Preparation of Fluorinated Phenoxathiin Dioxide Monoamine Oxidase-A Inhibitors: Intramolecular Radical Substitution at Sulfur *versus* the Mauthner Synthesis

Eric E. Boros*, William R. Hall, Morton Harfenist, James L. Kelley,§
Mark D. Reeves and Virgil L. Styles

Division of Chemistry, Glaxo Wellcome, Five Moore Drive, Research Triangle Park, NC 27709
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Five unique fluorinated analogs, **8a-c** and **15a,b,** of the monoamine oxidase-A inhibitor 3-isopropoxyphenoxathiin 10,10-dioxide (**II**) were prepared *via* oxidation of the corresponding phenoxathiins **7** and **14**. 3-Fluoro-7-isopropoxy- **7a**, 2-fluoro-3-isopropoxy- **7b**, and 2,7-difluoro-3-isopropoxyphenoxathiin (**7c**) were prepared by a modification of the Mauthner synthesis which involved cyclization of the corresponding 2-hydroxy-4-isopropoxythiophenols **4** with the appropriate 2-halonitrobenzenes **5** in the presence of potassium *tert*-butoxide. Preparation of 2,8-difluoro-3-isopropoxyphenoxathiin (**14b**) from **4b** and 2,4-difluoronitrobenzene (**5c**) employing similar methods failed, leading instead to a novel macrocycle **9**. Attempts to obtain 2-fluoro-7-isopropoxyphenoxathiin (**14a**) and the 2,8-difluoro analog **14b** *via* trifluoroacetic acid deprotection of intermediate thio-protected 2-nitrophenyl 2-thiophenyl ethers **11a** and **c** followed by cyclization of the resulting thiols were also unsuccessful. Deprotection of **11a** with trifluoroacetic acid produced only complex product mixtures, while similar deprotection of **11c** and treatment of the resulting crude product with potassium *tert*-butoxide in refluxing dimethylformamide produced the 2,7-difluorophenoxathiin analog **7c**, a result consistent with a Smiles rearrangement of the intermediate thiol **12** prior to ring closure. The phenoxathiins **14** were ultimately prepared by a modification of a relatively unexploited phenoxathiin synthesis involving the intramolecular radical substitution at sulfur of 2-aminophenyl 2-thiophenyl ethers **13** containing *para*-methoxybenzyl and methoxymethylthio-protecting groups.

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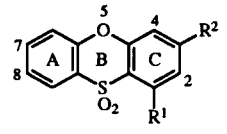
Introduction.

A number of 1-substituted phenoxathiin 10,10-dioxides prepared in these laboratories by Harfenist *et al.* have exhibited potent and selective inhibition of monoamine oxidase-A and represent an unusual class of non-nitrogen containing monoamine oxidase-A inhibitors. 1-Ethyl phenoxathiin 10,10-dioxide (**I**) subsequently emerged as a potent and selective monoamine oxidase-A inhibitor with potential as an antidepressant agent [1]. More recently, 3-isopropoxyphenoxathiin 10,10-dioxide (**II**) was also found to be a potent and selective monoamine oxidase-A inhibitor and analogs of **II** with enhanced lipophilicity and lowered susceptibility to metabolic oxidation were of interest. Consequently, the preparation of ring fluorinated and side chain fluorinated analogs of **II** was proposed with the goal of retaining or enhancing potent and selective monoamine oxidase-A inhibition [2]. Herein are described the syntheses of five novel ring fluorinated analogs of **II, 8a-c** and **15a,b**.

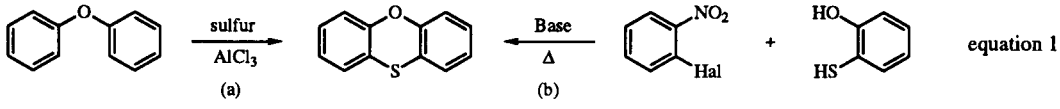
The two classical methods employed in phenoxathiin synthesis involve sulfurization of diaryl ethers in the presence of aluminum chloride, as originally reported by Ferrario [3] (equation 1a), and the cyclization of 2-hydroxythiophenols with 2-halonitrobenzenes, which was first described by Mauthner (equation 1b) [4,5]. The latter method appeared most favorable with regard to regioselective synthesis [6]. Therefore, we pursued the preparation of ring fluorinated analogs of **II** by initially exploring the commercial and synthetic availability of appropriately substituted 2-hydroxythiophenols and 2-halonitrobenzenes.



I: R^1 = Et; R^2 = H
II: R^1 = H; R^2 = OiPr

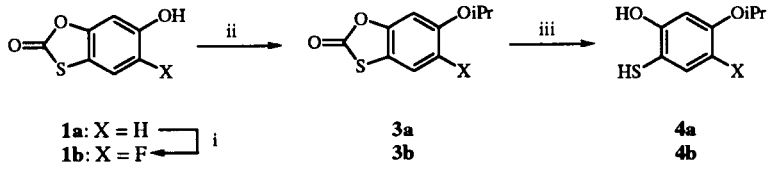
Results and Discussion.

