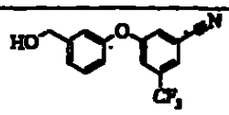
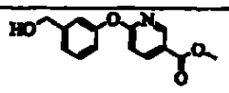
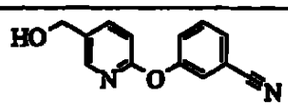
Prep. No.	Chemical name	Structure	Physical data
			(d, J = 8.5 Hz, 2H), 7.13 (dd, J = 5.0 Hz, 7.5 Hz, 1H), 4.77 (s, 2H).
7	3-(3-Hydroxymethyl-phenoxy)-5-trifluoromethyl-benzonitrile		^{1}H NMR ($CDCl_3$) 7.63 (s, 1H), 7.50-7.44 (m, 2H), 7.37 (s, 1H), 7.32-7.27 (m, 1H), 7.14 (s, 1H), 7.01 (dd, J = 2.1 Hz, 8.1 Hz, 1H), 4.78 (s, 2H).
8	2-(3-hydroxymethylphenoxy)-nicotinic acid methyl ester		^{1}H NMR ($CDCl_3$) 8.85 (d, J = 2.1 Hz, 1H), 8.31 (dd, J = 2.1 Hz, 8.7 Hz, 1H), 7.46 (t, J = 7.9 Hz, 1H), 7.31-7.27 (m, 1H), 7.22 (s, 1H), 7.11 (d, J = 7.9 Hz, 1H), 6.98 (d, J = 8.7 Hz, 1H), 4.77 (s, 2H), 3.95 (s, 3H).
9	3-(5-Hydroxymethyl-pyridin-2-yloxy)-benzonitrile		^{1}H NMR ($CDCl_3$) 8.17 (s, 1H), 7.83 (dd, J = 2.0 Hz, 8.6 Hz, 1H), 7.54-7.49 (m, 2H), 7.47 (s, 1H), 7.44-7.40 (m, 1H), 7.03 (d, J = 8.6 Hz, 1H), 4.72 (s, 2H).

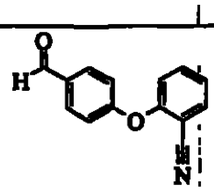
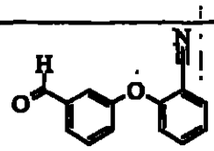
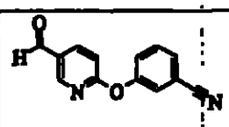
Preparation 10

Synthesis of 3-(4-formyl-phenoxy)-benzonitrile.

The title compound is prepared essentially as described in Preparation 1 substituting 4-fluorobenzaldehyde (0.85 mL, 8.06 mmol) for 3-hydroxybenzyl alcohol and 3-hydroxybenzonitrile (1.06 g, 8.86 mmol) for 6-chloronicotinitrile. Yield (0.90 g,

50%); ^{1}H NMR ($CDCl_3$) 10.01 (s, 1H), 7.95 (d, J = 8.5 Hz, 2H), 7.58-7.52 (m, 2H), 7.39-7.34 (m, 2H), 7.14 (d, J = 8.5 Hz, 2H).

The following compounds are prepared essentially as described in Preparation 10.

Prep. No.	Chemical name	Structure	Physical data
11	2-(4-Formyl-phenoxy)-benzonitrile		^{1}H NMR ($CDCl_3$) 10.01 (s, 1H), 7.96 (d, J = 8.4 Hz, 2H), 7.76 (d, J = 7.7 Hz, 1H), 7.70-7.61 (m, 2H), 7.20 (d, J = 8.4 Hz, 2H), 7.10 (d, J = 8.4 Hz, 1H).
12	2-(3-Formyl-phenoxy)-benzonitrile		^{1}H NMR ($CDCl_3$) 10.03 (s, 1H), 7.75 (t, J = 7.7 Hz, 2H), 7.63 (t, J = 8.0 Hz, 1H), 7.60-7.55 (m, 2H), 7.42 (d, J = 8.2 Hz, 1H), 7.26 (t, J = 7.7 Hz, 1H), 6.98 (d, J = 8.5 Hz, 1H).
13	3-(5-Formyl-pyridin-2-yloxy)-benzonitrile		^{1}H NMR ($CDCl_3$) 10.05 (s, 1H), 8.64 (d, J = 1.8 Hz, 1H), 8.29 (dd, J = 2.2 Hz, 8.6 Hz, 1H); 7.61-7.54 (m, 2H), 7.50-7.46 (m, 2H), 7.17 (d, J = 8.6 Hz, 1H).

