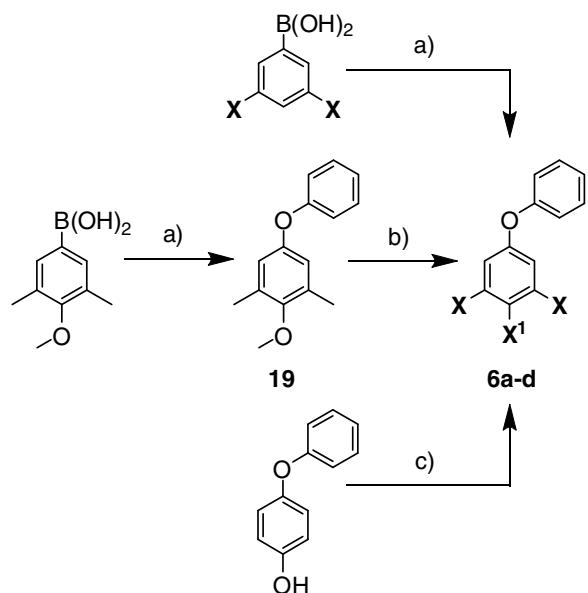
**Scheme S2:** Synthesis of biphenyls **3a-d**. a) Phenylboronic acid,  $\text{Pd}(\text{PPh}_3)_4$ ,  $\text{Na}_2\text{CO}_3$ , toluene, EtOH,  $\text{H}_2\text{O}$  (**3a**, 60%; **3b**, 44%; **15**, 93%); b)  $\text{BBr}_3$ ,  $\text{CH}_2\text{Cl}_2$  (**3c**, 98%); c)  $\text{Br}_2$ , EtOH (**3d**, 24%).

Biphenylamines **5a-d** were synthesized using palladium-mediated couplings between aryl bromides and aniline (**Scheme S3**), using published procedures by Petrassi *et al.* (Petrassi, H. M.; Johnson, S. M.; Purkey, H.; Chiang, K. P.; Walkup, T.; Jiang, X.; Powers, E. T.; Kelly, J. W. Potent and selective structure-based dibenzofuran inhibitors of transthyretin amyloidogenesis: Kinetic stabilization of the native state. *J. Am. Chem. Soc.* **2005**, 127, 6662-6671). Coupling of aniline to the bromine *para* to the sterically encumbering benzyloxy group of **16** afforded **17** in moderate yield, which was then hydrogenated to **5d** using the previously described  $ZnBr_2$  hydrogenation procedures, so as to minimize reduction of the bromine substituents.



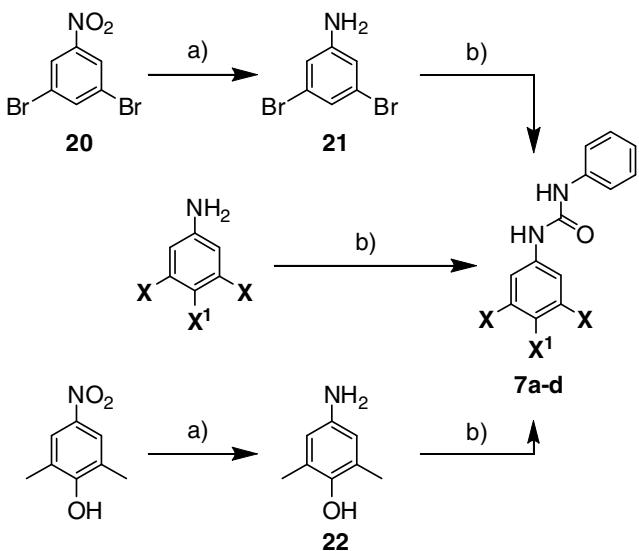
**Scheme S3:** Synthesis of biphenylamines **5a-d**. a) Benzyl bromide,  $K_2CO_3$ , DMF (**16**, 97%); b) Aniline,  $Pd_2(dba)_3$ ,  $(\pm)$ -BINAP,  $Cs_2CO_3$ , toluene (**5a**, 31%; **5b**, 17%; **17**, 41%; **18**, 12%); c)  $ZnBr_2$ , 10%  $Pd/C$ ,  $H_2$ ,  $EtOAc$  (**5d**, 34%); d)  $Br_3$ ,  $CH_2Cl_2$  (**5c**, 90%).

A copper-mediated coupling of substituted arylboronic acids to phenol, as described by Petrassi *et al.* (Petrassi, H. M.; Johnson, S. M.; Purkey, H.; Chiang, K. P.; Walkup, T.; Jiang, X.; Powers, E. T.; Kelly, J. W. Potent and selective structure-based dibenzofuran inhibitors of transthyretin amyloidogenesis: Kinetic stabilization of the native state. *J. Am. Chem. Soc.* **2005**, 127, 6662-6671), afforded biphenyl ethers **6a** & **b** and **19** (**Scheme S4**): the latter was demethylated using  $\text{BBr}_3$  to afford **6c** in high yield. Because of the lack of an appropriate arylboronic acid building block, alternate procedures were adopted for the synthesis of **6d**; bromination of 4-phenoxyphenol afforded **6d** in acceptable yield.

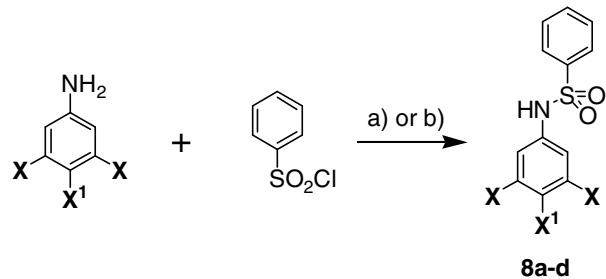


**Scheme S4:** Synthesis of biphenyl ethers **6a-d**. a) Phenol,  $\text{Cu}(\text{OAc})_2$ , pyridine, 4  $\text{\AA}$  molecular sieves,  $\text{CH}_2\text{Cl}_2$  (**6a**, 52%; **6b**, 69%; **19**, 60%); b)  $\text{BBr}_3$ ,  $\text{CH}_2\text{Cl}_2$  (**6c**, 80%); c)  $\text{Br}_2$ ,  $\text{EtOH}$  (**6d**, 24%).

Synthesis of bisarylureas **7a-d** (**Scheme S5**) and bisarylsulfonamides **8a-d** (**Scheme S6**) proceeded in high yields by coupling of the arylanilines (**21** and **22** requiring prior synthesis) with phenylisocyanate or benzenesulfonyl chloride, respectively. 3,5-Dibromonitrobenzene (**20**) was synthesized according to procedures previously published by Chanteau *et al.* (Chanteau, S. H.; Tour, J. M. Synthesis of anthropomorphic molecules: the NanoPutians. *J. Org. Chem.* **2003**, 68, 8750-8766) and was subsequently reduced to afford aniline **21** in moderate yield (n.b. aniline **22** was reduced analogously from 2,6-dimethyl-4-nitrophenol in high yield).

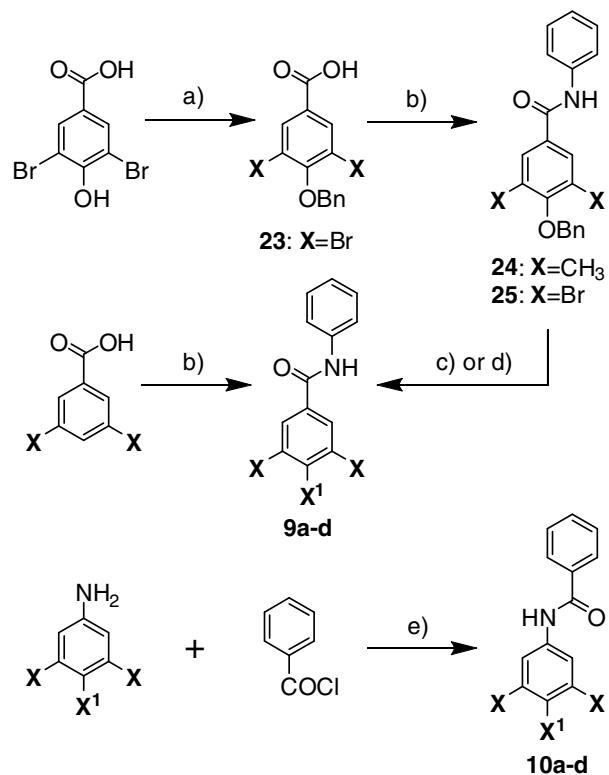


**Scheme S5:** Synthesis of bisarylureas **7a-d**. a) Sn, HCl/AcOH (**21**, 60%; **22**, 87%); b) Phenylisocyanate, pyridine, CH<sub>2</sub>Cl<sub>2</sub> (**7a**, 91%; **7b**, 47%; **7c**, 55%; **7d**, 91%).



**Scheme S6:** Synthesis of bisarylsulfonamides **8a-d**. a) Pyridine, CH<sub>2</sub>Cl<sub>2</sub> (**8a**, 78%; **8b**, 83%; **8c**, 74%); b) Pyridine, THF (**8d**, 91%).

The facile coupling between the arylanilines and benzoyl chloride afforded bisaryl amides **10a-d** in high yields (**Scheme S7**). Compounds **9a** & **b**, having the amide bond in the opposite orientation, were synthesized by direct coupling of the respective benzoic acids with aniline in the presence of DCC and DMAP. Coupling of the precursor benzyloxy compounds (3,5-dimethyl-4-benzyloxybenzoic acid and **23**) with aniline in the presence of DCC and DMAP, followed by benzyl hydrogenation (again in the presence of  $ZnBr_2$  for compound **25**), afforded **9c** & **d**.



**Scheme S7:** Synthesis of bisaryl amides **9a-d** and **10a-d**. a) Benzyl bromide,  $K_2CO_3$ , DMF, then  $LiOH \cdot H_2O$ , THF, MeOH,  $H_2O$  (**23**, 93%); b) Aniline, DCC, DMAP,  $CH_2Cl_2$  (**9a**, 42%; **9b**, 88%; **24**, 31%; **25**, 78%); c) **24**, 10% Pd/C,  $H_2$ , EtOAc (**9c**, 95%); d) **25**,  $ZnBr_2$ , 10% Pd/C,  $H_2$ , EtOAc (**9d**, 42%); e) Benzoyl chloride, pyridine,  $CH_2Cl_2$  (**10a**, 94%; **10b**, 85%; **10c**, 95%; **10d**, 75%).

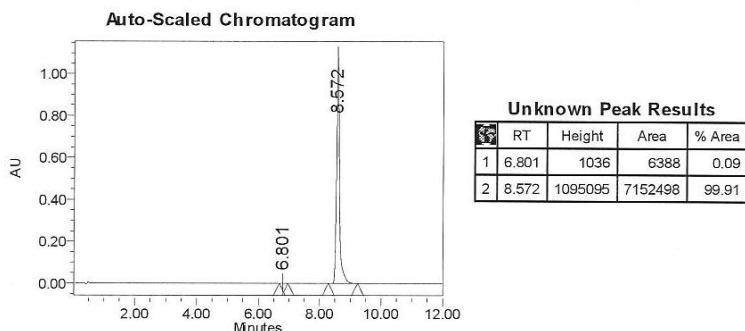
Including the four previously evaluated 2-arylbenzoxazole compounds (**1a-d**, main text, **Figure 3**), these syntheses culminated in a 40 compound library. Each member is composed of an unsubstituted aryl-Z ring tethered through linkages of variable structure to the aryl-X, **a-d** rings. These compounds were characterized by  $^1H$ - and  $^{13}C$ -NMR spectroscopy, mass spectrometry, and RP-HPLC.

## Experimental:

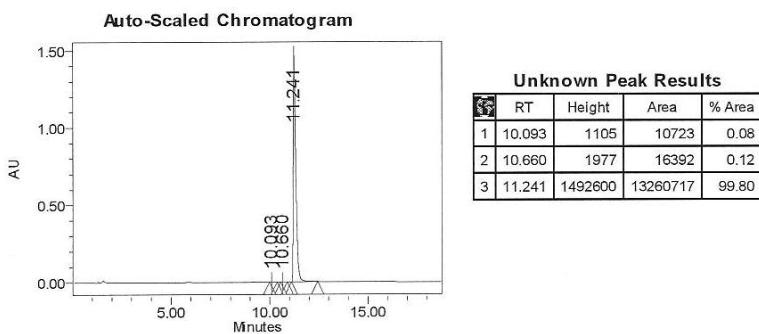
### 3,5-Dimethylstilbene (2a).

Triethylphosphite (1.56 mL, 8.97 mmol) and benzyl bromide (0.89 mL, 7.49 mmol) were stirred at 150°C for 3 h under an argon atmosphere. Anhydrous DMF (15.0 mL) was added and the reaction was then cooled at 0°C for 15 minutes, then NaH (60% in mineral oil, 456 mg, 11.4 mmol) was added and the reaction was stirred for an additional 30 minutes. 3,5-Dimethylbenzaldehyde (1.01 mL, 7.52 mmol) was then added and the reaction was stirred at room temperature for 18 h. The organics were extracted into EtOAc (100 mL) and washed with H<sub>2</sub>O (2x25 mL) and brine (25 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. Flash chromatographic purification over silica (100% hexanes to 9:1 hexanes:EtOAc gradient elution) afforded 3,5-dimethylstilbene (**2a**) as a pale yellow liquid (1.46 g, 94%). <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>) δ 7.48-7.52 (m, 2H), 7.32-7.37 (m, 2H), 7.24 (tt, *J*=1.2, 6.8 Hz, 1H), 7.14 (s, 2H), 7.06 (AB q, *J*=16.3 Hz, 2H), 6.89-6.92 (m, 1H), 2.33 (s, 6H); <sup>13</sup>C-NMR (125 MHz, CDCl<sub>3</sub>) δ 138.09, 137.48, 137.19, 129.42, 128.85, 128.64, 128.26, 127.44, 126.42, 124.41, 21.30; GC-MS 208 *m/z* [M]<sup>+</sup>, C<sub>16</sub>H<sub>16</sub> requires 208; RP-HPLC: >99% & >99% pure.

### Primary RP-HPLC Conditions Chromatographic Trace:



### Secondary RP-HPLC Conditions Chromatographic Trace:

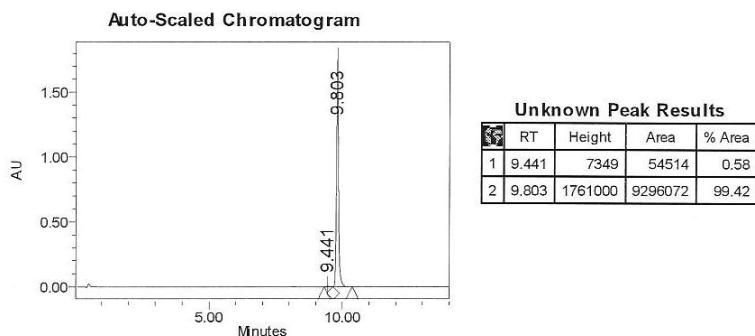


### 3,5-Dibromostilbene (2b).

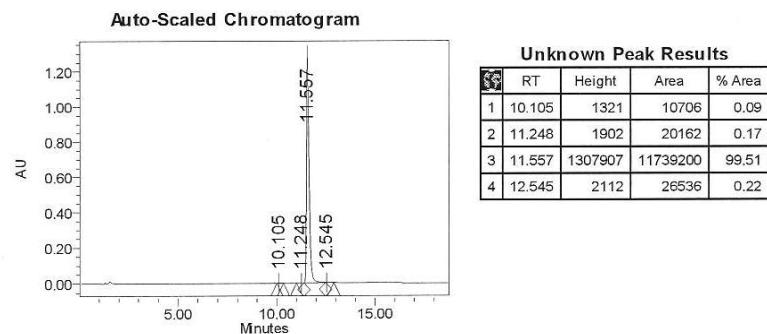
Triethylphosphite (1.56 mL, 8.97 mmol) and benzyl bromide (0.89 mL, 7.49 mmol) were stirred at 150°C for 3 h under an argon atmosphere. Anhydrous DMF (15.0 mL) was added and the reaction was then cooled at 0°C for 15 min, then NaH (60% in mineral oil, 452 mg, 11.3 mmol) was added and the reaction was stirred for an additional 30 min. 3,5-Dibromobenzaldehyde (1.99 g, 7.54 mmol) was then added and the reaction

was stirred at room temperature for 18 h. The organics were extracted into EtOAc (100 mL) and washed with H<sub>2</sub>O (2x25 mL) and brine (25 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. Flash chromatographic purification over silica (100% hexanes to 9:1 hexanes:EtOAc gradient elution), followed by prep-HPLC purification afforded 3,5-dibromostilbene (**2b**) as a white solid (342 mg, 14%). <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>) δ 7.56 (d, *J*=1.7 Hz, 2H), 7.53 (t, *J*=1.7 Hz, 1H), 7.47-7.51 (m, 2H), 7.35-7.40 (m, 2H), 7.30 (tt, *J*=1.2, 6.5 Hz, 1H), 7.09 (d, *J*=16.3 Hz, 1H), 6.92 (d, *J*=16.3 Hz, 1H); <sup>13</sup>C-NMR (125 MHz, CDCl<sub>3</sub>) δ 140.98, 136.26, 132.61, 131.53, 128.81, 128.45, 128.06, 126.79, 125.62, 123.20; GC-MS 336 *m/z* [M]<sup>+</sup>, C<sub>14</sub>H<sub>10</sub>Br<sub>2</sub> requires 336; RP-HPLC: >99% & >99% pure.