We first considered synthetic pathways to analogs of **II** with fluorine attached to the electron-rich isopropoxy-containing C ring. Commercially available 6-hydroxy-1,3-benzoxathiol-2-one (**1a**) was identified as an ideal



equation 1

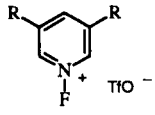
Scheme 1



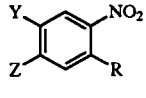
(i) **2b**, DCE, Δ; (ii) 2-iodopropane, *t*-BuOK, dimethylformamide; (iii) KOH, H_2O, MeOH

starting material for synthesis of 3-alkoxy-substituted-phenoxathiins, because it contained the correctly positioned hydroxyl free for isopropylation along with the required and appropriately masked 2-hydroxythiophenol regiochemistry. Accordingly, methods for the direct fluorination of **1a** were investigated.

Syntheses of the 2-hydroxythiophenol precursors **4** are illustrated in Scheme 1. Electrophilic fluorination of **1a** employing 1-fluoropyridinium triflates **2** [7] appeared promising in view of the electron-rich nature of the substrate and the procedural ease involved with these fluorinating reagents. However, we felt that application of this methodology could be problematic owing to the oxidative instability of the divalent sulfur in **1a**. Nevertheless, the reaction of **1a** with 1-fluoropyridinium triflate (**2a**) was examined. Unfortunately, no significant reaction resulted from stirring a mixture of **1a** with an excess of **2a** in dichloromethane at room temperature for several days. On the other hand, the more reactive 1-fluoro-3,5-dichloropyridinium triflate (**2b**) did effect partial conversion of **1a** to its 5-fluoro derivative **1b** at room temperature. Performing the same reaction in 1,2-dichloroethane at reflux increased the conversion, but the reaction was accompanied by significant tar formation and ultimately provided **1b** [8] in 28% isolated yield following flash chromatography.



2a: R = H
2b: R = Cl



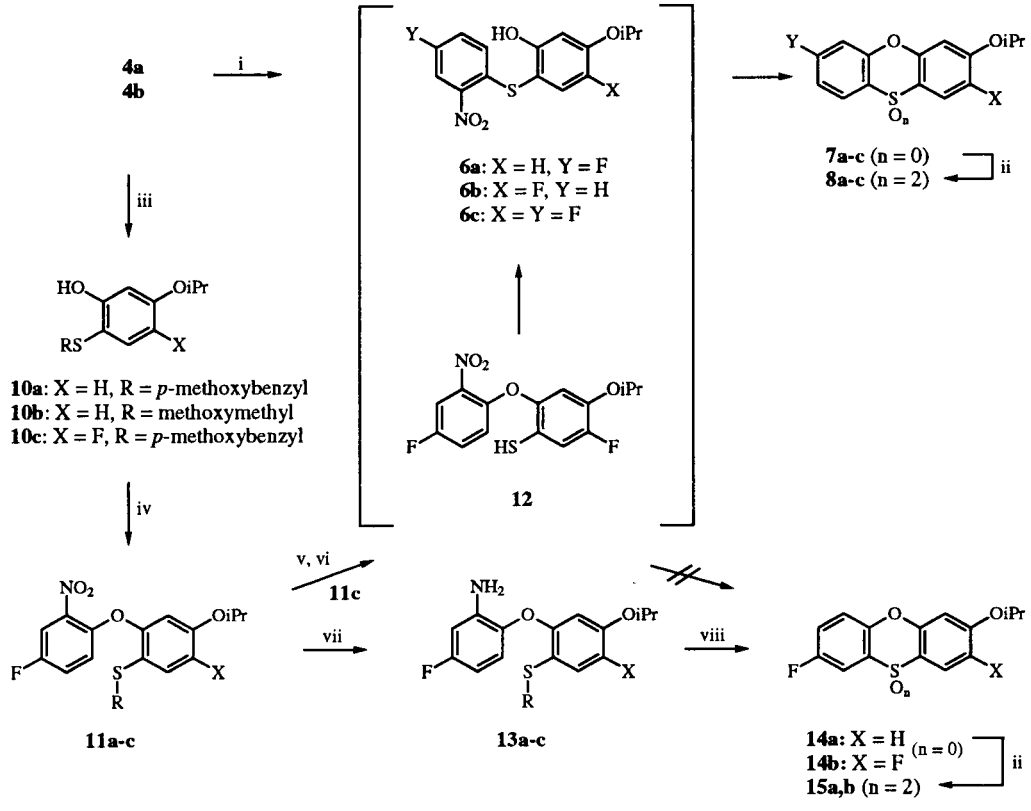
5a: R = Br, Y, Z = H
5b: R, Y = F, Z = H
5c: R, Z = F, Y = H

The phenols **1** were converted to the corresponding isopropyl ethers **3**, in 67-88% isolated yields, with 2-iodopropane and potassium carbonate in dimethylformamide [9]. Basic hydrolyses of **3** followed by acidification provided the necessary 2-hydroxythiophenols **4** in good yields. These compounds were used immediately without purification. In some instances, disulfide formation during hydrolyses of **3** occurred most noticeably during milligram-scale operations; thus, standard degassing precautions were typically employed. Any unwanted disulfide could be converted back to **4** by treatment with sodium borohydride in methanol.