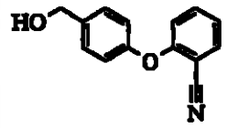
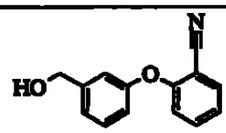
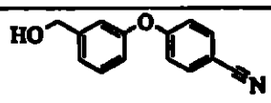
Preparation 14

Synthesis of 3-(4-hydroxymethyl-phenoxy)-benzonitrile.

Dissolve 3-(4-formyl-phenoxy)-benzonitrile of Preparation 10 (0.90 g, 4.04 mmol) in methanol (15 mL) and cool to 0 °C. Add sodium borohydride (0.31 g, 8.08 mmol) in three batches. After 1 hr, allow to warm to ambient temperature and stir overnight. Concentrate under reduced pressure to give a residue. Dilute with ethyl

acetate (50 mL) and wash with 1N hydrochloric acid (3 x 100 mL). Separate layers and dry the organic layer over magnesium sulfate, filter, and concentrate to a residue. Purification by flash chromatography, using 10% ethyl acetate/hexanes to 50% ethyl acetate/hexanes as a gradient eluent gives the title product (0.83 g, 91%): ^{1}H NMR ($CDCl_3$) 7.48-7.38 (m, 4H), 7.30-7.23 (m, 2H), 7.06 (d, J = 8.4 Hz, 2H), 4.75 (s, 2H).

The following compounds are prepared estentially as described in Preparation 14.

Prep. No.	Chemical name	Structure	Physical data
15	2-(4-Hydroxymethyl-phenoxy)-benzonitrile		^{1}H NMR ($CDCl_3$) 7.69 (d, J = 7.8 Hz, 1H), 7.50 (t, J = 8.2 Hz, 1H), 7.44 (d, J = 8.6 Hz, 2H), 7.17 (t, J = 7.6 Hz, 1H), 7.11 (d, J = 8.4 Hz, 2H), 6.89 (d, J = 8.4 Hz, 1H), 4.75 (s, 2H).
16	2-(3-Hydroxymethyl-phenoxy)-benzonitrile		^{1}H NMR ($CDCl_3$) 7.70 (d, J = 8.0 Hz, 1H), 7.51 (t, J = 8.0 Hz, 1H), 7.42 (t, J = 7.8 Hz, 1H), 7.24 (d, J = 7.6 Hz, 1H), 7.20-7.13 (m, 2H), 7.04 (d, J = 8.0 Hz, 1H), 6.92 (d, J = 8.6 Hz, 1H), 4.75 (s, 2H).
17	4-(3-Hydroxymethyl-phenoxy)-benzonitrile		^{1}H NMR ($CDCl_3$) 7.64 (d, J = 8.8 Hz, 2H), 7.44 (t, J = 7.8 Hz, 1H), 7.26 (t, J = 7.8 Hz, 1H), 7.13 (s, 1H), 7.06-7.01 (m, 3H), 4.76 (s, 2H).

General Method 1

General procedure for the preparation of regioisomers of (hydroxymethyl-phenylsulfanyl)-benzonitrile.

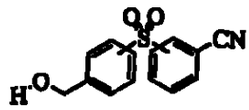
Add 2,2,6,6-tetramethyl-heptane-3,5-dione (0.250 mmol) to a solution of copper (I) chloride (0.500 mmol) in *N*-methylpyrrolidinone (0.300 *M*). Add cesium carbonate (2.00 mmol), the appropriate iodobenzonitrile (1.00 mmol), then the appropriate hydroxymethylthiophenol (2.00 mmol) and stir for 6 hours at 130 °C. Dilute with ethyl acetate and wash with water. Dry and concentrate organic layer. Purify the residue by flash chromatography, eluting with hexanes, ramping to 50% ethyl acetate/hexanes to provide the title compound listed below.