*Primary RP-HPLC Conditions Chromatographic Trace:*



*Secondary RP-HPLC Conditions Chromatographic Trace:*



**3,5-Dimethyl-4-methoxybenzaldehyde (**11**).**

3,5-Dimethyl-4-hydroxybenzaldehyde (1.54 g, 10.3 mmol), iodomethane (0.77 mL, 12.4 mmol), and K<sub>2</sub>CO<sub>3</sub> (1.71 g, 12.4 mmol) were stirred in DMF (10.0 mL) at room temperature. After 18 h the reaction was extracted into EtOAc (100 mL) and washed with H<sub>2</sub>O (2x25 mL) and brine (25 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. Flash chromatographic purification over silica (9:1 hexanes:EtOAc) afforded 3,5-dimethyl-4-methoxybenzaldehyde (**11**) as a white solid (1.60 g, 95%). <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>) δ 9.88 (s, 1H), 7.56 (s, 2H), 3.78 (s, 3H), 2.35 (s, 6H); <sup>13</sup>C-NMR (125 MHz, CDCl<sub>3</sub>) δ 191.69, 162.41, 132.25, 131.94, 130.73, 59.71, 16.19; GC-MS 163 *m/z* [MH]<sup>+</sup>, C<sub>10</sub>H<sub>12</sub>O<sub>2</sub> requires 163; RP-HPLC: >99% pure.

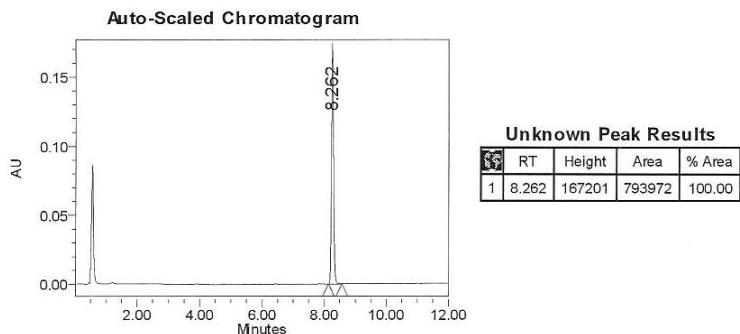
### 3,5-Dimethyl-4-methoxystilbene (13).

Triethylphosphite (1.85 mL, 10.6 mmol) and benzyl bromide (1.05 mL, 8.84 mmol) were stirred at 150°C for 3 h under an argon atmosphere. Anhydrous DMF (12.0 mL) was added and the reaction was then cooled at 0°C for 15 min, then NaH (60% in mineral oil, 518 mg, 13.0 mmol) was added and the reaction was stirred for an additional 30 min. A solution of **11** (1.45 g, 8.80 mmol) in anhydrous DMF (5.0 mL) was then added and the reaction was stirred at room temperature for 18 h. The organics were extracted into EtOAc (100 mL) and washed with H<sub>2</sub>O (2x25 mL) and brine (25 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. Flash chromatographic purification over silica (100% hexanes to 9:1 hexanes:EtOAc gradient elution) afforded 3,5-dimethyl-4-methoxystilbene (**13**) as a white waxy solid (1.98 g, 94%). <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>) δ 7.46-7.50 (m, 2H), 7.32-7.37 (m, 2H), 7.22 (tt, *J*=1.2, 6.9 Hz, 1H), 7.18 (s, 2H), 7.03 (d, *J*=16.4 Hz, 1H), 6.99 (d, *J*=16.4 Hz, 1H), 3.73 (s, 3H), 2.31 (s, 6H); <sup>13</sup>C-NMR (125 MHz, CDCl<sub>3</sub>) δ 156.77, 137.57, 132.87, 131.04, 128.64, 128.28, 127.57, 127.33, 126.98, 126.33, 59.77, 16.18; GC-MS 238 *m/z* [M]<sup>+</sup>, C<sub>17</sub>H<sub>18</sub>O requires 238; RP-HPLC: >99% pure.

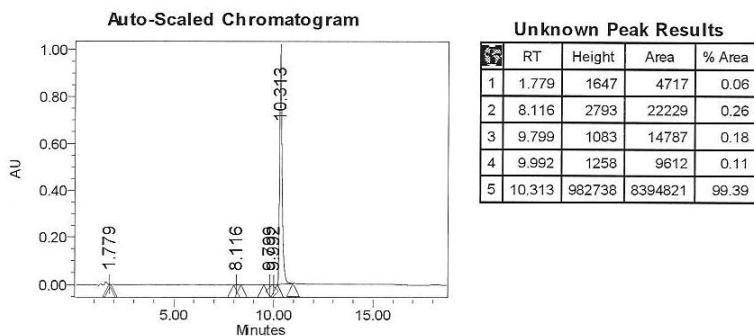
### 3,5-Dimethyl-4-hydroxystilbene (2c).

Boron tribromide (2.00 mL of 1 M BBr<sub>3</sub> in hexanes, 2.00 mmol) was added to a stirring mixture of **13** (157 mg, 0.659 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (5.0 mL) and the reaction was stirred at room temperature under an argon atmosphere. After 2 h the reaction was quenched with MeOH (5 mL), extracted into EtOAc (50 mL), and washed with sat. NaHCO<sub>3</sub> (2x25 mL) and brine (25 mL). The organics were then dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. Flash chromatographic purification over silica (4:1 hexanes:EtOAc) afforded 3,5-dimethyl-4-hydroxystilbene (**2c**) as a white solid (129 mg, 87%). <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>) δ 7.46-7.50 (m, 2H), 7.31-7.36 (m, 2H), 7.22 (tt, *J*=1.2, 6.9 Hz, 1H), 7.16 (s, 2H), 7.00 (d, *J*=16.3 Hz, 1H), 6.95 (d, *J*=16.3 Hz, 1H), 4.66 (s, 1H), 2.27 (s, 6H); <sup>13</sup>C-NMR (125 MHz, CDCl<sub>3</sub>) δ 152.07, 137.77, 129.57, 128.61, 128.45, 127.07, 126.93, 126.18, 123.17, 15.96; ESI-TOF 223.1131 *m/z* [M-H]<sup>+</sup>, C<sub>16</sub>H<sub>15</sub>O requires 223.1128; RP-HPLC: >99% & >99% pure.

#### Primary RP-HPLC Conditions Chromatographic Trace:



*Secondary RP-HPLC Conditions Chromatographic Trace:*



**3,5-Dibromo-4-methoxybenzaldehyde (12).**

3,5-Dibromo-4-hydroxybenzaldehyde (1.40 g, 5.01 mmol), iodomethane (0.37 mL, 5.94 mmol), and  $K_2CO_3$  (845 mg, 6.11 mmol) were stirred in DMF (5.0 mL) at room temperature. After 18 h, the reaction was extracted into EtOAc (100 mL) and washed with  $H_2O$  (2x25 mL) and brine (25 mL), dried over  $Na_2SO_4$ , filtered, and concentrated. Flash chromatographic purification over silica (9:1 hexanes:EtOAc) afforded 3,5-dibromo-4-methoxybenzaldehyde (**12**) as a white solid (1.22 g, 83%).  $^1H$ -NMR (500 MHz,  $CDCl_3$ )  $\delta$  9.86 (s, 1H), 8.03 (s, 2H), 3.97 (s, 3H);  $^{13}C$ -NMR (125 MHz,  $CDCl_3$ )  $\delta$  188.43, 159.12, 134.20, 133.91, 119.31, 60.88; GC-MS 292  $m/z$  [MH] $^+$ ,  $C_8H_6Br_2O_2$  requires 292; RP-HPLC: >99% pure.

**3,5-Dibromo-4-methoxystilbene (14).**

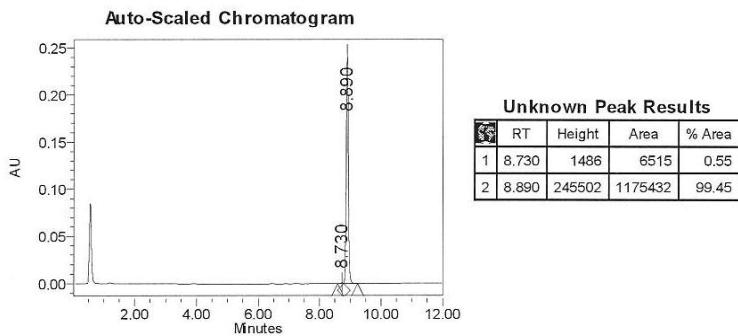
Triethylphosphite (0.83 mL, 4.77 mmol) and benzyl bromide (0.47 mL, 3.96 mmol) were stirred at 150°C for 3 h under an argon atmosphere. Anhydrous DMF (8.0 mL) was added and the reaction was then cooled at 0°C for 15 min, then NaH (60% in mineral oil, 231 mg, 5.78 mmol) was added and the reaction was stirred for an additional 30 min. A solution of **12** (1.16 g, 3.94 mmol) in anhydrous DMF (8.0 mL) was then added and the reaction was stirred at room temperature for 18 h. The organics were extracted into EtOAc (100 mL) and washed with  $H_2O$  (2x25 mL) and brine (25 mL), dried over  $Na_2SO_4$ , filtered, and concentrated. Flash chromatographic purification over silica (100% hexanes to 95:5 hexanes:EtOAc gradient elution) afforded 3,5-dibromo-4-methoxystilbene (**14**) as a yellow waxy solid (1.20 g, 83%).  $^1H$ -NMR (500 MHz,  $CDCl_3$ )  $\delta$  7.63 (d,  $J=0.4$  Hz, 2H), 7.46-7.50 (m, 2H), 7.35-7.40 (m, 2H), 7.29 (tt,  $J=1.2, 6.6$  Hz, 1H), 7.01 (d,  $J=16.3$  Hz, 1H), 6.90 (d,  $J=16.3$  Hz, 1H), 3.90 (s, 3H);  $^{13}C$ -NMR (125 MHz,  $CDCl_3$ )  $\delta$  153.21, 136.43, 136.18, 131.65, 130.62, 130.32, 128.78, 128.23, 126.65, 125.17, 118.39, 60.74; GC-MS 366  $m/z$  [M] $^+$ ,  $C_{17}H_{18}O$  requires 366; RP-HPLC: 98% pure.

**3,5-Dibromo-4-hydroxystilbene (2d).**

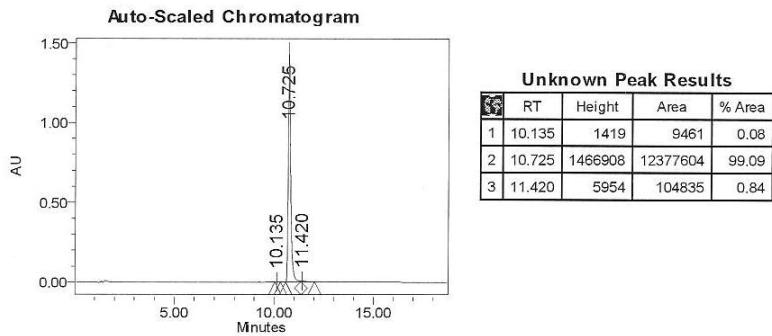
Boron tribromide (15.0 mL of 1 M  $BBr_3$  in hexanes, 15.0 mmol) was added to a stirring mixture of **14** (1.10 g, 2.97 mmol) in anhydrous  $CH_2Cl_2$  (10.0 mL) and the reaction was stirred at room temperature under an argon atmosphere. After 18 h, the reaction was quenched with MeOH (5 mL), extracted 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 (4:1-1:2

hexanes:EtOAc gradient elution), followed by prep-HPLC purification, afforded 3,5-dibromo-4-hydroxystilbene (**2d**) as an off-white crystalline solid (585 mg, 56%). <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>) δ 7.60 (s, 2H), 7.45-7.49 (m, 2H), 7.34-7.38 (m, 2H), 7.27 (tt, J=1.2, 6.7 Hz, 1H), 6.97 (d, J=16.3 Hz, 1H), 6.89 (d, J=16.3 Hz, 1H), 5.89 (s, 1H); <sup>13</sup>C-NMR (125 MHz, CDCl<sub>3</sub>) δ 148.61, 136.63, 132.66, 129.84, 129.27, 128.78, 128.00, 126.52, 125.33, 110.17; ESI-TOF 350.9025 *m/z* [M-H<sup>+</sup>]<sup>-</sup>, C<sub>14</sub>H<sub>9</sub>Br<sub>2</sub>O requires 350.9026; RP-HPLC: >99% & 99% pure.

*Primary RP-HPLC Conditions Chromatographic Trace:*



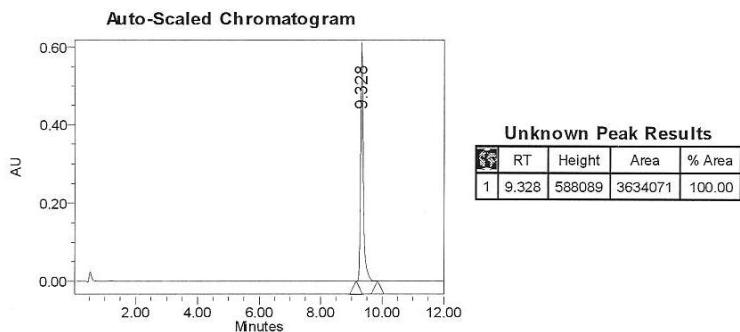
*Secondary RP-HPLC Conditions Chromatographic Trace:*



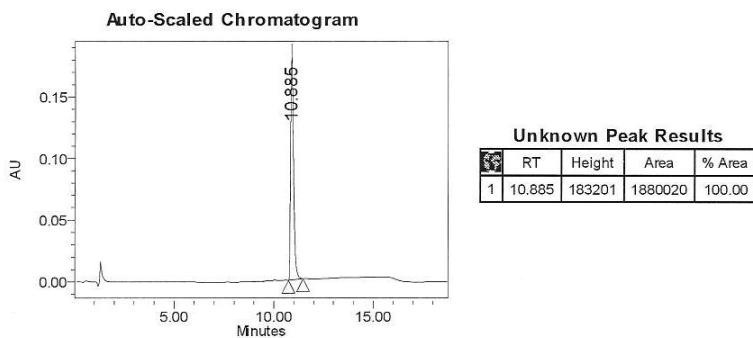
**3,5-Dimethylbiphenyl (**3a**).**

Phenylboronic acid (498 mg, 4.08 mmol), 5-bromo-*m*-xylene (374 mg, 2.02 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (234 mg, 0.202 mmol), and Na<sub>2</sub>CO<sub>3</sub> (1.07 g, 10.1 mmol) were stirred in a mixture of H<sub>2</sub>O/EtOH/toluene (4/2/10 mL) at 70°C under an argon atmosphere. After 18 h the reaction was extracted into EtOAc (50 mL) and washed with brine (25 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. Flash chromatographic purification over silica (100% hexanes to 95:5 hexanes:EtOAc gradient elution), followed by prep-HPLC purification, afforded 3,5-dimethylbiphenyl (**3a**) as a clear, colorless liquid (222 mg, 60%). <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>) δ 7.55-7.59 (m, 2H), 7.39-7.44 (m, 2H), 7.32 (tt, J=1.3, 6.8 Hz, 1H), 7.19-7.22 (m, 2H), 6.98-7.01 (m, 1H), 2.38 (q, J=0.6 Hz, 6H); <sup>13</sup>C-NMR (125 MHz, CDCl<sub>3</sub>) δ 141.45, 141.25, 138.23, 128.87, 128.62, 127.18, 127.07, 125.10, 21.41; GC-MS 182 *m/z* [M]<sup>+</sup>, C<sub>14</sub>H<sub>14</sub> requires 182; RP-HPLC: >99% & >99% pure.

*Primary RP-HPLC Conditions Chromatographic Trace:*



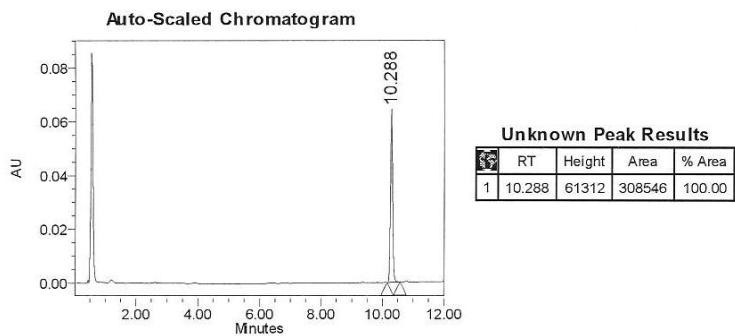
*Secondary RP-HPLC Conditions Chromatographic Trace:*



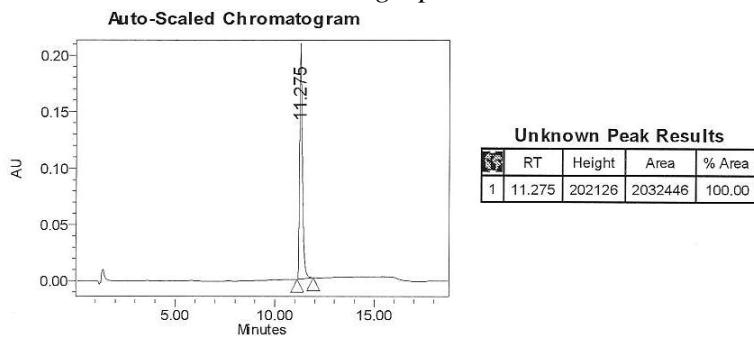
**3,5-Dibromobiphenyl (3b).**

Phenylboronic acid (212 mg, 1.74 mmol), 1,3,5-tribromobenzene (1.08 g, 3.44 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (203 mg, 0.176 mmol), and Na<sub>2</sub>CO<sub>3</sub> (925 mg, 8.73 mmol) were stirred in a mixture of H<sub>2</sub>O/EtOH/toluene (4/2/10 mL) at 70°C under an argon atmosphere. After 18 h, the reaction was extracted into EtOAc (50 mL) and washed with brine (25 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. Flash chromatographic purification over silica (100% hexanes to 95:5 hexanes:EtOAc gradient elution) afforded 3,5-dibromobiphenyl (**3b**) as a white solid (238 mg, 44%). <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>) δ 7.65 (d, *J*=1.7 Hz, 2H), 7.63 (t, *J*=1.7 Hz, 1H), 7.50-7.54 (m, 2H), 7.43-7.48 (m, 2H), 7.39 (tt, *J*=1.3, 6.2 Hz, 1H); <sup>13</sup>C-NMR (125 MHz, CDCl<sub>3</sub>) δ 144.79, 138.34, 132.56, 129.02, 129.00, 128.46, 127.10, 123.24; GC-MS 310 *m/z* [M]<sup>+</sup>, C<sub>12</sub>H<sub>8</sub>Br<sub>2</sub> requires 310; RP-HPLC: >99% & >99% pure.