With the necessary 2-hydroxythiophenols **4** in hand, we focused on their cyclizations with activated aromatics to generate phenoxathiins. The commercially available 2-bromonitrobenzene (**5a**), 2,5-difluoronitrobenzene (**5b**), and 2,4-difluoronitrobenzene (**5c**) were examined as electrophiles for phenoxathiin synthesis. We felt that these 2-halonitrobenzenes in combination with **4a** and **b** would provide the desired phenoxathiins **7a-c** and **14a,b**.

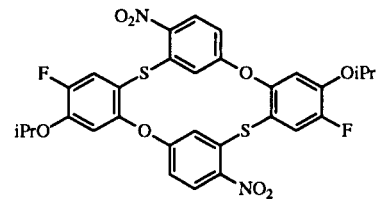
Reactions of **4** with **5** were performed in dimethylformamide in the presence of potassium *tert*-butoxide, using methods similar to those described by Martin *et al.* [5] and were monitored by high performance liquid chromatography [10]. The dianions of **4** react exclusively and rapidly at the thiolate position, displacing the halogen atom *ortho* to the nitro groups in **5** to generate the intermediate phenoxides of **6**, which were not isolated but were cyclized at reflux temperature (Scheme 2). The phenoxide of **6b**, obtained from **4b** and **5a**, cyclized to the 2-fluoro-3-isopropoxyphenoxathiin (**7b**) over a *ca.* 18-hour period at reflux ($t_{1/2}$ *ca.* 1 hour) and was isolated in 39% overall yield following flash chromatography. In contrast, cyclizations of the phenoxides of **6a**, obtained from **4a** and **5b**, and **6c**, obtained from **4b** and **5b**, to the phenoxathiins **7a** and **c**, respectively, were complete within 0.5 hour at reflux, which reflect the anticipated activation by the fluorine atom *meta* to the nitro group in the intermediates **6a** and **c**. The phenoxathiins **7a** and **c** were isolated in 41-45% yields following flash chromatography. Oxidations of **7** with hydrogen peroxide in trifluoroacetic acid produced the corresponding sulfone targets **8a-c** in 72-89% yields. The protons *ortho* to sulfur in the phenoxathiins are shifted *ca.* +0.9 ppm downfield in the ^1H nmr following oxidation to the 10,10-dioxides. This deshielding by the sulfone moiety in conjunction with the noticeable *ortho* and *meta* ^1H-^{19}F coupling constants provided useful probes for confirming the structural assignments of the monoamine oxidase-A inhibitor targets.

Scheme 2



Key:
(i) **5a** or **b**, *t*-BuOK, dimethylformamide, Δ; (ii) H_2O_2, trifluoroacetic acid; (iii) *p*-methoxybenzyl chloride or bromomethyl methyl ether, *t*-BuOK, dimethylformamide; (iv) **5b**, NaH, 18-crown-6, diglyme, Δ; (v) trifluoroacetic acid, Δ; (vi) *t*-BuOK, dimethylformamide, Δ: (vii) Zn°, HOAc, H_2O, MeOH, tetrahydrofuran; (viii) *i*-amyl nitrite, EtOAc, Δ.

Considerably more challenging were the preparation of analogs of **II** with fluorine incorporated in the A ring *para* to the phenoxathiin oxygen. Syntheses of phenoxathiins **14** employing 2,4-difluoronitrobenzene (**5c**) were considered potentially troublesome, because positions *ortho* and *para* to the nitro group of **5c** are susceptible to substitution by nucleophiles. Stirring an equimolar mixture of **4b** and **5c** in dimethylformamide in the presence of one equivalent of potassium *tert*-butoxide at 0° produced an intermediate [11], which, upon addition of a second equivalent of potassium *tert*-butoxide, underwent no detectable cyclization after 1 day at room temperature. However, when the reaction mixture was slowly heated to reflux, rapid cyclodimerization occurred to give predominantly the macrocycle **9** [12]. The crude product mixture contained less than 3% of any phenoxathiin product, as determined by high performance liquid chromatography. Based on this result, we considered alternative methods of phenoxathiin synthesis for the preparation of **14a** and **b**.