Prep. No.	Chemical Name	Physical Data
18	3-(4-Hydroxymethyl-phenylsulfanyl)-benzonitrile	MS (m/z): 242 (M+1).
19	3-(2-Hydroxymethyl-phenylsulfanyl)-benzonitrile	^{1}H NMR (400 MHz, $CDCl_3$) δ 4.77 (s, 2H), 7.34 (m, 4H), 7.45 (m, 1H), 7.49 (m, 2H), 7.60 (m, 1H)
20	4-(3-Hydroxymethyl-phenylsulfanyl)-benzonitrile	^{1}H NMR (400 MHz, $CDCl_3$) δ 4.72 (s, 2H), 7.18 (d, *J* = 9.0 Hz, 2H), 7.42 (s, 3H), 7.48 (d, *J* = 9.0 Hz, 2H), 7.53 (s, 1H)
21	4-(2-Hydroxymethyl-phenylsulfanyl)-benzonitrile	^{1}H NMR (400 MHz, $CDCl_3$) δ 4.76 (s, 2H), 7.06 (d, J = 7.6 Hz, 2H), 7.38 (t, *J* = 11.3 Hz, 1H), 7.46 (d, *J* = 8.6 Hz, 2H), 7.51 (m, 2H), 7.64 (d, *J* = 7.0 Hz, 1H)
22	2-(4-Hydroxymethyl-phenylsulfanyl)-benzonitrile	^{1}H NMR (400 MHz, $CDCl_3$) δ 4.73 (s, 2H), 7.13 (d, *J* = 8.6 Hz, 1H), 7.26 (m, 2H), 7.40 (d, *J* = 8.6 Hz, 2H), 7.47 (d, *J* = 6.2 Hz, 2H), 7.63 (d, *J* = 9.0 Hz, 1H).
23	2-(3-Hydroxymethyl-phenylsulfanyl)-benzonitrile	^{1}H NMR (400 MHz, $CDCl_3$) δ 4.69 (s, 2H), 7.18 (d, *J* = 8.2 Hz, 1H), 7.27 (m, 1H), 7.38 (s, 3H), 7.41 (m, 1H), 7.48 (s, 1H), 7.64 (d, *J* = 9.4 Hz,

Prep. No.	Chemical Name	Physical Data
		1H).
24	4-(4-Hydroxymethyl-phenylsulfanyl)-benzonitrile	MS (m/z): 242 (M+1).
25	3-(4-Hydroxymethyl-phenylsulfanyl)-benzonitrile	MS (m/z): 242 (M+1).
26	3-(3-Hydroxymethyl-phenylsulfanyl)-benzoic acid ethyl ester	MS (m/z): 289 (M+1).
27	3-(4-Hydroxymethyl-phenylsulfanyl)-benzoic acid ethyl ester	MS (m/z): 289 (M+1).
28	4-(4-Hydroxymethyl-phenylsulfanyl)-benzoic acid ethyl ester	MS (m/z): 275 (M+1).

General Method 2

General procedure for the preparation of regioisomers of (hydroxymethyl-benzenesulfonyl)-benzonitriles.

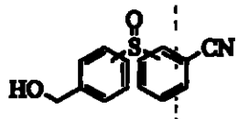


Add potassium peroxymonosulfate (1.00 g, 1.66 mmol) in water (0.5M) at room temperature to a solution of the appropriate hydroxymethylbenzenesulfanylbenzonitrile (0.829 mmol) in methanol (0.2M) at 0°C. Stir overnight and allow solution to warm to room temperature. Dilute with dichloromethane and 2N hydrochloric acid. Collect organic layer and extract aqueous layer with dichloromethane (3x). Dry organic layers with sodium sulfate and evaporate to dryness to afford the title compound listed below.

Prep. No.	Chemical Name	Physical Data
29	2-(3-Hydroxymethyl-benzenesulfonyl)-benzonitrile	MS (m/z): 274 (M+1).
30	3-(3-Hydroxymethyl-benzenesulfonyl)-benzonitrile	MS (m/z): 274 (M+1).
31	4-(4-Hydroxymethyl-benzenesulfonyl)-benzonitrile	MS (m/z): 274 (M+1).
32	3-(4-Hydroxymethyl-benzenesulfonyl)-benzonitrile	MS (m/z): 274 (M+1).
33	4-(3-Hydroxymethyl-benzenesulfonyl)-benzonitrile	MS (m/z): 274 (M+1).
34	3-(3-Hydroxymethyl-benzenesulfonyl)-benzoic acid ethyl ester	MS (m/z): 321 (M+1).
35	3-(4-Hydroxymethyl-benzenesulfonyl)-benzoic acid ethyl ester	MS (m/z): 321 (M+1).
36	4-(4-Hydroxymethyl-benzenesulfonyl)-benzoic acid methyl ester	MS (m/z): 307 (M+1).

General Method 3

General procedure for the preparation of regioisomers of (hydroxymethyl-benzenesulfinyl)-benzonitrile.



Add potassium peroxymonosulfate (1.00 g, 0.829) in water (0.5M) at 0 °C to a solution of the appropriate hydroxymethylbenzenesulfanylbenzonitrile (0.829 mmol) in methanol (0.2M) at 0°C over 1 min. Quench reaction after 10 min with sodium bisulfite (sat). Dilute the mixture with 2N hydrochloric acid and extract with ethyl acetate (3x). Dry the organic layers with sodium sulfate and concentrate to dryness. Purify the resulting residue by flash chromatography, eluting with hexanes to 50% ethyl acetate/hexanes to provide the title compound listed below.