*Primary RP-HPLC Conditions Chromatographic Trace:*



*Secondary RP-HPLC Conditions Chromatographic Trace:*



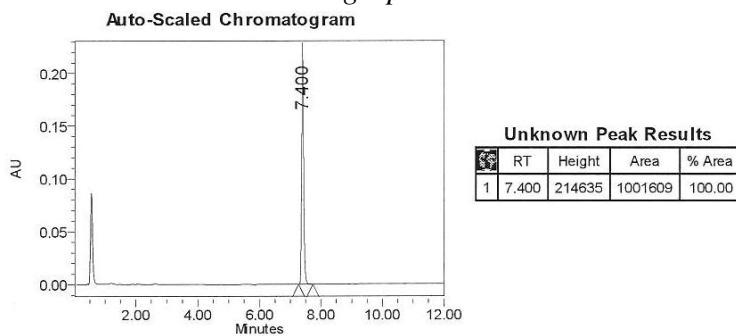
**3,5-Dimethyl-4-methoxybiphenyl (15).**

Phenylboronic acid (485 mg, 3.98 mmol), 4-bromo-2,6-dimethylanisole (423 mg, 1.97 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (229 mg, 0.198 mmol), and Na<sub>2</sub>CO<sub>3</sub> (1.05 g, 9.89 mmol) were stirred in a mixture of H<sub>2</sub>O/EtOH/toluene (4/2/10 mL) at 70°C under an argon atmosphere. After 18 h, the reaction was extracted into EtOAc (50 mL) and washed with brine (25 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. Flash chromatographic purification over silica (100% hexanes to 9:1 hexanes:EtOAc gradient elution) afforded 3,5-dimethyl-4-methoxybiphenyl (**15**) as a clear, pale yellow liquid (387 mg, 93%). <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>) δ 7.52-7.56 (m, 2H), 7.38-7.43 (m, 2H), 7.30 (tt, *J*=1.2, 6.8 Hz, 1H), 7.24 (s, 2H), 3.76 (s, 3H), 2.35 (s, 6H); <sup>13</sup>C-NMR (125 MHz, CDCl<sub>3</sub>) δ 156.54, 140.97, 136.78, 131.09, 128.61, 127.58, 126.97, 126.83, 59.77, 16.26; ESI-MS 213 *m/z* [MH]<sup>+</sup>, C<sub>15</sub>H<sub>17</sub>O requires 213; RP-HPLC: 96% pure.

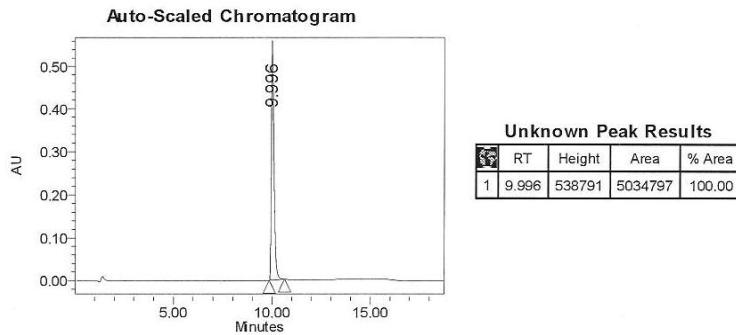
**3,5-Dimethyl-4-hydroxybiphenyl (3c).**

Boron tribromide (3.40 mL of 1 M BBr<sub>3</sub> in hexanes, 3.40 mmol) was added to a stirring mixture of **15** (145 mg, 0.684 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (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<sub>2</sub>O (2x25 mL) and brine (25 mL). The organics were then dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. Flash chromatographic purification over silica (4:1 hexanes:EtOAc) afforded 3,5-dimethyl-4-hydroxybiphenyl (**3c**) as a white solid (132 mg, 98%). <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>) δ 7.51-7.55 (m, 2H), 7.37-7.42 (m, 2H), 7.28 (tt, *J*=1.2, 6.9 Hz, 1H), 7.22 (s, 2H), 4.65 (s, 1H), 2.31 (s, 6H); <sup>13</sup>C-NMR (125 MHz, CDCl<sub>3</sub>) δ 151.82, 141.08, 133.36, 128.61, 127.38, 126.74, 126.49, 123.26, 16.06; ESI-TOF 197.0968 *m/z* [M-H]<sup>+</sup>, C<sub>14</sub>H<sub>13</sub>O requires 197.0972; RP-HPLC: >99% & >99% pure.

*Primary RP-HPLC Conditions Chromatographic Trace:*



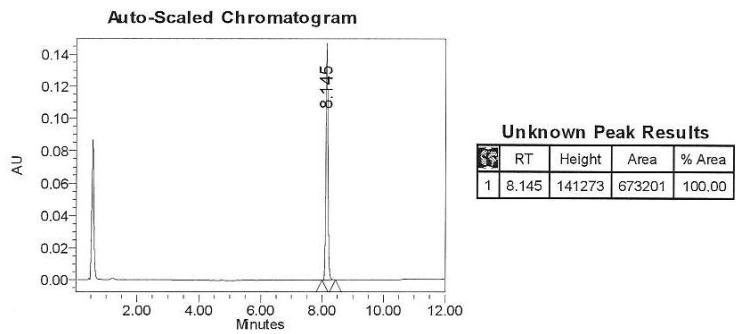
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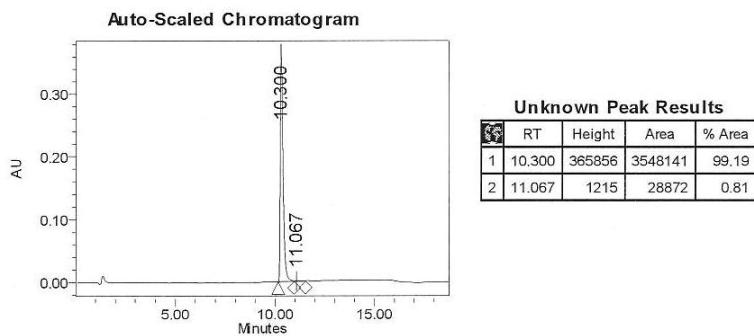
**3,5-Dibromo-4-hydroxybiphenyl (3d).**

Bromine (0.16 mL, 3.12 mmol) and 4-phenylphenol (242 mg, 1.42 mmol) were stirred in EtOH (7.0 mL). After 2 days the reaction was concentrated and pre-purified by flash chromatographic purification over silica (100% hexanes to 9:1 hexanes:EtOAc gradient elution), then was purified again by prep-HPLC to afford 3,5-dibromo-4-hydroxybiphenyl (**3d**) as a white solid (112 mg, 24%). <sup>1</sup>H-NMR (500 MHz, *d*<sub>6</sub>-DMSO) δ 10.05 (s, 1H), 7.82 (s, 2H), 7.61-7.65 (m, 2H), 7.40-7.45 (m, 2H), 7.34 (tt, *J*=1.1, 6.7 Hz, 1H); <sup>13</sup>C-NMR (125 MHz, *d*<sub>6</sub>-DMSO) δ 150.22, 137.25, 134.59, 130.22, 128.99, 127.66, 126.46, 112.59; ESI-TOF 324.8855 *m/z* [M-H<sup>+</sup>]<sup>-</sup>, C<sub>12</sub>H<sub>7</sub>Br<sub>2</sub>O requires 324.8869; RP-HPLC: >99% & >99% pure.

*Primary RP-HPLC Conditions Chromatographic Trace:*



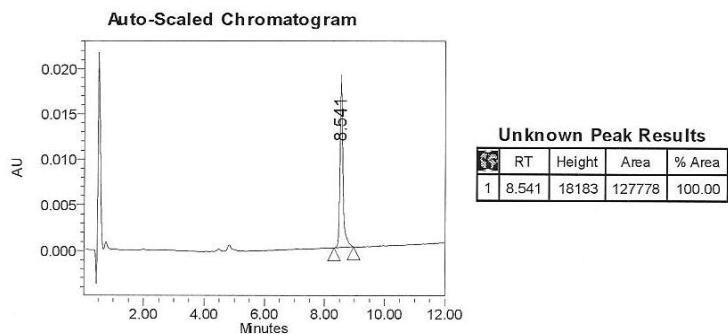
*Secondary RP-HPLC Conditions Chromatographic Trace:*



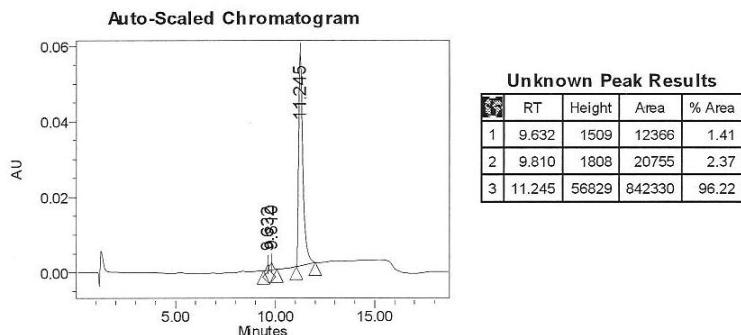
**1,3-Dimethyl-5-phenethylbenzene (4a).**

3,5-Dimethylstilbene (**2a**, 492 mg, 2.36 mmol) and 10% Pd/C (126 mg, 0.119 mmol) were stirred in MeOH (12.0 mL) under a hydrogen atmosphere for 2 h. The atmosphere was then purged with argon and the reaction quenched with DCM, filtered through celite, and concentrated. Flash chromatographic purification over silica (100% hexanes to 9:1 hexanes:EtOAc gradient elution) afforded 1,3-dimethyl-5-phenethylbenzene (**4a**) as a clear, pale yellow liquid (464 mg, 93%). <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>) δ 7.26-7.31 (m, 2H), 7.17-7.22 (m, 3H), 6.84 (br s, 1H), 6.83 (br s, 2H), 2.80-2.92 (m, 4H), 2.29 (s, 6H); <sup>13</sup>C-NMR (125 MHz, CDCl<sub>3</sub>) δ 142.07, 141.79, 137.83, 128.40, 128.33, 127.55, 126.24, 125.87, 38.11, 37.92, 21.28; GC-MS 210 *m/z* [M]<sup>+</sup>, C<sub>16</sub>H<sub>18</sub> requires 210; RP-HPLC: 98% & 96% pure.

*Primary RP-HPLC Conditions Chromatographic Trace:*



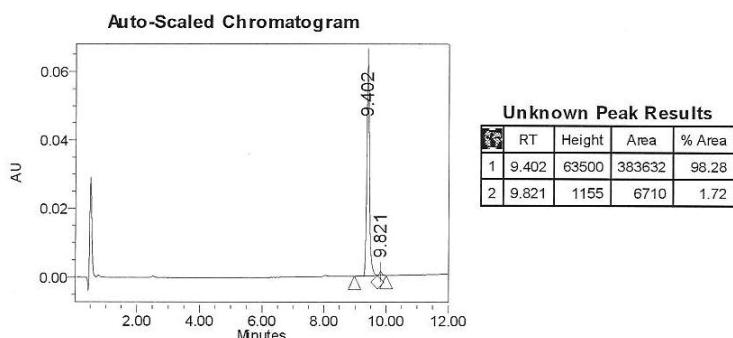
*Secondary RP-HPLC Conditions Chromatographic Trace:*



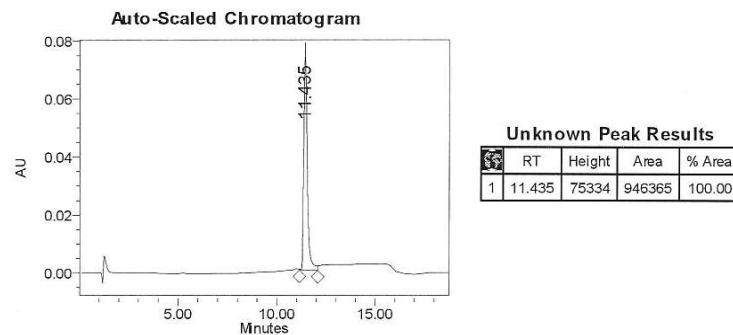
### 1,3-Dibromo-5-phenethylbenzene (4b).

3,5-Dibromostilbene (**2b**, 109 mg, 0.322 mmol),  $ZnBr_2$  (72.8 mg, 0.323 mmol), and 10% Pd/C (35.3 mg, 0.0332 mmol) were stirred in EtOAc (5.0 mL) under a hydrogen atmosphere for 2 h. The atmosphere was then purged with argon and the reaction quenched with DCM, filtered through celite, and concentrated. Flash chromatographic purification over silica (100% hexanes to 95:5 hexanes:EtOAc gradient elution) afforded 1,3-dibromo-5-phenethylbenzene (**4b**) as a clear, colorless syrup (50.0 mg, 46%).  $^1H$ -NMR (500 MHz,  $CDCl_3$ )  $\delta$  7.50 (d,  $J$ =1.7 Hz, 1H), 7.27-7.32 (m, 2H), 7.24 (d,  $J$ =1.7 Hz, 2H), 7.21 (tt,  $J$ =1.3, 6.6 Hz, 1H), 7.13-7.17 (m, 2H), 2.83-2.91 (m, 4H);  $^{13}C$ -NMR (125 MHz,  $CDCl_3$ )  $\delta$  145.59, 140.65, 131.64, 130.37, 128.49, 128.39, 126.27, 122.73, 37.38, 37.27; GC-MS 338  $m/z$  [M] $^+$ ,  $C_{14}H_{12}Br_2$  requires 338; RP-HPLC: 98% & >99% pure.

#### Primary RP-HPLC Conditions Chromatographic Trace:



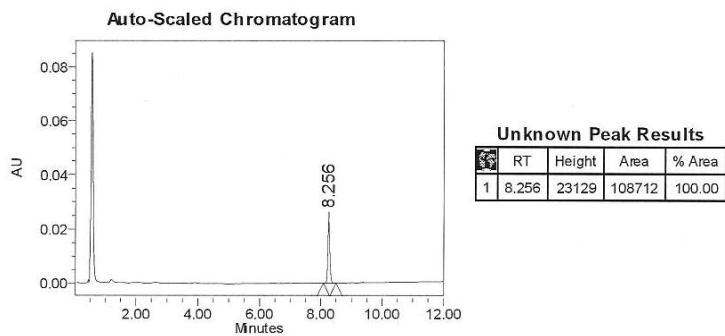
#### Secondary RP-HPLC Conditions Chromatographic Trace:



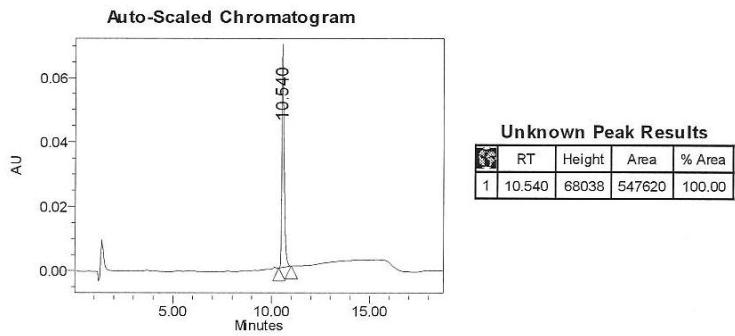
### 1,3-Dimethyl-4-hydroxy-5-phenethylbenzene (4c).

3,5-Dimethyl-4-hydroxystilbene (**2c**, 86.6 mg, 0.386 mmol) and 10% Pd/C (44.5 mg, 0.0418 mmol) were stirred in MeOH (8.0 mL) under a hydrogen atmosphere for 2 h. The atmosphere was then purged with argon and the reaction quenched with DCM, filtered through celite, and concentrated. Flash chromatographic purification over silica (4:1 hexanes:EtOAc) afforded 1,3-dimethyl-4-hydroxy-5-phenethylbenzene (**4c**) as a white solid (79.4 mg, 91%).  $^1H$ -NMR (500 MHz,  $CDCl_3$ )  $\delta$  7.26-7.31 (m, 2H), 7.17-7.22 (m, 3H), 6.81 (s, 2H), 4.47 (s, 1H), 2.75-2.81 (m, 2H), 2.82-2.89 (m, 2H), 2.22 (s, 6H);  $^{13}C$ -NMR (125 MHz,  $CDCl_3$ )  $\delta$  150.29, 142.09, 133.51, 128.50, 128.42, 128.30, 125.83, 122.81, 38.43, 37.17, 15.90; ESI-TOF 225.1279  $m/z$  [M-H] $^+$ ,  $C_{16}H_{17}O$  requires 225.1285; RP-HPLC: >99% & >99% pure.