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Successful syntheses of **14** and the corresponding sulfones **15** were accomplished by methods also shown in Scheme 2. Our approach was to first establish the requisite *p*-fluorophenoxy regiochemistry exhibited in these phenoxathiins and then effect intramolecular carbon-sulfur bond formation. Selective protection of the thiol functionalities in **4** was achieved cleanly, in 76-98% yields, with *p*-methoxybenzyl chloride or bromomethyl methyl ether in dimethylformamide employing potassium *tert*-butoxide as the base. Reaction of the resulting thiol-protected 2-hydroxythiophenols **10** with **5b** and sodium hydride in the presence of 18-crown-6 provided the necessary diaryl ethers **11** in 60-72% yields.

With the *p*-fluorophenoxy regiochemistry in **11** temporarily secured, we turned our attention to intramolecular carbon-sulfur bond formation at the nitro-bearing carbon. A simple deprotection-cyclization protocol with

11c was examined. This approach also served as a probe for a Smiles rearrangement [13] of the intermediate thiol **12**. Accordingly, **11c** was deprotected in refluxing trifluoroacetic acid. When the crude thiol intermediate **12** was treated with potassium *tert*-butoxide in dimethylformamide at room temperature, a compound of similar retention time, but with an ultraviolet spectrum characteristic of the phenol intermediates **6**, was observed [14]. When the reaction mixture was heated to reflux, phenoxathiin formation ensued; however, the product was not the desired 2,8-difluorophenoxathiin analog **14b** but was found to be the 2,7-difluoro analog **7c**, a result consistent with a Smiles rearrangement of the intermediate thiolate of **12** to the phenoxide of **6c** followed by ring closure.

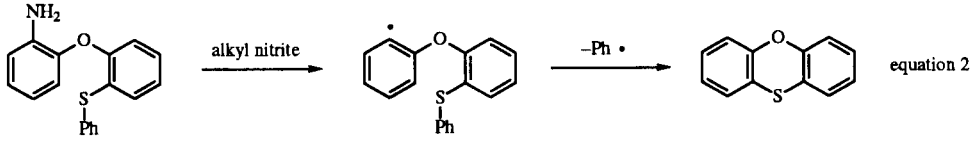
Similar deprotection of **11a** led only to complex product mixtures during the trifluoroacetic acid deprotection step. Apparently, the fluorine atom adjacent to the isopropoxy group in **11c** protects the aromatic ring from electrophilic substitution so that a relatively clean deprotection is feasible. The absence of this fluorine atom in **11a** renders the substrate susceptible to alkylation by the electron-deficient benzylic species produced during the deprotection. Regardless of the problematic deprotection with **11a**, the Smiles rearrangement of **12** did not bode well for this deprotection-cyclization approach.

The nitro group is essential for Smiles rearrangement of intermediates such as **12** [13]. We reasoned that reductions of **11** to the corresponding amines **13** would at least alleviate the problem of an unwanted Smiles rearrangement but would probably enhance the difficulties associated with a clean removal of the thiol protecting group. Nevertheless, it occurred to us that diazotization of the intermediate amines **13** could conceivably result in the simultaneous deblocking of the thiol group and subsequent ring closure to the desired phenoxathiins **14**. At this point, close inspection of the literature revealed one report by Tundo and coworkers [15] concerning the cyclization of 2-aminophenyl 2-phenylthiophenyl ether to phenoxathiin by aprotic diazotization (equation 2) [16]. The authors provided evidence that phenoxathiin formation occurred through the intermediacy of an aryl radical followed by carbon-sulfur bond formation and concomitant loss of a phenyl radical. Although a number of thianthrenes were prepared by this procedure, the synthesis of substituted phenoxathiins by this method was not described.

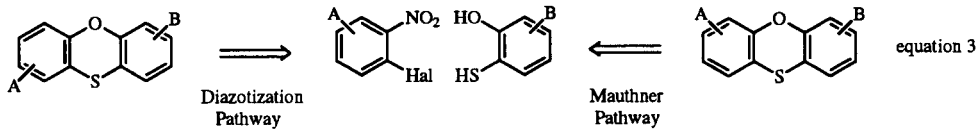
We felt that similar cyclizations of **13** would be feasible and a useful extension of the methodology [17] especially considering the potential for stabilization of *p*-methoxybenzyl [18,19] and methoxymethyl radicals and the mild conditions employed in the selective introduction of these protecting groups. In addition, substrates **13a-c** provided an opportunity to investigate synthesis of ring fluorinated analogs of **II** by this procedure while making use of different radical leaving groups at sulfur. To this end, the nitro derivatives **11** were reduced to their corresponding amines **13** in near quantitative yields, setting the stage for their aprotic diazotization and cyclization to the phenoxathiins **14**. Indeed, reaction of **13a** with 2 equivalents of isoamyl nitrite in an ethyl acetate solution at *ca.* 55° effected ring closure to the 2-fluoro-7-isopropoxyphenoxathiin (**14a**), which was isolated in 41% yield following a simple flash chromatography. Similar treatment of **13b** provided the 2,8-difluoro-3-isopropoxy derivative **14b** in 46% yield. Methoxymethyl derivative **13b** was likewise converted to phenoxathiin **14a** in 59% isolated yield. Phenoxathiins were the predominant products of these cyclizations with no other major products (>5%) detected by high performance liquid chromatography. Some background degradation stemming from the oxidative instability of the divalent sulfur may account for the moderate yields observed. Oxidation of the phenoxathiins **14** with hydrogen peroxide in trifluoroacetic acid produced the corresponding sulfone targets **15**, which were isolated in 53-73% yields. Although the diazonium-mediated cyclizations shown in Scheme 2 were carried out in ethyl acetate solutions, we have achieved similar results in benzene and toluene solutions (50-100°) employing both methyl and benzyl leaving groups at sulfur.