Prep. No.	Chemical Name	Physical Data
37	3-(2-Hydroxymethyl-benzenesulfinyl)-benzonitrile	MS (m/z): 258 (M+1).
38	2-(3-Hydroxymethyl-benzenesulfinyl)-benzonitrile	MS (m/z): 258 (M+1).
39	4-(4-Hydroxymethyl-benzenesulfinyl)-benzonitrile	MS (m/z): 258 (M+1).
40	3-(4-Hydroxymethyl-benzenesulfinyl)-benzonitrile	MS (m/z): 258 (M+1).
41	3-(3-Hydroxymethyl-benzenesulfinyl)-benzonitrile	MS (m/z): 258 (M+1).

Preparation 42

Synthesis of 6-[3-(4-acetyl-3-hydroxy-2-propyl-phenoxymethyl)-phenoxy]-nicotinonitrile.

Mix 6-(3-hydroxymethyl-phenoxy)-nicotinonitrile (1.63 g, 7.18 mmol) and 1-(2,4-dihydroxy-3-propyl-phenyl)-ethanone (1.33 g, 6.84 mmol) in 2:1 toluene/dichloromethane (24 mL). Cool to –20 °C and add tributylphosphine (2.6 mL, 10.26 mmol) dropwise. After stirring for 5 minutes, add 1,1'-(azodicarbonyl)dipiperidine in three batches. Allow the reaction mixture to warm to ambient temperature overnight. Concentrate under reduced pressure to give a yellow solid. Dilute with diethyl ether (50 mL) and cool to 0 °C. Filter the white precipitate and concentrate the filtrate under reduced pressure to give a residue. Purification by flash chromatography, using 5% ethyl acetate/hexanes to 30% ethyl acetate/hexanes as a gradient eluent yields the title compound (0.91 g, 33%): MS (m/z): 401.2 (M-1). ^{1}H NMR ($CDCl_3$) 12.78 (s, 1H), 8.50 (s, 1H), 7.97 (dd, J = 2.2 Hz, 8.8 Hz, 1H), 7.62 (d, J = 8.8 Hz, 1H), 7.51 (t, J = 8.0 Hz, 1H), 7.36 (d, J = 7.8 Hz, 1H), 7.25 (s, 1H), 7.16 (d, J = 8.0 Hz, 1H), 7.09 (d, J = 8.8 Hz, 1H), 6.51 (d, J = 8.8 Hz, 1H), 5.22 (s, 2H), 2.72 (t, J = 7.6 Hz, 2H), 2.60 (s, 3H), 1.62-1.53 (m, 2H), 0.94 (t, J = 7.6 Hz, 3H).

Preparation 43

Synthesis of 2-[3-(3-hydroxy-2-methyl-4-propionyl-phenoxymethyl)-phenoxy]-isonicotinonitrile.

Mix polymer-supported triphenylphosphine (2.33 mmol/g load capacity, 0.85 g, 1.99 mmol), imidazole (0.14 g, 1.99 mmol) and iodine (0.51 g, 1.99 mmol) in dichloromethane (8 mL) in a vial (0.75 oz). Seal and shake for 10 minutes. Add a solution of 2-(3-hydroxymethyl-phenoxy)-isonicotinonitrile (0.30 g, 1.33 mmol) in dichloromethane (3 mL) and shake for 2 hrs. Filter the resin and wash with dichloromethane (50 mL). Concentrate the filtrate under reduced pressure to give a residue. Dissolve the residue in ethyl acetate (25 mL), wash with saturated sodium thiosulfate solution (2 x 25 mL) and dry over sodium sulfate. Filter and concentrate to give 2-(3-iodomethyl-phenoxy)-isonicotinonitrile as a yellow solid (0.25 g, 53%). Mix the yellow solid (0.25 g, 0.70 mmol), 1-(2,4-dihydroxy-3-methyl-phenyl)-propan-1-one (0.14 g, 0.77 mmol) and cesium carbonate (0.25 g, 0.77 mmol) in acetone (7 mL). Heat to 50 °C for 2.5 hrs. Allow the reaction to cool to ambient temperature and concentrate under reduced pressure to give a solid. Dilute with ethyl acetate (25 mL) and filter. Concentrate the filtrate under reduced pressure to give an oil. Triturate with methanol (50 mL) and filter to give a solid. Purification by flash chromatography using 5% ethyl acetate/hexanes to 20% ethyl acetate/hexanes as gradient eluent yields the title compound (0.16 g, 60%): MS (m/z): 387.2 (M-1). ^{1}H NMR ($CDCl_3$) 12.91 (s, 1H), 8.34 (d, J = 5.1 Hz, 1H), 7.65 (d, J = 9.0 Hz, 1H), 7.50 (t, J = 8.0 Hz, 1H), 7.36 (d, J = 7.8 Hz, 1H), 7.31-7.24 (m, 2H), 7.21 (s, 1H), 7.15 (d, J = 8.0 Hz, 1H), 6.51 (d, J = 9.0 Hz, 1H), 5.23 (s, 2H), 3.00 (q, J = 7.5 Hz, 2H), 2.19 (s, 3H), 1.26 (t, J = 7.5 Hz, 3H).