*Primary RP-HPLC Conditions Chromatographic Trace:*



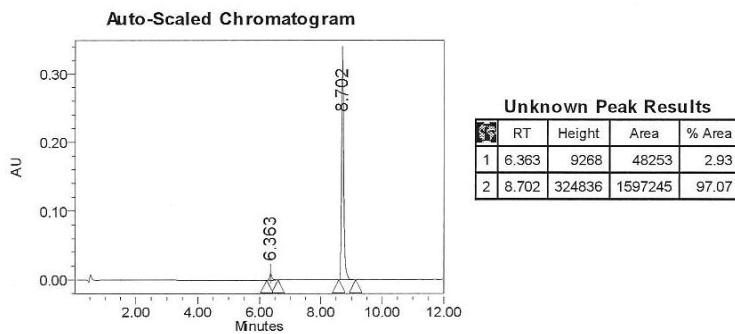
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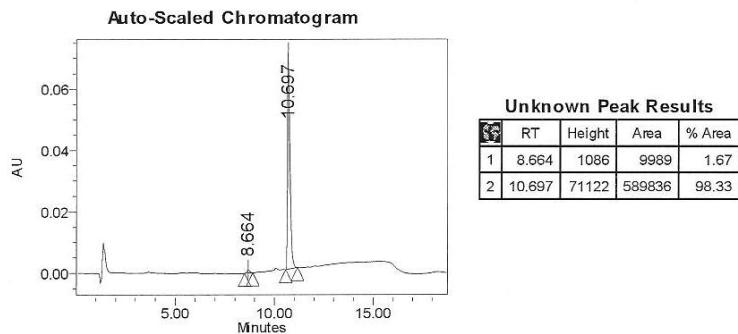
**1,3-Dibromo-4-hydroxy-5-phenethylbenzene (4d).**

3,5-Dibromo-4-hydroxystilbene (**2d**, 124 mg, 0.351 mmol), ZnBr<sub>2</sub> (82.0 mg, 0.364 mmol), and 10% Pd/C (44.6 mg, 0.0419 mmol) were stirred in EtOAc (5.0 mL) under a hydrogen atmosphere for 1 h. The atmosphere was then purged with argon and the reaction quenched with DCM, filtered through celite, and concentrated. Flash chromatographic purification over silica (100% hexanes to 95:5 hexanes:EtOAc gradient elution) afforded 1,3-dibromo-4-hydroxy-5-phenethylbenzene (**4d**) as a clear, colorless syrup (102 mg, 82%). <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>) δ 7.26-7.31 (m, 2H), 7.23 (s, 2H), 7.21 (tt, *J*=1.3, 6.6 Hz, 1H), 7.12-7.16 (m, 2H), 5.74 (s, 1H), 2.84-2.89 (m, 2H), 2.78-2.83 (m, 2H); <sup>13</sup>C-NMR (125 MHz, CDCl<sub>3</sub>) δ 147.49, 140.80, 136.35, 131.90, 128.45, 128.42, 126.20, 109.51, 37.71, 36.45; ESI-TOF 352.9173 *m/z* [M-H<sup>+</sup>]<sup>-</sup>, C<sub>14</sub>H<sub>11</sub>Br<sub>2</sub>O requires 352.9182; RP-HPLC: 97% & 98% pure.

*Primary RP-HPLC Conditions Chromatographic Trace:*



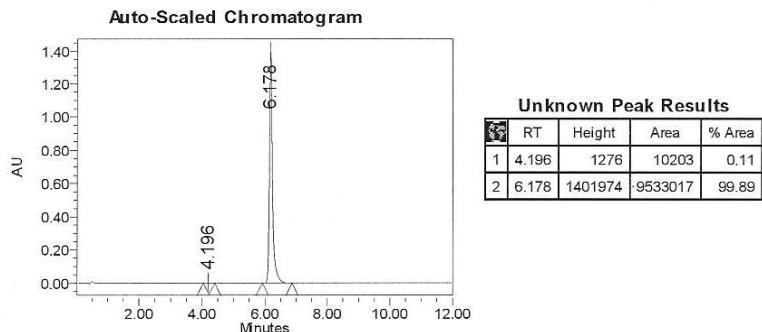
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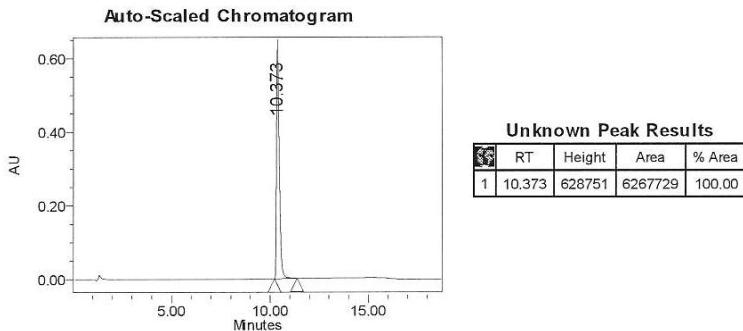
**(3,5-Dimethylphenyl)phenylamine (5a).**

Aniline (0.19 mL, 2.09 mmol), 5-bromo-*m*-xylene (316 mg, 1.71 mmol), Pd<sub>2</sub>(dba)<sub>3</sub> (84.3 mg, 0.0921 mmol), (±)-Binap (78.6 mg, 0.126 mmol), and Cs<sub>2</sub>CO<sub>3</sub> (799 mg, 2.45 mmol) were refluxed in anhydrous toluene (17.0 mL) under an argon atmosphere. After 18 h the reaction was filtered through celite and concentrated. Flash chromatographic purification over silica (100% hexanes to 9:1 hexanes:EtOAc gradient elution), followed by prep-HPLC purification, afforded (3,5-dimethylphenyl)phenylamine (**5a**) as an off-white solid (106 mg, 31%). <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>) δ 7.23-7.29 (m, 2H), 7.04-7.07 (m, 2H), 6.91 (tt, *J*=1.1, 7.3 Hz, 1H), 6.70 (s, 2H), 6.58 (s, 1H), 5.60 (br s, 1H), 2.26 (s, 6H); <sup>13</sup>C-NMR (125 MHz, CDCl<sub>3</sub>) δ 143.29, 143.01, 139.04, 129.29, 122.87, 120.75, 117.85, 115.57, 21.41; ESI-TOF 198.1281 *m/z* [MH]<sup>+</sup>, C<sub>14</sub>H<sub>16</sub>N requires 198.1277; RP-HPLC: >99% & >99% pure.

*Primary RP-HPLC Conditions Chromatographic Trace:*



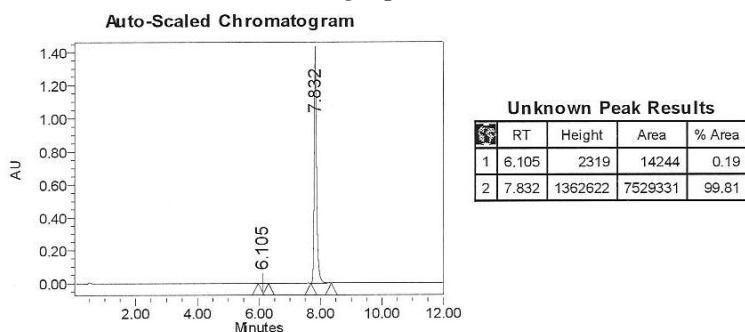
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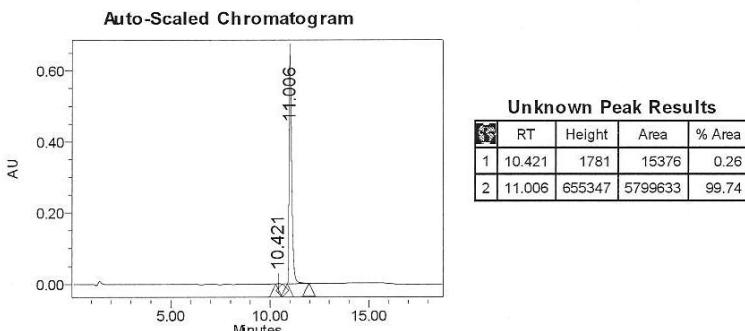
**(3,5-Dibromophenyl)phenylamine (5b).**

Aniline (0.17 mL, 1.87 mmol), 1,3,5-tribromobenzene (1.13 g, 3.60 mmol),  $\text{Pd}_2(\text{dba})_3$  (101 mg, 0.111 mmol), ( $\pm$ )-Binap (101 mg, 0.163 mmol), and  $\text{Cs}_2\text{CO}_3$  (877 mg, 2.69 mmol) were refluxed in anhydrous toluene (19.0 mL) under an argon atmosphere. After 18 h, the reaction was filtered through celite and concentrated. Flash chromatographic purification over silica (95:5-4:1 hexanes:EtOAc gradient elution), followed by prep-HPLC purification, afforded (3,5-dibromophenyl)phenylamine (**5b**) as a clear amber syrup (104 mg, 17%).  $^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.31-7.35 (m, 2H), 7.13 (t,  $J=1.6$  Hz, 1H), 7.04-7.11 (m, 5H), 5.71 (s, 1H);  $^{13}\text{C-NMR}$  (125 MHz,  $\text{CDCl}_3$ )  $\delta$  146.24, 140.76, 129.63, 125.27, 123.47, 123.20, 120.14, 117.57; ESI-TOF 323.9026  $m/z$  [M-H $^+$ ],  $\text{C}_{12}\text{H}_8\text{Br}_2\text{N}$  requires 323.9029; RP-HPLC: >99% & >99% pure.

*Primary RP-HPLC Conditions Chromatographic Trace:*



*Secondary RP-HPLC Conditions Chromatographic Trace:*



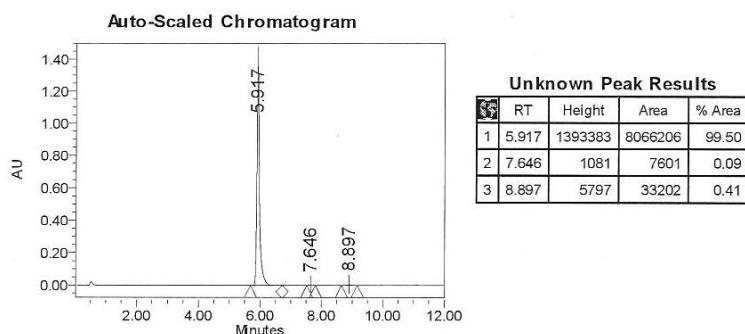
**(3,5-Dimethyl-4-methoxyphenyl)phenylamine (16).**

Aniline (0.21 mL, 2.30 mmol), 4-bromo-2,6-dimethylanisole (414 mg, 1.92 mmol),  $\text{Pd}_2(\text{dba})_3$  (86.3 mg, 0.0942 mmol), ( $\pm$ )-Binap (88.1 mg, 0.141 mmol), and  $\text{Cs}_2\text{CO}_3$  (875 mg, 2.69 mmol) were refluxed in anhydrous toluene (20.0 mL) under an argon atmosphere. After 18 h, the reaction was filtered through celite and concentrated. Flash chromatographic purification over silica (100% hexanes to 9:1 hexanes:EtOAc gradient elution), followed by prep-HPLC purification, afforded (3,5-dimethyl-4-methoxyphenyl)phenylamine (**16**) as an amber syrup (52.0 mg, 12%).  $^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.21-7.25 (m, 2H), 6.97-7.01 (m, 2H), 6.87 (tt,  $J=1.1, 7.3$  Hz, 1H), 6.75 (s, 2H), 5.70 (s, 1H), 3.70 (s, 3H), 2.25 (s, 6H);  $^{13}\text{C-NMR}$  (125 MHz,  $\text{CDCl}_3$ )  $\delta$  151.70, 144.11, 138.39, 131.62, 129.29, 120.14, 119.16, 116.83, 59.90, 16.22; ESI-MS 228  $m/z$  [MH] $^+$ ,  $\text{C}_{15}\text{H}_{18}\text{NO}$  requires 228; RP-HPLC: 88% pure.

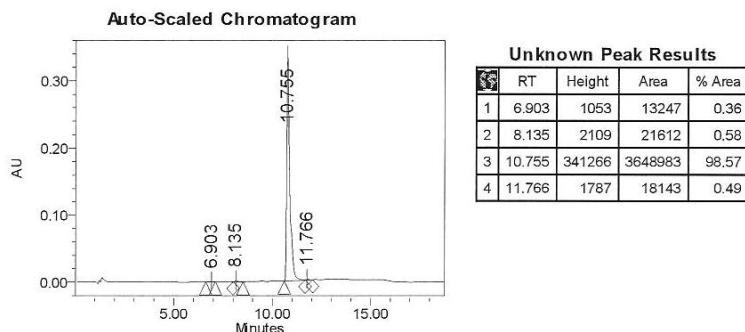
**(3,5-Dimethyl-4-hydroxyphenyl)phenylamine (5c).**

Boron tribromide (1.08 mL of 1 M BBr<sub>3</sub> in hexanes, 1.08 mmol) was added to a stirring mixture of **16** (49.3 mg, 0.217 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (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<sub>2</sub>O (2x25 mL) and brine (25 mL). The organics were then dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. Flash chromatographic purification over silica (4:1-2:1 hexanes:EtOAc gradient elution) afforded 3,5-dimethyl-4-hydroxyphenyl)phenylamine (**5c**) as a tan solid (41.7 mg, 90%). <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>) δ 7.18-7.23 (m, 2H), 6.88-6.92 (m, 2H), 6.81 (tt, *J*=1.1, 7.3 Hz, 1H), 6.78 (s, 2H), 5.39 (br s, 1H), 4.41 (s, 1H), 2.22 (s, 6H); <sup>13</sup>C-NMR (125 MHz, CDCl<sub>3</sub>) δ 147.81, 145.35, 134.96, 129.26, 124.01, 121.36, 119.34, 115.62, 16.09; ESI-TOF 214.1225 *m/z* [M-H<sup>+</sup>]<sup>-</sup>, C<sub>14</sub>H<sub>14</sub>NO requires 214.1226; RP-HPLC: >99% & 98% pure.

*Primary RP-HPLC Conditions Chromatographic Trace:*



*Secondary RP-HPLC Conditions Chromatographic Trace:*



**2-Benzyl-1,3,5-tribromobenzene (17).**

2,4,6-Tribromophenol (5.02 g, 15.2 mmol), benzyl bromide (2.00 mL, 16.8 mmol), and K<sub>2</sub>CO<sub>3</sub> (2.33 g, 16.9 mmol) were stirred in DMF (30 mL) at room temperature. After 18 h, the reaction was diluted with H<sub>2</sub>O and the precipitate was filtered, rinsed with H<sub>2</sub>O, and dried to afford 2-benzyl-1,3,5-tribromobenzene (**17**) as a white solid (6.23 g, 97%). <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>) δ 7.68 (s, 2H), 7.56-7.60 (m, 2H), 7.39-7.44 (m, 2H), 7.35-7.39 (m, 1H), 5.01 (s, 2H); <sup>13</sup>C-NMR (125 MHz, CDCl<sub>3</sub>) δ 152.34, 135.85, 135.10, 128.55, 128.52, 128.51, 119.30, 117.68, 74.79; RP-HPLC: >99% pure.

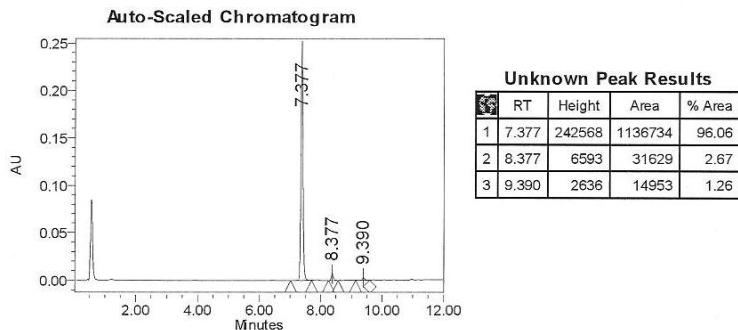
**(3,5-Dibromo-4-benzyloxyphenyl)phenylamine (18).**

Aniline (0.23 mL, 2.52 mmol), **17** (2.08 g, 4.94 mmol),  $\text{Pd}_2(\text{dba})_3$  (121 mg, 0.132 mmol), ( $\pm$ )-Binap (110 mg, 0.176 mmol), and  $\text{Cs}_2\text{CO}_3$  (1.15 g, 3.53 mmol) were refluxed in anhydrous toluene (25.0 mL) under an argon atmosphere. After 18 h, the reaction was filtered through celite and concentrated. Flash chromatographic purification over silica (95:5-4:1 hexanes:EtOAc gradient elution) afforded (3,5-dibromo-4-benzyloxyphenyl)phenylamine (**18**) as a dark red syrup (446 mg, 41%).  $^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.58-7.62 (m, 2H), 7.38-7.43 (m, 2H), 7.33-7.38 (m, 1H), 7.28-7.33 (m, 2H), 7.19 (s, 2H), 7.03-7.07 (m, 2H), 7.01 (tt,  $J=1.1, 7.4$  Hz, 1H), 5.62 (s, 1H), 4.98 (s, 2H);  $^{13}\text{C-NMR}$  (125 MHz,  $\text{CDCl}_3$ )  $\delta$  146.30, 141.68, 141.65, 136.48, 129.60, 128.50, 128.45, 128.32, 122.43, 120.69, 119.01, 118.75, 60.42; ESI-MS  $430\text{ m/z } [\text{M}-\text{H}^+]$ ,  $\text{C}_{19}\text{H}_{14}\text{Br}_2\text{NO}$  requires 430; RP-HPLC: 90% pure.

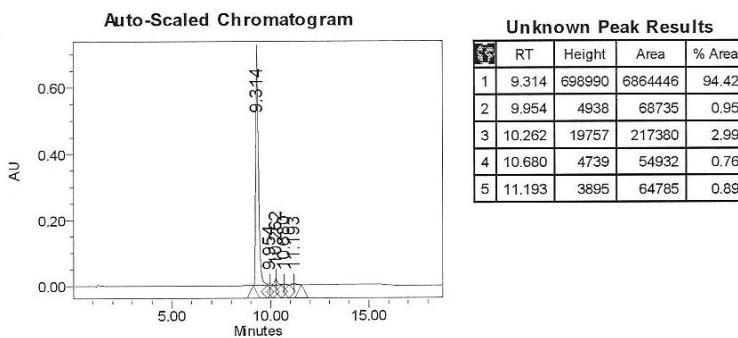
**(3,5-Dibromo-4-hydroxyphenyl)phenylamine (5d).**

3,5-Dibromo-4-benzyloxyphenyl)phenylamine (**18**, 140 mg, 0.323 mmol),  $\text{ZnBr}_2$  (93.1 mg, 0.413 mmol), and 10% Pd/C (35.6 mg, 0.0335 mmol) were stirred in EtOAc (10.0 mL) under a hydrogen atmosphere for 1.5 h. The atmosphere was then purged with argon and the reaction quenched with DCM, filtered through celite, and concentrated. Flash chromatographic purification over silica (9:1-2:1 hexanes:EtOAc gradient elution) afforded (3,5-dibromo-4-hydroxyphenyl)phenylamine (**5d**) as a clear, pale amber syrup (37.8 mg, 34%).  $^1\text{H-NMR}$  (500 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  7.19-7.24 (m, 4H), 6.95-7.00 (m, 2H), 6.84 (tt,  $J=1.1, 7.3$  Hz, 1H);  $^{13}\text{C-NMR}$  (125 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  145.87, 145.02, 139.97, 130.28, 122.72, 121.49, 118.08, 113.05; ESI-TOF  $341.9122\text{ m/z } [\text{MH}]^+$ ,  $\text{C}_{12}\text{H}_{10}\text{Br}_2\text{NO}$  requires 341.9124; RP-HPLC: 96% & 95% pure.