Summary.

In summation, five novel ring fluorinated derivatives of the monoamine oxidase-A inhibitor 3-isopropoxyphenoxathiin 10,10-dioxide (**II**) were synthesized *via* oxidation of the corresponding phenoxathiins **7** and **14**. The intermediate phenoxathiins **7** were obtained by standard methods which involved cyclization of 2-hydroxythiophenols **4** with the appropriate 2-halonitrobenzenes **5**, whereas phenoxathiins **14** were prepared by a modified diazonium-mediated cyclization of thio-protected 2-aminophenyl 2-thiophenyl ethers **13**. The latter methodology was found to be a viable phenoxathiin synthesis, and, in conjunction with the Mauthner cyclization [4,5], allows for the divergent and selective preparation of two phenoxathiin targets from the same 2-hydroxythiophenol



and substituted 2-halonitrobenzene precursors (equation 3). The aprotic diazotization pathway employs mild reaction conditions and provides phenoxathiins in yields similar to those achieved by classical methods.



equation 3

Some of the phenoxathiins **8** and **15** are potent and selective inhibitors of monoamine oxidase-A and their biological activities will be reported elsewhere.

EXPERIMENTAL

General Methods.

Melting points are uncorrected. An aqueous workup refers to washing an organic solution of the crude product mixture with water and brine followed by drying over magnesium sulfate, filtration, and concentration *in vacuo*. The ^{1}H nmr spectra were recorded at 200 and 300 MHz. The ^{19}F nmr spectra were recorded at 280 MHz. The ^{1}H nmr coupling constants are in Hz and are ^{1}H-^{1}H unless noted otherwise. The ^{1}H nmr chemical shifts are reported in ppm relative to the residual protonated solvent resonance: deuteriochloroform, δ 7.26; deuteriodimethyl sulfoxide, δ 2.50. The ^{19}F nmr chemical shifts are reported in ppm relative to trifluoroacetic acid. Analytical high performance liquid chromatography analyses were performed on a Waters Nova-Pak Phenyl column (5 x 100 mm, 4 micron particle), eluting with 70% (system A) or 80% (system B) methanol/water/0.1% trifluoroacetic acid/0.1% triethyl amine at 1.0 ml/minute. High performance liquid chromatography-ultraviolet spectral data were obtained using a Waters 990 photodiode array detector. Mass spectral analyses were performed by Oneida Research Services, Whitesboro, NY. Elemental analyses were performed by Atlantic Microlabs, Norcross, GA.

5-Fluoro-6-hydroxy-1,3-benzoxathiol-2-one (**1b**).

A mixture of 6-hydroxy-1,3-benzoxathiol-2-one (**1a**) (1.51 g, 8.98 mmoles) and 1,2-dichloroethane (90 ml) was heated to 60°, and 3,5-dichloro-1-fluoropyridinium triflate (**2b**) (4.98 g, 15.76 mmoles) was added in 1 g portions over a 30 minute period. The reaction mixture was heated to reflux and maintained for 20 minutes and then allowed to cool to room temperature. The mixture was diluted with ethyl acetate to dissolve the insoluble material and the crude product was absorbed onto silica gel. Flash chromatography on silica gel eluting with dichloromethane provided the product **1b** [8] (0.470 g, 2.52 mmoles, 28% yield) as an off-white solid: mp 141-143°; ^{1}H nmr (deuteriodimethyl sulfoxide): δ 10.51 (1H, br s), 7.64 (1H, d, J_{HF} = 10.5), 7.06 (1H, d, J_{HF} = 7.2); ^{19}F nmr δ –58.0 (1F, t, J_{FH} = 9); cims: m/z 187 (M+1, 100), 159 (15).

Anal. Calcd. for $C_7H_3FO_3S$: C, 45.16; H, 1.62; S, 17.22. Found: C, 45.17; H, 1.67; S, 17.13.