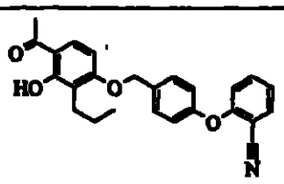
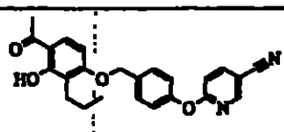
Preparation 44

Synthesis of 3-[4-(4-acetyl-3-hydroxy-2-trifluoromethyl-phenoxymethyl)-phenoxy]-benzonitrile.

3-(4-Iodomethyl-phenoxy)-benzonitrile is prepared by an analogous procedure described in Preparation 43. Add half of a solution of 3-(4-iodomethyl-phenoxy)-benzonitrile (470 mg, 1.4 mmol) in anhydrous dimethylformamide (10 mL) to 1-(2,4-dihydroxy-3-trifluoromethyl-phenyl)-ethanone (300 mg, 1.4 mmol) and Li_2CO_3 (228 mg, 3.1 mmol) in anhydrous dimethylformamide (18 mL)dimethylformamide. Heat the reaction mixture to 60 °C and stir for 1 h. Add the other half of the 3-(4-iodomethyl-phenoxy)-benzonitrile solution to the reaction mixture. Stirred at 60 °C for an additional 1h, cool to room temperature, and quench with water (75 mL). Extract the aqueous

mixture with ethyl acetate (3 x 75 mL). Combine the organic layers, wash with brine, dry over sodium sulfatesodium sulfate, and concentrate. Purify the residue by flash column chromatography using 50% ethyl acetate/hexane as the eluent to give the title compound (302 mg, 50%). LC-MS (m/e): 426 (M-1)

The following compounds are prepared esentially as described for Preparation 42, 43 or 44. The corresponding method is designated in the table below.

Prep. No.	Method	Chemical name	Structure	Physical data
45	Method of Preparation 42	2-[4-(4-Acetyl-3-hydroxy-2-propyl-phenoxymethyl)-phenoxy]-benzonitrile		MS (m/z): 400.2 (M-1). ^{1}H NMR ($CDCl_3$) 12.79 (s, 1H), 7.71 (d, J = 8.0 Hz, 1H), 7.63 (d, J = 8.8 Hz, 1H), 7.53 (t, J = 8.0 Hz, 1H), 7.48 (d, J = 8.2 Hz, 2H), 7.19 (t, J = 7.6 Hz, 1H), 7.15 (d, J = 8.2 Hz, 2H), 6.95 (d, J = 8.5 Hz, 1H), 6.53 (d, J = 8.8 Hz, 1H), 5.19 (s, 2H), 2.74 (t, J = 7.5 Hz, 2H), 2.61 (s, 3H), 1.66-1.56 (m, 2H), 0.99 (t, J = 7.5 Hz, 3H).
46	Method of Preparation 42	6-[4-(4-Acetyl-3-hydroxy-2-propyl-phenoxymethyl)-phenoxy]-nicotinonitrile		MS (m/z): 401.2 (M-1). ^{1}H NMR ($CDCl_3$) 12.79 (s, 1H), 8.51 (s, 1H), 7.97 (dd, J = 2.2 Hz, 8.8 Hz, 1H), 7.64 (d, J = 9.1 Hz, 1H), 7.53 (d, J = 8.4 Hz, 2H), 7.22 (d, J = 8.4 Hz, 2H), 7.09 (d, J = 8.8 Hz, 1H), 6.55 (d, J = 9.1 Hz, 1H), 5.22 (s, 2H), 2.74 (t, J = 7.4 Hz, 2H), 2.61 (s, 3H), 1.67-1.57 (m, 2H), 0.99 (t, J = 7.4 Hz, 3H).