*Primary RP-HPLC Conditions Chromatographic Trace:*



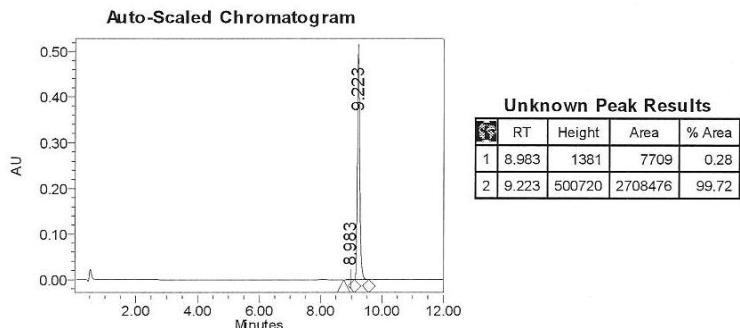
*Secondary RP-HPLC Conditions Chromatographic Trace:*



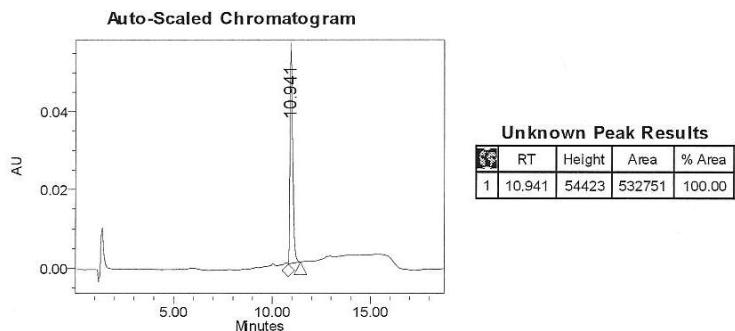
### 1,3-Dimethyl-5-phenoxybenzene (6a).

Pyridine (0.99 mL, 12.1 mmol) was added to a stirring mixture of 3,5-dimethylphenylboronic acid (730 mg, 4.87 mmol), phenol (228 mg, 2.42 mmol), Cu(OAc)<sub>2</sub> (441 mg, 2.43 mmol), and freshly activated 4 Å molecular sieves in CH<sub>2</sub>Cl<sub>2</sub> (24.0 mL) under an air atmosphere. After 18 h the reaction was filtered and concentrated. Flash chromatographic purification over silica (100% hexanes to 9:1 hexanes:EtOAc gradient elution), followed by prep-HPLC purification, afforded 1,3-dimethyl-5-phenoxybenzene (**6a**) as a clear, colorless liquid (251 mg, 52%). <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>) δ 7.29-7.35 (m, 2H), 7.08 (tt, *J*=1.1, 7.4 Hz, 1H), 6.98-7.02 (m, 2H), 6.73-6.76 (m, 1H), 6.62-6.65 (m, 2H), 2.28 (q, *J*=0.6 Hz, 6H); <sup>13</sup>C-NMR (125 MHz, CDCl<sub>3</sub>) δ 157.40, 157.12, 139.56, 129.63, 124.97, 122.95, 118.82, 11.57, 21.31; ESI-TOF 199.1117 *m/z* [MH]<sup>+</sup>, C<sub>14</sub>H<sub>15</sub>O requires 199.1117; RP-HPLC: >99% & >99% pure.

#### Primary RP-HPLC Conditions Chromatographic Trace:



#### Secondary RP-HPLC Conditions Chromatographic Trace:

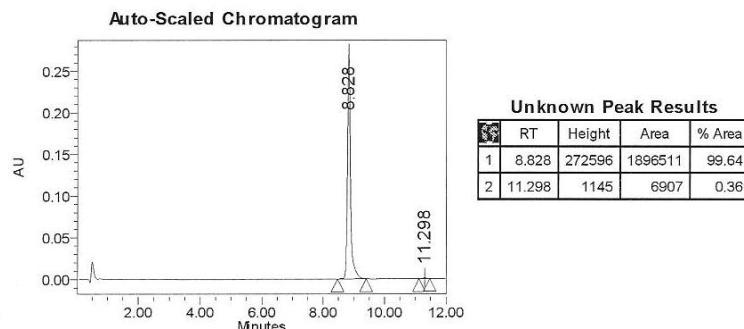


### 1,3-Dibromo-5-phenoxybenzene (6b).

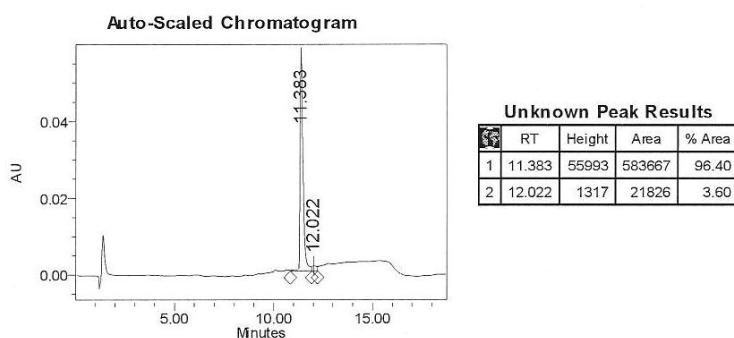
Pyridine (0.75 mL, 9.20 mmol) was added to a stirring mixture of 3,5-dibromophenylboronic acid (1.09 g, 3.67 mmol), phenol (172 mg, 1.83 mmol), Cu(OAc)<sub>2</sub> (330 mg, 1.82 mmol), and freshly activated 4 Å molecular sieves in CH<sub>2</sub>Cl<sub>2</sub> (20.0 mL) under an air atmosphere. After 18 h, the reaction was filtered and concentrated. Flash chromatographic purification over silica (100% hexanes to 9:1 hexanes:EtOAc gradient elution), followed by prep-HPLC purification, afforded 1,3-dibromo-5-phenoxybenzene (**6b**) as a clear, colorless liquid (417 mg, 69%). <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>) δ 7.37-7.42 (m, 2H), 7.36 (t, *J*=1.6 Hz, 1H), 7.20 (tt, *J*=1.1, 7.4 Hz, 1H), 7.06 (d, *J*=1.6 Hz, 2H), 7.01-7.05 (m, 2H); <sup>13</sup>C-NMR (125 MHz, CDCl<sub>3</sub>) δ 159.06, 155.42, 130.14, 128.47,

124.72, 123.23, 120.12, 119.82; GC-MS 326  $m/z$  [M]<sup>+</sup>, C<sub>12</sub>H<sub>8</sub>Br<sub>2</sub>O requires 326; RP-HPLC: >99% & 96% pure.

*Primary RP-HPLC Conditions Chromatographic Trace:*



*Secondary RP-HPLC Conditions Chromatographic Trace:*



**1,3-Dimethyl-2-methoxy-5-phenoxybenzene (19).**

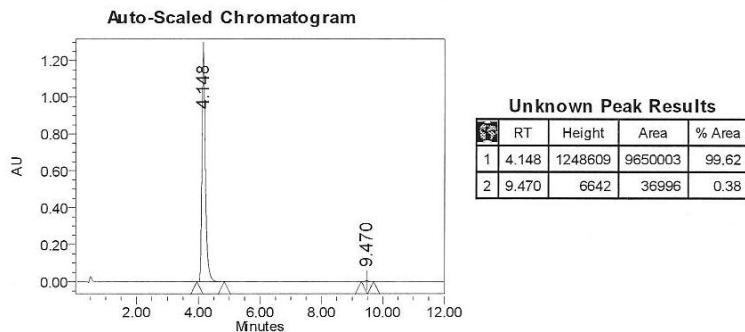
Pyridine (0.91 mL, 11.2 mmol) was added to a stirring mixture of 3,5-dimethyl-4-methoxyphenylboronic acid (808 mg, 4.49 mmol), phenol (209 mg, 2.22 mmol), Cu(OAc)<sub>2</sub> (406 mg, 2.24 mmol), and freshly activated 4 Å molecular sieves in CH<sub>2</sub>Cl<sub>2</sub> (22.0 mL) under an air atmosphere. After 18 h, the reaction was filtered and concentrated. Flash chromatographic purification over silica (100% hexanes to 9:1 hexanes:EtOAc gradient elution), followed by prep-HPLC purification, afforded 1,3-dimethyl-2-methoxy-5-phenoxybenzene (**19**) as a clear, colorless liquid (305 mg, 60%). <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.29-7.34 (m, 2H), 7.06 (tt, *J*=1.1, 7.4 Hz, 1H), 6.96-7.00 (m, 2H), 6.67 (s, 2H), 3.71 (s, 3H), 2.25 (s, 6H); <sup>13</sup>C-NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  157.91, 152.85, 152.33, 132.18, 129.61, 122.68, 119.17, 118.28, 59.88, 16.22; ESI-MS 229  $m/z$  [MH]<sup>+</sup>, C<sub>15</sub>H<sub>17</sub>O<sub>2</sub> requires 229; RP-HPLC: >99% pure.

**1,3-Dimethyl-2-hydroxy-5-phenoxybenzene (6c).**

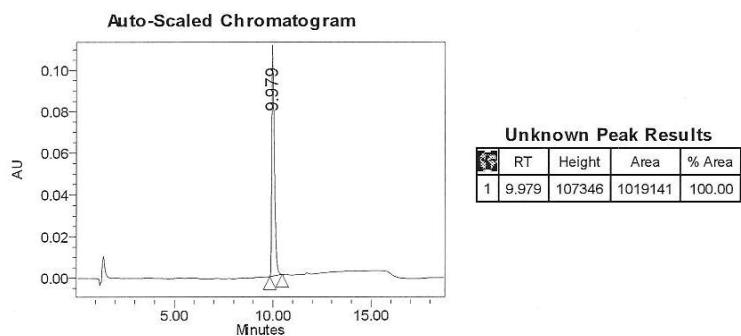
Boron tribromide (2.30 mL of 1 M BBr<sub>3</sub> in hexanes, 2.30 mmol) was added to a stirring mixture of **19** (105 mg, 0.459 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (5.0 mL) and the reaction was stirred at room temperature under an argon atmosphere. After 18 h, the reaction was quenched with MeOH (5 mL), extracted into EtOAc (50 mL), and washed with H<sub>2</sub>O (2x25 mL) and brine (25 mL). The organics were then dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. Flash chromatographic purification over silica (4:1-2:1 hexanes:EtOAc gradient elution) afforded 1,3-dimethyl-2-hydroxy-5-phenoxybenzene

**(6c)** as a pale yellow syrup (79.0 mg, 80%).  $^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.26-7.31 (m, 2H), 7.02 (tt,  $J=1.1, 7.4$  Hz, 1H), 6.92-6.96 (m, 2H), 6.69 (s, 2H), 4.46 (s, 1H), 2.21 (s, 6H);  $^{13}\text{C-NMR}$  (125 MHz,  $\text{CDCl}_3$ )  $\delta$  159.07, 149.66, 148.81, 129.95, 124.79, 122.63, 120.22, 117.96, 16.52; ESI-TOF 213.0918  $m/z$  [M-H $^+$ ] $^-$ ,  $\text{C}_{14}\text{H}_{13}\text{O}_2$  requires 213.0921; RP-HPLC: >99% & >99% pure.

*Primary RP-HPLC Conditions Chromatographic Trace:*



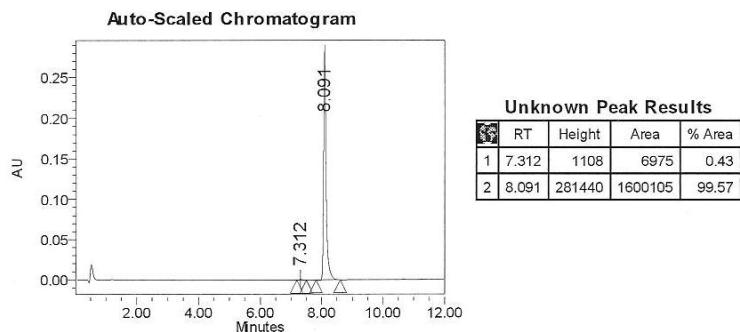
*Secondary RP-HPLC Conditions Chromatographic Trace:*



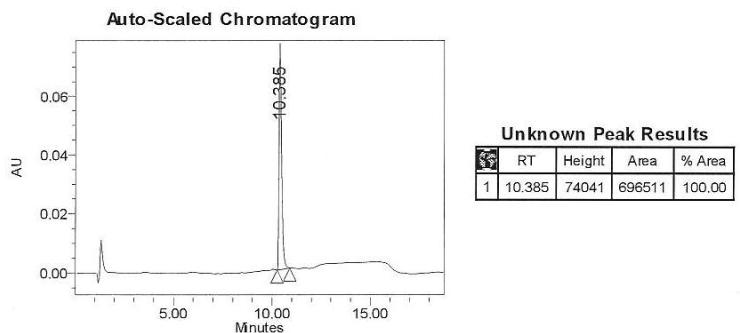
**1,3-Dibromo-2-hydroxy-5-phenoxybenzene (6d).**

Bromine (0.14 mL, 2.73 mmol) and 4-phenoxyphenol (239 mg, 1.28 mmol) were stirred in EtOH (13.0 mL). After 18 h, the reaction was concentrated and pre-purified by flash chromatographic purification over silica (95:5-2:1 hexanes:EtOAc gradient elution), then was purified again by prep-HPLC to afford 1,3-dibromo-2-hydroxy-5-phenoxybenzene (**6d**) as a pale yellow solid (107 mg, 24%).  $^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.32-7.37 (m, 2H), 7.16 (s, 2H), 7.11-7.15 (m, 1H), 6.95-6.99 (m, 2H), 5.70 (br s, 1H);  $^{13}\text{C-NMR}$  (125 MHz,  $\text{CDCl}_3$ )  $\delta$  156.99, 150.74, 145.79, 129.95, 123.75, 122.85, 118.44, 109.69; ESI-TOF 340.8810  $m/z$  [M-H $^+$ ] $^-$ ,  $\text{C}_{12}\text{H}_7\text{Br}_2\text{O}_2$  requires 340.8818; RP-HPLC: >99% & >99% pure.

*Primary RP-HPLC Conditions Chromatographic Trace:*



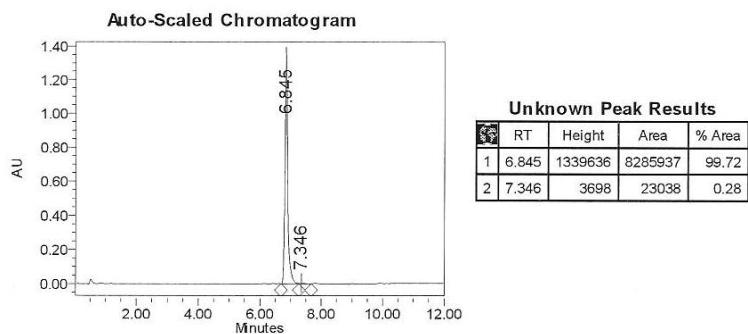
*Secondary RP-HPLC Conditions Chromatographic Trace:*



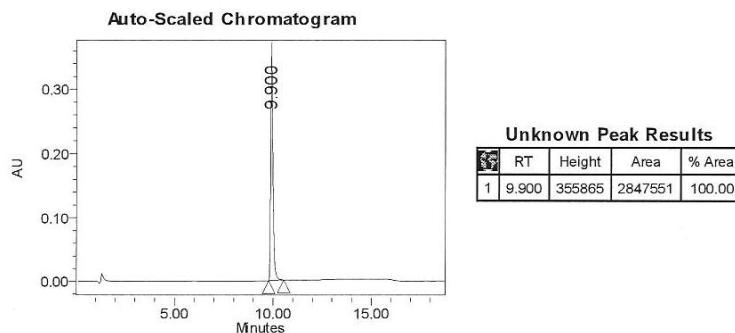
**1-(3,5-Dimethylphenyl)-3-phenylurea (7a).**

Phenylisocyanate (124 mg, 1.04 mmol), 3,5-dimethylaniline (0.13 mL, 1.04 mmol), and pyridine (85.0  $\mu$ L, 1.04 mmol) were stirred in  $\text{CH}_2\text{Cl}_2$  (10.0 mL). After 18 h the reaction was extracted into EtOAc (50 mL) and washed with 1 N HCl (2x25 mL) and brine (25 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated. Flash chromatographic purification over silica (2:1-1:1 hexanes:EtOAc gradient elution) afforded 1-(3,5-dimethylphenyl)-3-phenylurea (**7a**) as a white solid (227 mg, 91%).  $^1\text{H-NMR}$  (500 MHz,  $d_6$ -DMSO)  $\delta$  8.61 (s, 1H), 8.48 (s, 1H), 7.43 (d,  $J=7.7$  Hz, 2H), 7.26 (t,  $J=7.9$  Hz, 2H), 7.06 (s, 2H), 6.95 (t,  $J=7.3$  Hz, 1H), 6.60 (s, 1H), 2.22 (s, 6H);  $^{13}\text{C-NMR}$  (125 MHz,  $d_6$ -DMSO)  $\delta$  152.49, 139.78, 139.55, 137.73, 128.79, 123.45, 121.75, 118.11, 115.93, 21.15; ESI-TOF 241.1332  $m/z$  [MH] $^+$ ,  $\text{C}_{15}\text{H}_{17}\text{N}_2\text{O}$  requires 241.1335; RP-HPLC: >99% & >99% pure.