Isopropoxybenzoxathiolones **3**.

In a typical procedure, anhydrous potassium carbonate (8 mmoles) was added to a solution of the hydroxybenzoxathiolone **1** (4 mmoles) and isopropyl iodide (14 mmoles) in dimethylformamide (18 ml), and the mixture was stirred at room temperature for 3.5 hours. The dimethylformamide was removed by rotovap and the crude material was dissolved in ethyl acetate. Aqueous workup followed by flash chromatography on silica gel eluting with 6-7.5% ethyl acetate/hexanes provided the product.

6-Isopropoxy-1,3-benzoxathiol-2-one (**3a**).

This compound was prepared from **1a** and isolated as a colorless oil in 88% yield; ^{1}H nmr (deuteriochloroform): δ 7.24 (1H, d, J = 8.7), 6.86 (1H, d, J = 2), 6.80 (1H, dd, J = 8.7, 2), 4.52 (1H, sept, J = 6), 1.34 (6H, d, J = 6); eims: m/z 210 (M, 100), 112 (53).

Anal. Calcd. for $C_{10}H_{10}O_3S$: C, 57.13; H, 4.79; S, 15.25. Found: C, 57.25; H, 4.75; S, 15.18.

5-Fluoro-6-isopropoxy-1,3-benzoxathiol-2-one (**3b**).

This compound was prepared from **1b** and isolated as a white solid in 67% yield, mp 52-54°; ^{1}H nmr (deuteriochloroform): δ 7.13 (1H, d, J_{HF} = 9.6), 6.97 (1H, d, J_{HF} = 6.6), 4.52 (1H, sept, J = 6), 1.39 (6H, d, J = 6); ^{19}F nmr (deuteriochloroform): δ –59.2 (1F, t, J_{FH} ~ 9).

Anal. Calcd. for $C_{10}H_9FO_3S$: C, 52.62; H, 3.97; S, 14.04. Found: C, 52.69; H, 3.96; S, 14.13.

2-Hydroxy-4-isopropoxythiophenol (**4a**) and 3-Fluoro-6-hydroxy-4-isopropoxythiophenol (**4b**).

A solution of potassium hydroxide (4 mmoles) in water (1 ml) and methanol (0.5 ml) was added to a stirring solution of the isopropoxybenzoxathiolone **3** (1.5 mmoles) in methanol (3 ml). The resulting solution was stirred 10 minutes at room temperature and acidified (cautiously!) with concentrated hydrochloric acid to *p*H ~1. The methanol was removed at reduced pressure and the aqueous mixture extracted with ethyl acetate. The ethyl acetate layers were dried over magnesium sulfate, filtered, and concentrated to provide the product (100% crude yield) as a light-yellow oil, which was used immediately without further purification.

Phenoxathiins **7**.

A solution of the 2-hydroxythiophenol (**4**) (1.5 mmoles) in dimethylformamide (3 ml) was added dropwise to a stirring mixture of potassium *tert*-butoxide (3 mmoles) in dimethylformamide (2 ml) cooled in an ice bath. The resulting mixture was stirred 15 minutes and a solution of the 2-halonitrobenzene **5** (1.5 mmoles) in dimethylformamide (3.5 ml) was added dropwise. The ice bath was removed and the mixture was heated to reflux for 1-18 hours. When the reaction was judged complete, the mixture was allowed to cool to room temperature and the dimethylformamide was removed by rotovap. The resulting material was dissolved in ethyl acetate, and an aqueous workup

provided the crude product, which was purified by flash chromatography on silica gel eluting with 2-2.5% ethyl acetate/hexanes.

3-Fluoro-7-isopropoxyphenoxathiin (**7a**).

This compound was prepared from **4a** and **5b** and isolated as a white solid in 42% yield, mp 63-65°; ^{1}H nmr (deuteriochloroform): δ 7.01 (1H, br dd, J = 8, J_{HF} = 6), 6.97 (1H, br d, J = 9), 6.77 (1H, d, J = 9), 6.73 (1H, m), 6.59 (2H, m), 4.48 (1H, sept, J = 6), 1.33 (6H, d, J = 6); ^{19}F nmr (deuteriochloroform): δ –36.8 (1F, m); cims: m/z 277 (M+1, 100), 276 (M, 67), 235 (16).

Anal. Calcd. for $C_{15}H_{13}FO_2S$: C, 65.20; H, 4.74; S, 11.60. Found: C, 65.25; H, 4.76; S, 11.55.

2-Fluoro-3-isopropoxyphenoxathiin (**7b**).