*Primary RP-HPLC Conditions Chromatographic Trace:*



*Secondary RP-HPLC Conditions Chromatographic Trace:*



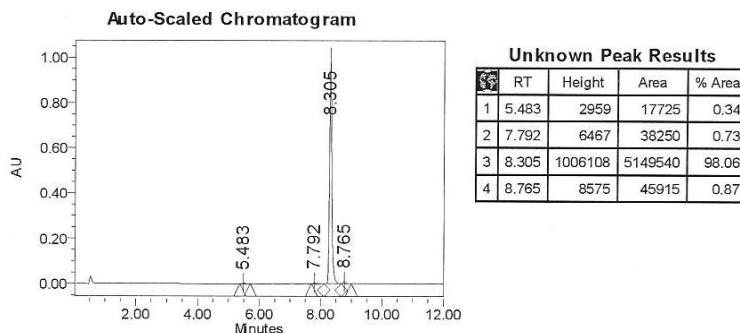
**3,5-Dibromoaniline (21).**

3,5-Dibromonitrobenzene (**20**, 2.48 g, 8.83 mmol) and tin powder (3.15 g, 26.5 mmol) were stirred in an HCl/AcOH mixture (2.0/20.0 mL). After 18 h the reaction was diluted with H<sub>2</sub>O (500 mL) and neutralized with NaOH pellets. The precipitate was filtered and rinsed with H<sub>2</sub>O, then extracted into EtOAc, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. Re-precipitation from MeOH/H<sub>2</sub>O afforded 3,5-dibromoaniline (**21**) as a pale yellow powder (1.32 mg, 60%). <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>) δ 7.01 (t, *J*=1.6 Hz, 1H), 6.74 (d, *J*=1.6 Hz, 2H), 3.76 (br s, 2H); <sup>13</sup>C-NMR (125 MHz, CDCl<sub>3</sub>) δ 148.61, 123.69, 123.34, 116.50.

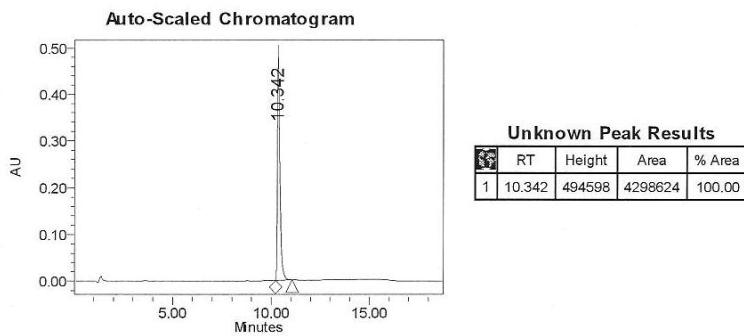
**1-(3,5-Dibromophenyl)-3-phenylurea (7b).**

Phenylisocyanate (73.0  $\mu$ L, 0.672 mmol), 3,5-dibromoaniline (**21**, 167 mg, 0.667 mmol), and pyridine (54.0  $\mu$ L, 0.662 mmol) were stirred in CH<sub>2</sub>Cl<sub>2</sub> (6.0 mL). After 18 h, the reaction was extracted into EtOAc (50 mL) and washed with 1 N HCl (2x25 mL) and brine (25 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. Flash chromatographic purification over silica (2:1-1:2 hexanes:EtOAc gradient elution) afforded 1-(3,5-dibromophenyl)-3-phenylurea (**7b**) as a white solid (115 mg, 47%). <sup>1</sup>H-NMR (500 MHz, *d*<sub>6</sub>-DMSO) δ 8.98 (s, 1H), 8.82 (s, 1H), 7.69 (d, *J*=1.7 Hz, 2H), 7.43-7.47 (m, 2H), 7.36 (t, *J*=1.7 Hz, 1H), 7.26-7.31 (m, 2H), 6.99 (tt, *J*=1.1, 7.4 Hz, 1H); <sup>13</sup>C-NMR (125 MHz, *d*<sub>6</sub>-DMSO) δ 152.16, 142.62, 139.12, 128.78, 126.13, 122.36, 122.33, 119.48, 118.62; ESI-TOF 368.9226 *m/z* [MH]<sup>+</sup>, C<sub>13</sub>H<sub>11</sub>Br<sub>2</sub>N<sub>2</sub>O requires 368.9233; RP-HPLC: 98% & >99% pure.

*Primary RP-HPLC Conditions Chromatographic Trace:*



*Secondary RP-HPLC Conditions Chromatographic Trace:*



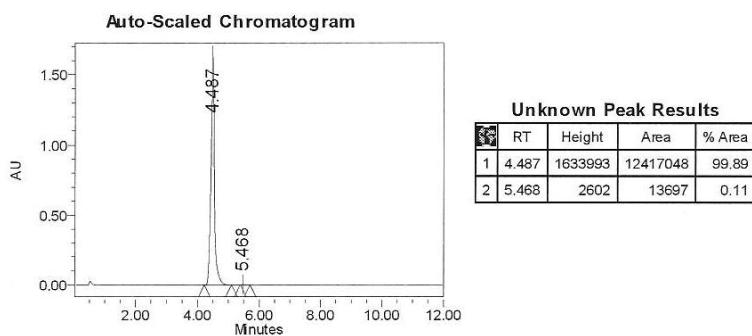
**3,5-Dimethyl-4-hydroxyaniline (22).**

2,6-Dimethyl-4-nitrophenol (1.02 g, 6.12 mmol) and tin powder (2.29 g, 19.3 mmol) were stirred in an HCl/AcOH mixture (1.2/12.0 mL). After 2 days, the reaction was diluted with H<sub>2</sub>O (100 mL), neutralized with NaHCO<sub>3</sub>, extracted into EtOAc (100 mL) and the organics were washed with sat. NaHCO<sub>3</sub> (2x25 mL) and brine (50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to afford 3,5-dimethyl-4-hydroxyaniline (**22**) as an orange solid (729 mg, 87%). <sup>1</sup>H-NMR (500 MHz, *d*<sub>6</sub>-DMSO) δ 7.15 (s, 1H), 6.15 (s, 2H), 4.27 (s, 2H), 2.02 (s, 6H); <sup>13</sup>C-NMR (125 MHz, *d*<sub>6</sub>-DMSO) δ 143.94, 140.85, 125.23, 114.30, 16.83; ESI-MS 138 *m/z* [MH]<sup>+</sup>, C<sub>8</sub>H<sub>12</sub>NO requires 138.

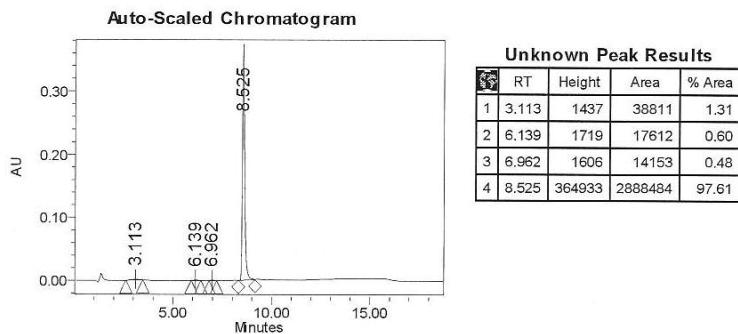
**1-(3,5-Dimethyl-4-hydroxyphenyl)-3-phenylurea (7c).**

Phenylisocyanate (103 mg, 0.866 mmol), 4-amino-2,6-dimethylphenol (**22**, 120 mg, 0.877 mmol), and pyridine (71.0 μL, 0.870 mmol) were stirred in CH<sub>2</sub>Cl<sub>2</sub> (9.0 mL). After 18 h, the reaction was extracted into EtOAc (50 mL) and washed with 1 N HCl (2x25 mL) and brine (25 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. Flash chromatographic purification over silica (1:2 hexanes:EtOAc to 100% EtOAc to 9:1 EtOAc:MeOH gradient elution) afforded 1-(3,5-dimethyl-4-hydroxyphenyl)-3-phenylurea (**7c**) as a tan solid (121 mg, 55%). <sup>1</sup>H-NMR (500 MHz, *d*<sub>6</sub>-DMSO) δ 8.50 (s, 1H), 8.19 (s, 1H), 7.86 (s, 1H), 7.42 (d, *J*=7.7 Hz, 2H), 7.24 (t, *J*=7.9 Hz, 2H), 6.97 (s, 2H), 6.92 (t, *J*=7.3 Hz, 1H), 2.13 (s, 6H); <sup>13</sup>C-NMR (125 MHz, *d*<sub>6</sub>-DMSO) δ 152.74, 148.35, 140.06, 131.17, 128.75, 124.61, 121.46, 119.04, 117.96, 16.85; ESI-TOF 257.1283 *m/z* [MH]<sup>+</sup>, C<sub>15</sub>H<sub>17</sub>N<sub>2</sub>O<sub>2</sub> requires 257.1284; RP-HPLC: >99% & 97% pure.

*Primary RP-HPLC Conditions Chromatographic Trace:*



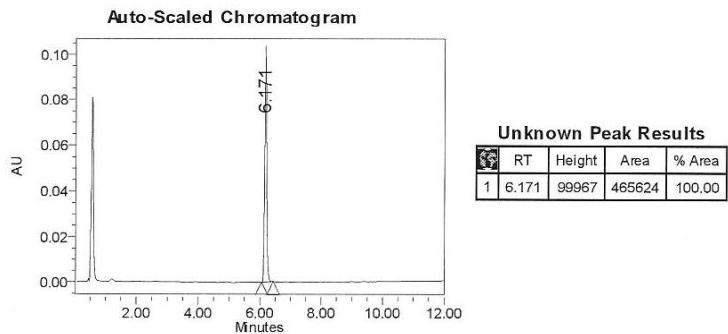
*Secondary RP-HPLC Conditions Chromatographic Trace:*



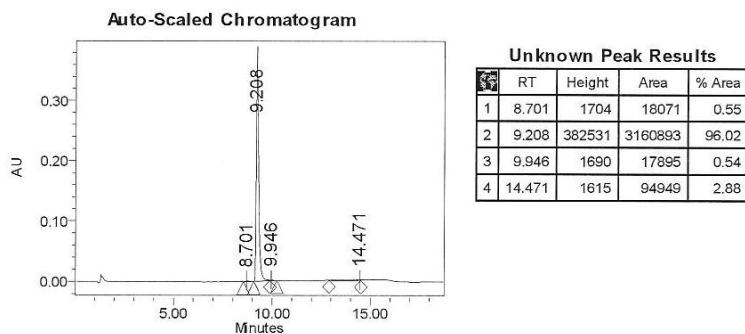
**1-(3,5-Dibromo-4-hydroxyphenyl)-3-phenylurea (7d).**

Phenylisocyanate (149 mg, 1.25 mmol), 4-amino-2,6-dibromophenol (355 mg, 1.27 mmol), and pyridine (0.10 mL, 1.23 mmol) were stirred in  $\text{CH}_2\text{Cl}_2$  (12.5 mL). After 18 h, the reaction was extracted into EtOAc (50 mL) and washed with 1 N HCl (2x25 mL) and brine (25 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated. Flash chromatographic purification over silica (1:2 hexanes:EtOAc to 100% EtOAc to 9:1 EtOAc:MeOH gradient elution) afforded 1-(3,5-dibromo-4-hydroxyphenyl)-3-phenylurea (**7d**) as a tan solid (438 mg, 91%).  $^1\text{H-NMR}$  (500 MHz,  $d_6$ -DMSO)  $\delta$  9.50 (s, 1H), 8.71 (s, 1H), 8.64 (s, 1H), 7.64 (s, 2H), 7.42 (d,  $J=7.7$  Hz, 2H), 7.26 (t,  $J=7.9$  Hz, 2H), 6.96 (t,  $J=7.3$  Hz, 1H);  $^{13}\text{C-NMR}$  (125 MHz,  $d_6$ -DMSO)  $\delta$  152.51, 145.53, 139.49, 134.12, 128.77, 122.10, 122.01, 118.43, 112.21; ESI-TOF  $384.9187\text{ m/z [MH]}^+$ ,  $\text{C}_{13}\text{H}_{11}\text{Br}_2\text{N}_2\text{O}_2$  requires 384.9182; RP-HPLC: >99% Z& 99% pure.

*Primary RP-HPLC Conditions Chromatographic Trace:*



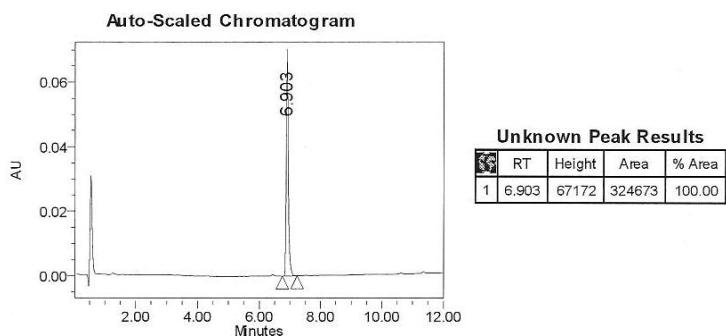
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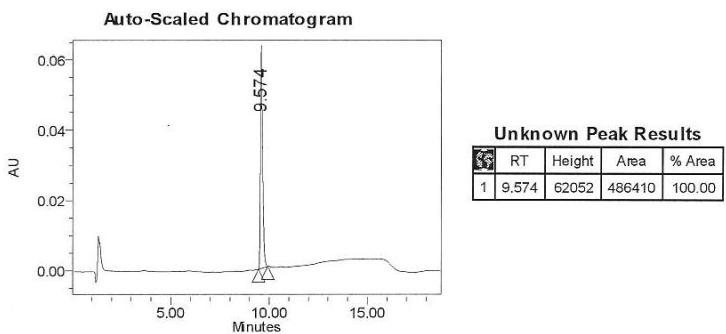
***N*-(3,5-Dimethylphenyl)benzenesulfonamide (8a).**

Benzenesulfonyl chloride (0.23 mL, 1.80 mmol), 3,5-dimethylaniline (200 mg, 1.65 mmol), and pyridine (0.14 mL, 1.72 mmol) were stirred in  $\text{CH}_2\text{Cl}_2$  (5.0 mL). After 18 h the reaction was concentrated and flash chromatographic purification over silica (4:1:1:1 hexanes:EtOAc gradient elution) afforded *N*-(3,5-dimethylphenyl)benzenesulfonamide (**8a**) as a white solid (336 mg, 78%).  $^1\text{H}$ -NMR (500 MHz,  $d_6$ -DMSO)  $\delta$  10.14 (s, 1H), 7.73-7.77 (m, 2H), 7.59 (tt,  $J$ =1.3, 6.3 Hz, 1H), 7.51-7.56 (m, 2H), 6.69-6.61 (m, 2H), 6.62-6.64 (m, 1H), 2.12 (q,  $J$ =0.5 Hz, 6H);  $^{13}\text{C}$ -NMR (125 MHz,  $d_6$ -DMSO)  $\delta$  139.65, 138.20, 137.57, 132.83, 129.23, 126.64, 125.63, 117.55, 20.96; ESI-TOF 262.0898  $m/z$  [MH] $^+$ ,  $\text{C}_{14}\text{H}_{16}\text{NO}_2\text{S}$  requires 262.0896; RP-HPLC: >99% & >99% pure.

*Primary RP-HPLC Conditions Chromatographic Trace:*



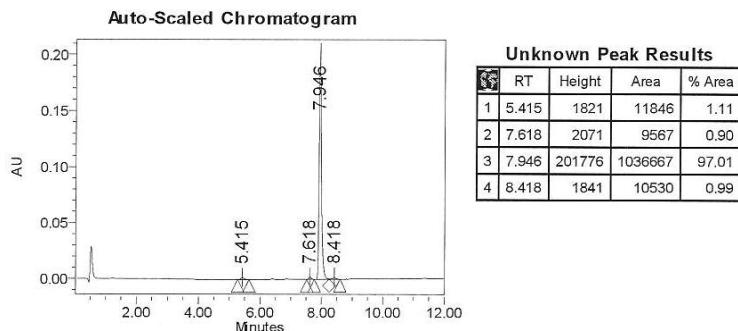
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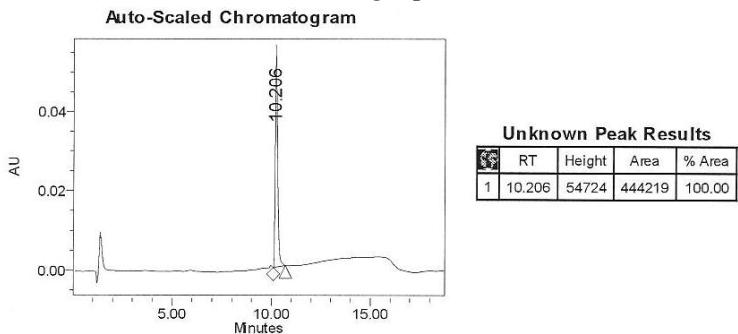
***N*-(3,5-Dibromophenyl)benzenesulfonamide (8b).**

Benzenesulfonyl chloride (84.0  $\mu\text{L}$ , 0.658 mmol), 3,5-dibromoaniline (**21**, 165 mg, 0.656 mmol), and pyridine (54.0  $\mu\text{L}$ , 0.662 mmol) were stirred in  $\text{CH}_2\text{Cl}_2$  (6.0 mL). After 18 h, the reaction was extracted into EtOAc (50 mL) and washed with 1 N HCl (2x25 mL) and brine (25 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated. Flash chromatographic purification over silica (4:1:1:1 hexanes:EtOAc gradient elution) afforded *N*-(3,5-dibromophenyl)benzenesulfonamide (**8b**) as a white solid (214 mg, 83%).  $^1\text{H}$ -NMR (500 MHz,  $d_6$ -DMSO)  $\delta$  10.82 (s, 1H), 7.77-7.81 (m, 2H), 7.65 (tt,  $J$ =1.3, 6.5 Hz, 1H), 7.57-7.62 (m, 2H), 7.46 (t,  $J$ =1.7 Hz, 1H), 7.25 (d,  $J$ =1.7 Hz, 2H);  $^{13}\text{C}$ -NMR (125 MHz,  $d_6$ -DMSO)  $\delta$  140.54, 138.76, 133.49, 129.59, 128.57, 126.61, 122.74, 120.58; ESI-TOF 411.8610  $m/z$  [MNa] $^+$ ,  $\text{C}_{12}\text{H}_9\text{Br}_2\text{NaNO}_2\text{S}$  requires 411.8613; RP-HPLC: 97% & >99% pure.

*Primary RP-HPLC Conditions Chromatographic Trace:*



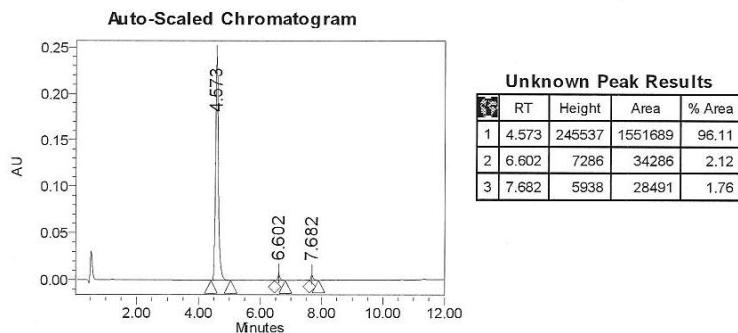
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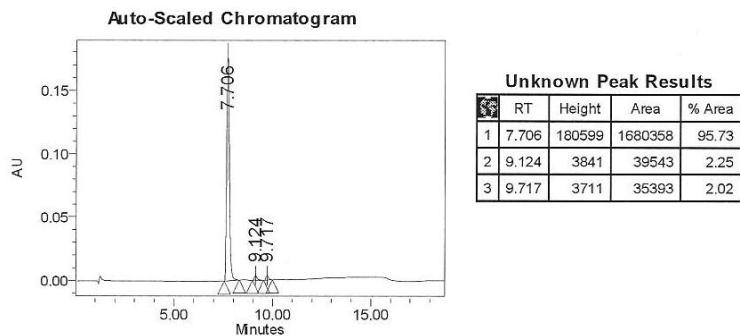
***N-(3,5-Dimethyl-4-hydroxyphenyl)benzenesulfonamide (8c).***

Benzenesulfonyl chloride (0.18 mL, 1.41 mmol), 4-amino-2,6-dimethylphenol (179 mg, 1.30 mmol), and pyridine (0.11 mL, 1.35 mmol) were stirred in  $\text{CH}_2\text{Cl}_2$  (5.0 mL). After 18 h, the reaction was concentrated and flash chromatographic purification over silica (2:1:1:1 hexanes:EtOAc gradient elution) afforded *N*-(3,5-dimethyl-4-hydroxyphenyl)benzenesulfonamide (**8c**) as a peach solid (267 mg, 74%).  $^1\text{H-NMR}$  (500 MHz,  $d_6$ -DMSO)  $\delta$  9.67 (s, 1H), 8.09 (s, 1H), 7.65-7.69 (m, 2H), 7.57 (tt,  $J=1.3, 6.4$  Hz, 1H), 7.49-7.53 (m, 2H), 6.59 (s, 2H), 2.01 (s, 6H);  $^{13}\text{C-NMR}$  (125 MHz,  $d_6$ -DMSO)  $\delta$  150.58, 139.71, 132.57, 129.05, 128.52, 126.70, 124.83, 122.23, 16.70; ESI-TOF 300.0661  $m/z$  [MNa] $^+$ ,  $\text{C}_{14}\text{H}_{15}\text{NaNO}_3\text{S}$  requires 300.0665; RP-HPLC: 96% & 96% pure.

*Primary RP-HPLC Conditions Chromatographic Trace:*



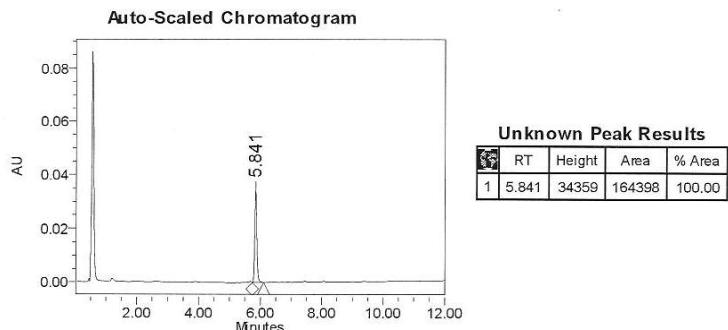
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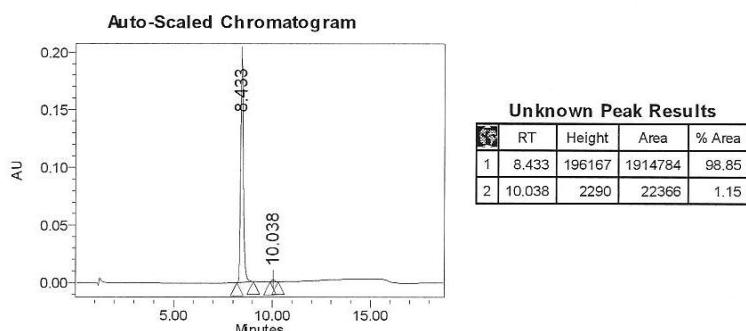
***N-(3,5-Dibromo-4-hydroxyphenyl)benzenesulfonamide (8d).***

Benzenesulfonyl chloride (114  $\mu$ L, 0.893 mmol), 4-amino-2,6-dibromophenol (249 mg, 0.890 mmol), and pyridine (73.0  $\mu$ L, 0.895 mmol) were stirred in THF (3.0 mL). After 2 h, the reaction was extracted into EtOAc (50 mL) and washed with 1 N HCl (2x25 mL) and brine (25 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated. Flash chromatographic purification over silica (2:1-1:1 hexanes:EtOAc gradient elution) and trituration with 2:1 hexanes: $\text{CH}_2\text{Cl}_2$  afforded *N*-(3,5-dibromo-4-hydroxyphenyl)benzenesulfonamide (**8d**) as an off-white solid (273 mg, 75%).  $^1\text{H}$ -NMR (500 MHz,  $d_6$ -DMSO)  $\delta$  10.23 (s, 1H), 9.84 (s, 1H), 7.69-7.72 (m, 2H), 7.63 (tt,  $J$ =1.3, 6.4 Hz, 1H), 7.55-7.60 (m, 2H), 7.18 (s, 2H);  $^{13}\text{C}$ -NMR (125 MHz,  $d_6$ -DMSO)  $\delta$  148.07, 138.79, 133.21, 131.35, 129.41, 126.67, 124.94, 112.11; ESI-TOF 427.8560  $m/z$  [MNa] $^+$ ,  $\text{C}_{12}\text{H}_9\text{Br}_2\text{NaNO}_3\text{S}$  requires 427.8562; RP-HPLC: 98% & 99% pure.

*Primary RP-HPLC Conditions Chromatographic Trace:*



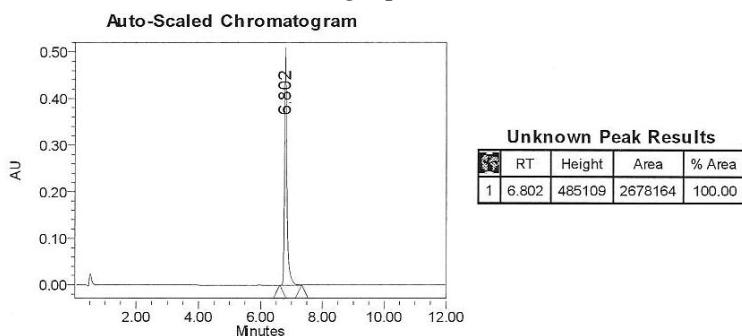
*Secondary RP-HPLC Conditions Chromatographic Trace:*



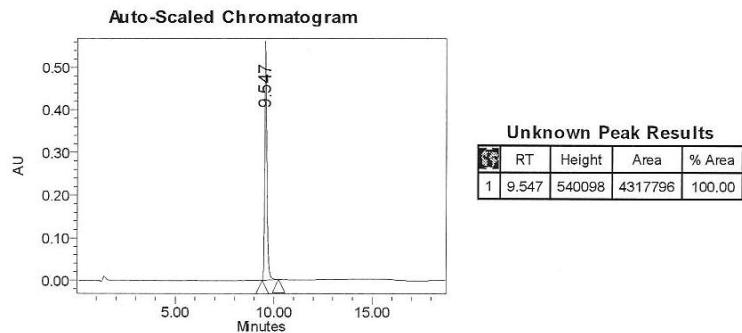
### 3,5-Dimethyl-N-phenylbenzamide (9a).

Aniline (98.0  $\mu$ L, 1.08 mmol), 3,5-dimethylbenzoic acid (134 mg, 0.894 mmol), DCC (222 mg, 1.07 mmol), and DMAP (12.0 mg, 0.098 mmol) were stirred in anhydrous  $\text{CH}_2\text{Cl}_2$  (9.0 mL) under an argon atmosphere. After 18 h the reaction was concentrated and flash chromatographic purification over silica (9:1-2:1 hexanes:EtOAc gradient elution), followed by prep-HPLC purification, afforded 3,5-dimethyl-N-phenylbenzamide (**9a**) as a white powder (84.1 mg, 42%).  $^1\text{H}$ -NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.88 (br s, 1H), 7.62-7.67 (m, 2H), 7.45 (s, 2H), 7.34-7.39 (m, 2H), 7.11-7.18 (m, 2H), 2.37 (s, 6H);  $^{13}\text{C}$ -NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  166.14, 138.50, 138.05, 135.00, 133.42, 129.05, 124.78, 124.41, 120.14, 21.27; ESI-TOF 226.1231  $m/z$  [MH] $^+$ ,  $\text{C}_{15}\text{H}_{16}\text{NO}$  requires 226.1226; RP-HPLC: >99% & >99% pure.

#### Primary RP-HPLC Conditions Chromatographic Trace:



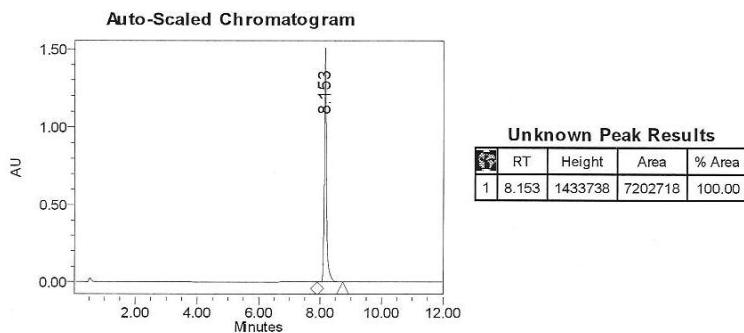
#### Secondary RP-HPLC Conditions Chromatographic Trace:



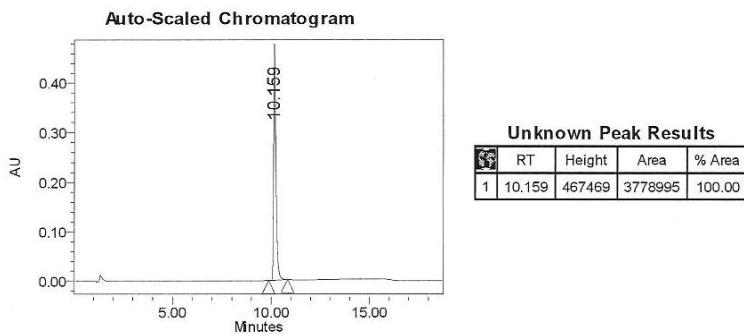
### 3,5-Dibromo-N-phenylbenzamide (9b).

Aniline (86.0  $\mu$ L, 0.944 mmol), 3,5-dibromobenzoic acid (219 mg, 0.784 mmol), DCC (192 mg, 0.931 mmol), and DMAP (9.8 mg, 0.080 mmol) were stirred in anhydrous  $\text{CH}_2\text{Cl}_2$  (8.0 mL) under an argon atmosphere. After 18 h, the reaction was concentrated and flash chromatographic purification over silica (9:1-4:1 hexanes:EtOAc gradient elution) afforded 3,5-dibromo-N-phenylbenzamide (**9b**) as a white solid (144 mg, 52%).  $^1\text{H}$ -NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  10.40 (s, 1H), 8.13 (d,  $J=1.7$  Hz, 2H), 8.08 (t,  $J=1.7$  Hz, 1H), 7.34 (d,  $J=7.8$  Hz, 2H), 7.36 (t,  $J=7.9$  Hz, 2H), 7.12 (t,  $J=7.4$  Hz, 1H);  $^{13}\text{C}$ -NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  162.50, 138.63, 138.45, 136.22, 129.67, 128.70, 124.15, 122.63, 120.46; ESI-TOF 353.9108  $m/z$  [MH] $^+$ ,  $\text{C}_{13}\text{H}_{10}\text{Br}_2\text{NO}$  requires 353.9124; RP-HPLC: >99% & >99% pure.

*Primary RP-HPLC Conditions Chromatographic Trace:*



*Secondary RP-HPLC Conditions Chromatographic Trace:*



**3,5-Dibromo-4-benzyloxybenzoic acid (23).**

3,5-Dibromo-4-hydroxybenzoic acid (1.40 g, 4.73 mmol), benzyl bromide (1.24 mL, 10.4 mmol), and  $\text{K}_2\text{CO}_3$  (1.45 g, 10.5 mmol) were stirred in DMF (10 mL) at room temperature. After 18 h the reaction was extracted into EtOAc (150 mL) and washed with  $\text{H}_2\text{O}$  (2x50 mL) and brine (50 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated. The benzyl ester intermediate was then stirred with  $\text{LiOH}\cdot\text{H}_2\text{O}$  (794 mg, 18.9 mmol) in  $\text{H}_2\text{O}/\text{MeOH}/\text{THF}$  (5/5/15 mL) for 3 h. The reaction was then diluted with  $\text{H}_2\text{O}$  (100 mL) and acidified with 30% HCl, and the resulting precipitate was filtered, rinsed with  $\text{H}_2\text{O}$ , and dried to afford 3,5-dibromo-4-benzyloxybenzoic acid (**23**) as a white solid (1.69 g, 93%).  $^1\text{H-NMR}$  (500 MHz,  $d_6$ -DMSO)  $\delta$  13.55 (br s, 1H), 8.12 (s, 2H), 7.54-7.58 (m, 2H), 7.37-7.46 (m, 3H), 5.03 (s, 2H);  $^{13}\text{C-NMR}$  (125 MHz,  $d_6$ -DMSO)  $\delta$  164.57, 155.67, 135.70, 133.68, 129.74, 128.57, 128.48, 118.25, 74.52; ESI-MS 407  $m/z$  [MNa] $^+$ ,  $\text{C}_{14}\text{H}_{10}\text{Br}_2\text{NaO}_3$  requires 407; RP-HPLC: 94% pure.

**3,5-Dimethyl-4-benzyloxy-N-phenylbenzamide (24).**

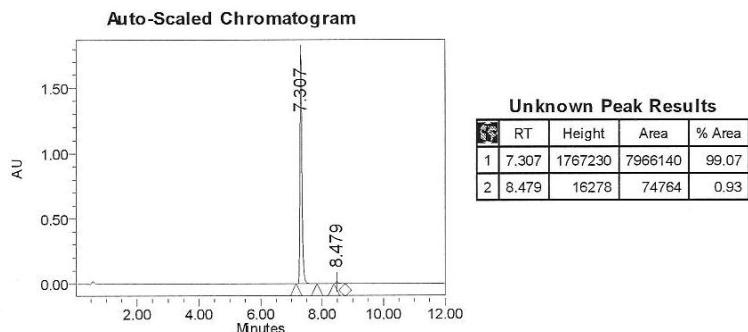
Aniline (82.0  $\mu\text{L}$ , 0.900 mmol), 3,5-dimethyl-4-benzyloxybenzoic acid (192 mg, 0.748 mmol), DCC (184 mg, 0.891 mmol), and DMAP (10.9 mg, 0.089 mmol) were stirred in anhydrous  $\text{CH}_2\text{Cl}_2$  (8.0 mL) under an argon atmosphere. After 18 h, the reaction was concentrated and flash chromatographic purification over silica (9:1-2:1 hexanes:EtOAc gradient elution) afforded 3,5-dimethyl-4-benzyloxy-N-phenylbenzamide (**24**) as an off-white solid (75.7 mg, 31%).  $^1\text{H-NMR}$  (500 MHz,  $d_6$ -DMSO)  $\delta$  10.11 (s, 1H), 7.74-7.79 (m, 2H), 7.67 (s, 2H), 7.48-7.53 (m, 2H), 7.40-7.45 (m, 2H), 7.31-7.39 (m, 3H), 7.08 (tt,  $J=1.1$ , 7.4 Hz, 1H), 4.86 (s, 2H), 2.31 (s, 6H);  $^{13}\text{C-NMR}$  (125 MHz,  $d_6$ -DMSO)  $\delta$  165.22, 158.06, 139.33, 137.28, 130.76, 130.40, 128.58, 128.45, 128.42,

128.12, 128.08, 123.48, 120.24, 73.52, 16.31; ESI-MS 332 *m/z* [MH]<sup>+</sup>, C<sub>22</sub>H<sub>22</sub>NO<sub>2</sub> requires 332; RP-HPLC: >99% pure.