This compound was prepared from **4b** and **5a** and isolated as a colorless oil in 39% yield; ^{1}H nmr (deuteriochloroform): δ 7.10 (2H, m), 7.03 (1H, d, J = 7), 6.98 (1H, d, J = 7), 6.84 (1H, d, J_{HF} = 10.6), 6.71 (1H, d, J_{HF} = 7.3), 4.49 (1H, sept, J = 6), 1.37 (6H, d, J = 6); ^{19}F nmr (deuteriochloroform): δ –62.4 (1F, t, J_{FH} ~ 10); eims: m/z 276 (M, 100), 234 (59).

Anal. Calcd. for $C_{15}H_{13}FO_2S$: C, 65.20; H, 4.74; S, 11.60. Found: C, 65.18; H, 4.77; S, 11.51.

2,7-Difluoro-3-isopropoxyphenoxathiin (**7c**).

This compound was prepared from **4b** and **5b** and isolated as an off-white solid in 45% yield, mp 56-58°; ^{1}H nmr (deuteriochloroform): δ 7.03 (1H, br dd, J = 8, J_{HF} = 6), 6.83 (1H, d, J_{HF} = 10), 6.77 (1H, m), 6.75 (1H, br d, J_{HF} = 9), 6.69 (1H, d, J_{HF} = 7.3), 4.48 (1H, sept, J = 6.2), 1.36 (6H, d, J = 6.2); ^{19}F nmr (deuteriochloroform): δ –38.1 (1F, m), –61.8 (1F, m); cims: m/z 295 (M+1, 100), 253 (42).

Anal. Calcd. for $C_{15}H_{12}F_2O_2S\cdot(0.2\ H_2O)$: C, 60.47; H, 4.20; S, 10.76. Found: C, 60.34; H, 4.16; S, 10.80.

Phenoxathiin 10,10-Dioxides **8**.

In a typical procedure, a solution of the phenoxathiin **7** (0.5 mmole) in trifluoroacetic acid (2 ml) was cooled in an ice bath and 30% hydrogen peroxide (0.3 ml) was added dropwise. The reaction mixture was stirred at ice-bath temperature for 15 minutes and then stirred at room temperature until the reaction was judged complete (3-18 hours). The trifluoroacetic acid was partially removed by rotovap and the crude material was partitioned between dichloromethane and saturated sodium bicarbonate. The layers were separated, and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated. The product was purified by flash chromatography on silica gel eluting with dichloromethane/hexanes or by recrystallization from ethyl acetate/hexanes.

3-Fluoro-7-isopropoxyphenoxathiin 10,10-Dioxide (**8a**).

This compound was prepared from **7a** and isolated as a white solid in 72% yield, mp 132.5-134.5°; ^{1}H nmr (deuteriochloroform): δ 8.05 (1H, dd, J = 9, J_{HF} = 5.6), 7.92 (1H, d, J = 8.9), 7.12 (1H, ddd, J_{HF} = 10, J = 9, 2.4), 7.06 (1H, dd, J_{HF} = 9, J = 2.4), 6.92 (1H, dd, J = 8.9, 2.4), 6.78 (1H, d, J = 2.4), 4.65 (1H, sept, J = 6.2), 1.39 (6H, d, J = 6.2); ^{19}F nmr (deuteriochloroform): δ –23.9 (1F, ddd, J_{FH} = 8.9, 7.6, 5.6); cims: m/z 309 (M+1, 100).

Anal. Calcd. for $C_{15}H_{13}FO_4S$: C, 58.43; H, 4.25; S, 10.40. Found: C, 58.53; H, 4.22; S, 10.47.

2-Fluoro-3-isopropoxyphenoxathiin 10,10-Dioxide (**8b**).

This compound was prepared from **7b** and isolated as a white solid in 72% yield, mp 166-167°; ^{1}H nmr (deuteriochloroform): δ 8.03 (1H, dd, J = 8, 1.5), 7.69 (1H, d, J_{HF} = 9.5), 7.63 (1H, ddd, J = 8, 8, 1.5), 7.40 (1H, ddd, J = 8, 8, 1), 7.34 (1H, dd, J = 8, 1), 6.89 (1H, d, J_{HF} = 6.5), 4.67 (1H, sept, J = 6), 1.44 (6H, d, J = 6); ^{19}F nmr (deuteriochloroform): δ –58.8 (1F, t, J_{FH} ~ 8); cims: m/z 309 (M+1, 100), 267 (19).

Anal. Calcd. for $C_{15}H_{13}FO_4S$: C, 58.43; H, 4.25; S, 10.40. Found: C, 58.33; H, 4.23; S, 10.35.

2,7-Difluoro-3-isopropoxyphenoxathiin 10,10-Dioxide (**8c**).