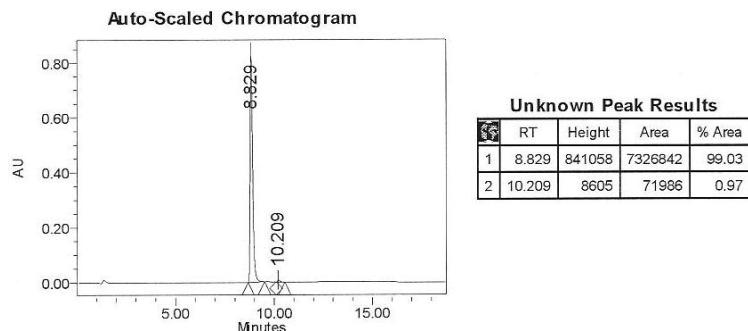
**3,5-Dimethyl-4-hydroxy-N-phenylbenzamide (9c).**

3,5-Dimethyl-4-benzyloxy-N-phenylbenzamide (**24**, 55.2 mg, 0.167 mmol) and 10% Pd/C (20.3 mg, 0.0191 mmol) were stirred in EtOAc (5.0 mL) under a hydrogen atmosphere for 2 h. The atmosphere was then purged with argon and the reaction quenched with DCM, filtered through celite, and concentrated. Flash chromatographic purification over silica (1:1-1:2 hexanes:EtOAc gradient elution) afforded 3,5-dimethyl-4-hydroxy-N-phenylbenzamide (**9c**) as a white solid (38.2 mg, 95%). <sup>1</sup>H-NMR (500 MHz, CD<sub>3</sub>OD) δ 7.63-7.67 (m, 2H), 7.57 (s, 2H), 7.31-7.36 (m, 2H), 7.11 (tt, *J*=1.1, 7.4 Hz, 1H), 2.27 (s, 6H); <sup>13</sup>C-NMR (125 MHz, CD<sub>3</sub>OD) δ 169.08, 158.29, 140.10, 129.70, 129.27, 126.67, 125.34, 125.27, 122.30, 16.74; ESI-TOF 242.1165 *m/z* [MH]<sup>+</sup>, C<sub>15</sub>H<sub>16</sub>NO<sub>2</sub> requires 242.1175; RP-HPLC: 99% & 99% pure.

*Primary RP-HPLC Conditions Chromatographic Trace:*



*Secondary RP-HPLC Conditions Chromatographic Trace:*



**3,5-Dibromo-4-benzyloxy-N-phenylbenzamide (25).**

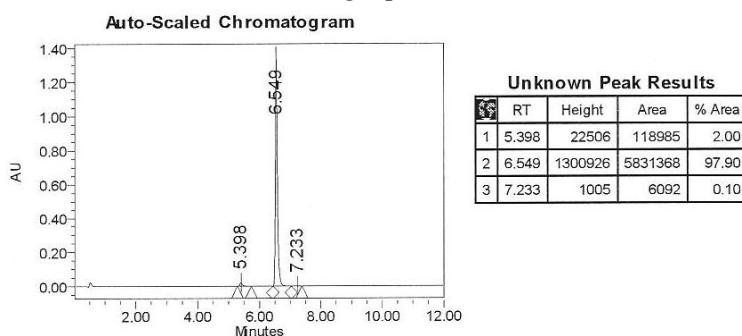
Aniline (79.0  $\mu$ L, 0.867 mmol), 3,5-dibromo-4-benzyloxybenzoic acid (**23**, 278 mg, 0.720 mmol), DCC (179 mg, 0.866 mmol), and DMAP (11.2 mg, 0.092 mmol) were stirred in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (8.0 mL) under an argon atmosphere. After 18 h, the reaction was concentrated and flash chromatographic purification over silica (9:1-2:1 hexanes:EtOAc gradient elution) afforded 3,5-dibromo-4-benzyloxy-N-phenylbenzamide (**25**) as a pale yellow solid (261 mg, 78%). <sup>1</sup>H-NMR (500 MHz, *d*<sub>6</sub>-DMSO) δ 10.36 (s, 1H), 8.27 (s, 2H), 7.73-7.77 (m, 2H), 7.56-7.60 (m, 2H), 7.34-7.47 (m, 5H), 7.12 (tt, *J*=1.1, 7.4 Hz, 1H), 5.05 (s, 2H); <sup>13</sup>C-NMR (125 MHz, *d*<sub>6</sub>-DMSO) δ 162.14, 154.55,

138.72, 135.78, 133.46, 132.29, 128.70, 128.56, 128.48, 124.08, 120.45, 118.07, 74.52; ESI-MS 460  $m/z$  [MH]<sup>+</sup>, C<sub>20</sub>H<sub>16</sub>Br<sub>2</sub>NO<sub>2</sub> requires 460; RP-HPLC: >99% pure.

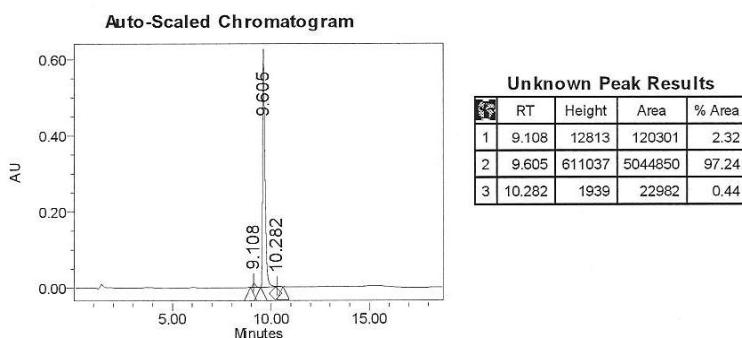
**3,5-Dibromo-4-hydroxy-N-phenylbenzamide (9d).**

3,5-Dibromo-4-benzyloxy-N-phenylbenzamide (**25**, 97.8 mg, 0.212 mmol), ZnBr<sub>2</sub> (49.0 mg, 0.218 mmol), and 10% Pd/C (25.6 mg, 0.0241 mmol) were stirred in EtOAc (5.0 mL) under a hydrogen atmosphere for 1 h. The atmosphere was then purged with argon and the reaction quenched with DCM, filtered through celite, and concentrated. Prep-HPLC purification afforded 3,5-dibromo-4-hydroxy-N-phenylbenzamide (**9d**) as an off-white solid (32.8 mg, 42%). <sup>1</sup>H-NMR (500 MHz, CD<sub>3</sub>OD)  $\delta$  8.12 (s, 2H), 7.63-7.68 (m, 2H), 7.33-7.38 (m, 2H), 7.11-7.16 (m, 1H); <sup>13</sup>C-NMR (125 MHz, CD<sub>3</sub>OD)  $\delta$  165.63, 155.90, 139.68, 133.08, 129.77, 129.29, 125.65, 122.30, 112.03; ESI-TOF 369.9065  $m/z$  [MH]<sup>+</sup>, C<sub>13</sub>H<sub>10</sub>Br<sub>2</sub>NO<sub>2</sub> requires 369.9065; RP-HPLC: 98% & 97% pure.

*Primary RP-HPLC Conditions Chromatographic Trace:*



*Secondary RP-HPLC Conditions Chromatographic Trace:*

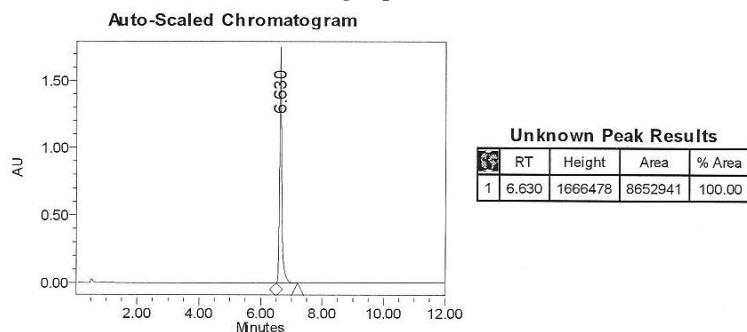


**N-(3,5-Dimethylphenyl)benzamide (10a).**

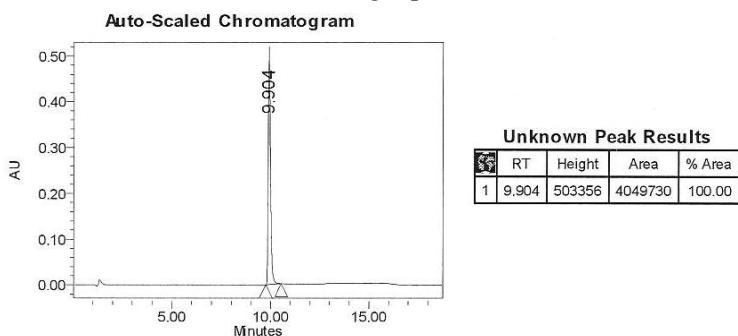
Benzoyl chloride (116 mg, 0.827 mmol), 3,5-dimethylaniline (0.10 mL, 0.800 mmol), and pyridine (67.0  $\mu$ L, 0.822 mmol) were stirred in CH<sub>2</sub>Cl<sub>2</sub> (8.0 mL). After 18 h the reaction was extracted into EtOAc (50 mL) and the organics were washed with 1 N HCl (2x25 mL) and brine (25 mL), then dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. Flash chromatographic purification over silica (2:1 hexanes:EtOAc gradient elution) afforded *N*-(3,5-dimethylphenyl)benzamide (**10a**) as a pale yellow solid (170 mg, 94%). <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.82-7.88 (m, 3H), 7.50-7.56 (m, 1H), 7.43-7.49 (m, 2H), 7.28 (s, 2H), 6.79 (s, 1H), 2.31 (s, 6H); <sup>13</sup>C-NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  165.68, 138.78,

137.75, 135.12, 131.72, 128.74, 126.98, 126.31, 117.96, 21.38; ESI-TOF 226.1227  $m/z$  [MH]<sup>+</sup>, C<sub>15</sub>H<sub>16</sub>NO requires 226.1226; RP-HPLC: >99% & >99% pure.

*Primary RP-HPLC Conditions Chromatographic Trace:*



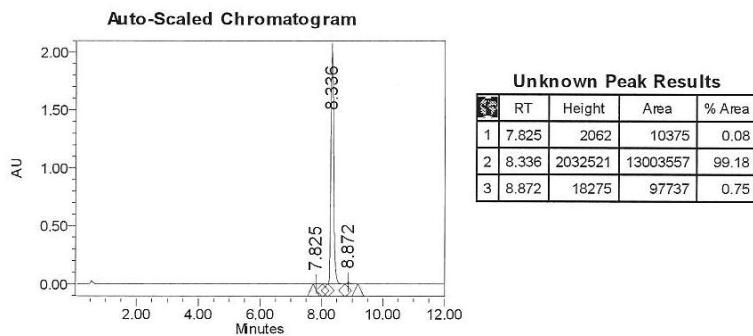
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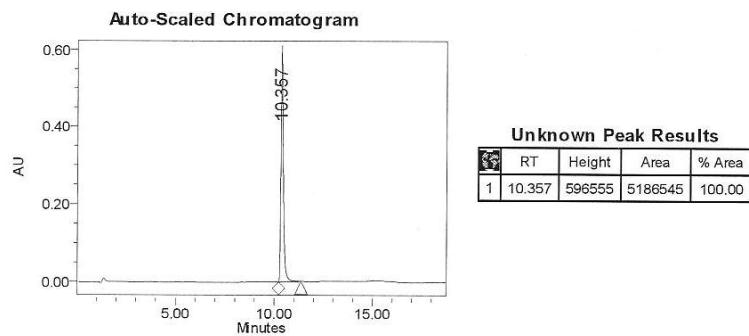
**N-(3,5-Dibromophenyl)benzamide (10b).**

Benzoyl chloride (75.0  $\mu$ L, 0.646 mmol), 3,5-dibromoaniline (**21**, 162 mg, 0.647 mmol), and pyridine (53.0  $\mu$ L, 0.650 mmol) were stirred in CH<sub>2</sub>Cl<sub>2</sub> (6.0 mL). After 18 h, the reaction was extracted into EtOAc (50 mL) and the organics were washed with 1 N HCl (2x25 mL) and brine (25 mL), then dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. Flash chromatographic purification over silica (9:1-4:1 hexanes:EtOAc gradient elution) afforded *N*-(3,5-dibromophenyl)benzamide (**10b**) as a white solid (194 mg, 85%). <sup>1</sup>H-NMR (500 MHz, *d*<sub>6</sub>-DMSO)  $\delta$  10.47 (s, 1H), 8.07 (d, *J*=1.7 Hz, 2H), 7.92-7.96 (m, 2H), 7.61 (tt, *J*=1.3, 6.5 Hz, 1H), 7.52-7.57 (m, 3H); <sup>13</sup>C-NMR (125 MHz, *d*<sub>6</sub>-DMSO)  $\delta$  165.92, 141.86, 134.12, 132.05, 128.50, 128.06, 127.72, 122.20, 121.42; ESI-TOF 353.9109  $m/z$  [MH]<sup>+</sup>, C<sub>13</sub>H<sub>9</sub>Br<sub>2</sub>NO requires 353.9124; RP-HPLC: >99% & >99% pure.

*Primary RP-HPLC Conditions Chromatographic Trace:*



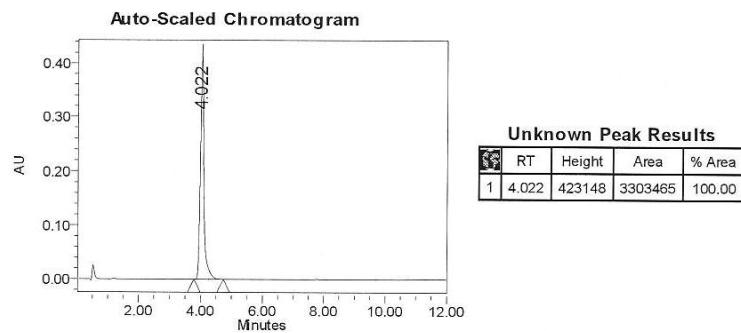
*Secondary RP-HPLC Conditions Chromatographic Trace:*



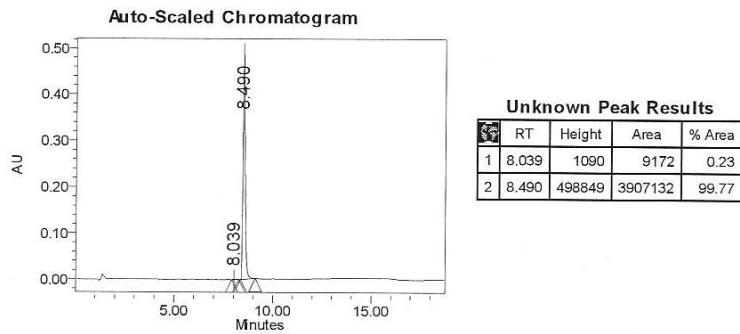
***N-(3,5-Dimethyl-4-hydroxyphenyl)benzamide (10c).***

Benzoyl chloride (115  $\mu$ L, 0.819 mmol), 4-amino-2,6-dimethylphenol (**22**, 112 mg, 0.819 mmol), and pyridine (67.0  $\mu$ L, 0.822 mmol) were stirred in  $\text{CH}_2\text{Cl}_2$  (8.0 mL). After 18 h, the reaction was extracted into EtOAc (50 mL) and the organics were washed with 1 N HCl (2x25 mL) and brine (25 mL), then dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated. Flash chromatographic purification over silica (2:1-1:1 hexanes:EtOAc gradient elution) afforded *N*-(3,5-dimethyl-4-hydroxyphenyl)benzamide (**10c**) as a white solid (187 mg, 95%).  $^1\text{H-NMR}$  (500 MHz,  $d_6$ -DMSO)  $\delta$  8.89 (s, 1H), 8.06 (s, 1H), 7.90-7.95 (m, 2H), 7.55 (tt,  $J=1.3, 6.3$  Hz, 1H), 7.47-7.52 (m, 2H), 7.30 (s, 2H), 2.16 (s, 6H);  $^{13}\text{C-NMR}$  (125 MHz,  $d_6$ -DMSO)  $\delta$  164.86, 149.55, 135.24, 131.25, 130.69, 128.33, 127.50, 124.23, 121.03, 16.86; ESI-TOF 242.1168  $m/z$  [MH] $^+$ ,  $\text{C}_{15}\text{H}_{16}\text{NO}_2$  requires 242.1175; RP-HPLC: >99% & >99% pure.

*Primary RP-HPLC Conditions Chromatographic Trace:*



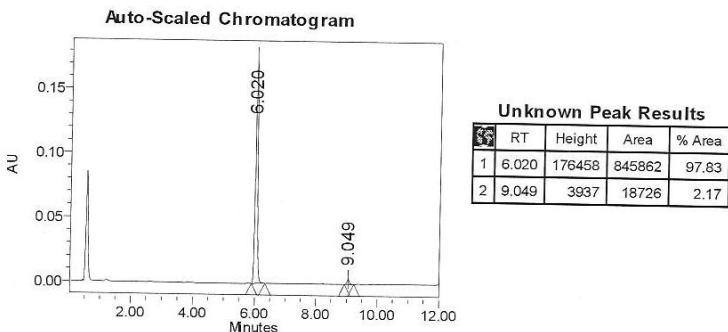
*Secondary RP-HPLC Conditions Chromatographic Trace:*



***N-(3,5-Dibromo-4-hydroxyphenyl)benzamide (10d).***

Benzoyl chloride (24.0  $\mu$ L, 0.207 mmol), 4-amino-2,6-dibromophenol (57.5 mg, 0.205 mmol), and pyridine (17.0  $\mu$ L, 0.208 mmol) were stirred in  $\text{CH}_2\text{Cl}_2$  (3.0 mL). After 18 h, the reaction was extracted into EtOAc (50 mL) and the organics were washed with 1 N HCl (2x25 mL) and brine (25 mL), then dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated. Flash chromatographic purification over silica (4:1-2:1 hexanes:EtOAc gradient elution) afforded *N*-(3,5-dibromo-4-hydroxyphenyl)benzamide (**10d**) as an off-white solid (57.1 mg, 75%).  $^1\text{H-NMR}$  (500 MHz,  $d_6$ -DMSO)  $\delta$  10.25 (s, 1H), 9.74 (s, 1H), 8.02 (s, 2H), 7.90-7.94 (m, 2H), 7.57-7.62 (m, 1H), 7.50-7.55 (m, 2H);  $^{13}\text{C-NMR}$  (125 MHz,  $d_6$ -DMSO)  $\delta$  165.38, 146.88, 134.40, 133.41, 131.80, 128.48, 127.59, 123.87, 111.74; ESI-TOF 369.9063  $m/z$  [MH] $^+$ ,  $\text{C}_{13}\text{H}_{10}\text{Br}_2\text{NO}_2$  requires 369.9073; RP-HPLC: 98% & 98% pure.

*Primary RP-HPLC Conditions Chromatographic Trace:*



*Secondary RP-HPLC Conditions Chromatographic Trace:*