This compound was prepared from **7c** and isolated as a white solid in 89% yield, mp 162-164°; ^{1}H nmr (deuteriochloroform): δ 8.04 (1H, dd, J = 8.7, J_{HF} = 5.8), 7.68 (1H, d, J_{HF} = 9.5), 7.13 (1H, ddd, J_{HF} = 11, J = 8, 2), 7.05 (1H, dd, J_{HF} = 9, J = 2), 6.88 (1H, d, J_{HF} = 6.5), 4.67 (1H, sept, J = 6), 1.44 (6H, d, J = 6); ^{19}F nmr (deuteriochloroform): δ –26.1 (1F, m), –58.2 (1F, dd, J_{FH} = 9.3, 7.1); cims: m/z 327 (M+1, 100), 285 (20).

Anal. Calcd. for $C_{15}H_{12}F_2O_4S$: C, 55.21; H, 3.71; S, 9.82. Found: C, 55.11; H, 3.73; S, 9.74.

Thio-protected 2-Hydroxythiophenols **10**.

A solution of the 2-hydroxythiophenol (**4**) (4 mmoles) in dimethylformamide (10 ml) was added dropwise to a stirring mixture of potassium *tert*-butoxide (4 mmoles) in dimethylformamide (10 ml) cooled to 0°. The mixture was stirred for 5 minutes at ice bath temperature and a solution of *para*-methoxybenzyl chloride or methoxymethyl bromide (4 mmoles) in dimethylformamide (5 ml) was added dropwise. The reaction mixture was then allowed to warm to room temperature. The dimethylformamide was removed by rotovap and the crude material was dissolved in ethyl acetate. An aqueous workup provided a product of sufficient purity for use in the next step (76-98% crude yield). Analytical samples were obtained by flash chromatography on silica gel eluting with 10-15% ethyl acetate/hexanes.

5-Isopropoxy-2-((4-methoxybenzyl)thio)phenol (**10a**).

This compound was prepared from **4a** and isolated as a colorless oil; ^{1}H nmr (deuteriochloroform): δ 7.11 (1H, d, J = 8.4), 6.99 (2H, d, J = 8.7), 6.78 (2H, d, J = 8.7), 6.57 (1H, s), 6.47 (1H, d, J = 2.6), 6.36 (1H, dd, J = 8.4, 2.6), 4.50 (1H, sept, J = 6.1), 3.78 (3H, s), 3.73 (2H, s), 1.32 (6H, d, J = 6.1); cims: m/z 121 (100), 305 (M+1, 14), 525 (M+121, 16).

Anal. Calcd. for $C_{17}H_{20}O_3S$: C, 67.08; H, 6.62; S, 10.53. Found: C, 67.14; H, 6.57; S, 10.62.

5-Isopropoxy-2-((methoxymethyl)thio)phenol (**10b**).

This compound was prepared from **4a** and isolated as a light yellow oil; ^{1}H nmr (deuteriodimethylsulfoxide): δ 9.67 (1H, s), 7.21 (1H, d, J = 8.4), 6.40 (1H, d, J = 2.6), 6.36 (1H, dd, J = 8.4, 2.6), 4.79 (2H, s), 4.48 (1H, sept, J = 6), 3.28 (3H, s), 1.24 (6H, d, J = 6).

Anal. Calcd. for $C_{11}H_{16}O_3S$: C, 57.87; H, 7.06; S, 14.04. Found: C, 57.78; H, 7.08; S, 14.03.

4-Fluoro-5-isopropoxy-2-((4-methoxybenzyl)thio)phenol (**10c**).

This compound was prepared from **4b** and isolated as a colorless oil; ^{1}H nmr (deuteriodimethyl sulfoxide): δ 9.64 (1H, s), 7.17 (2H, d, J = 8.7), 6.95 (1H, d, J_{HF} = 11.8), 6.82 (2H, d, J = 8.7), 6.58 (1H, d, J_{HF} = 7.6), 4.43 (1H, sept, J = 6), 3.97 (2H, s), 3.69 (3H, s), 1.24 (6H, d, J = 6); eims: m/z 322 (M, 6), 121 (100).

Anal. Calcd. for $C_{17}H_{19}FO_3S$: C, 63.33; H, 5.94; S, 9.94. Found: C, 63.54; H, 6.03; S, 10.04.

Thio-protected 2-Nitrophenyl 2-Thiophenyl Ethers **11**.

A solution of the phenol **10** (1.3 mmoles) in diglyme (3 ml) was added dropwise to a stirring suspension of sodium hydride (2.6 mmoles) in diglyme (4 ml) at room temperature. The mixture was stirred for 15 minutes and a solution of 2,5-difluoronitrobenzene (**5b**) (1.3 mmoles) in diglyme (3 ml) was added dropwise followed by the addition of 18-Crown-6 (0.3 mmole) *via* spatula. The reaction mixture was refluxed for 1-2 hours and then allowed to cool to room temperature. The diglyme was removed by rotovap and the crude material was dissolved in ethyl acetate. Aqueous workup followed by flash chromatography on silica gel eluting with 15% ethyl acetate/hexanes provided the product.

5-Isopropoxy-2-((4-methoxybenzyl)thio)phenyl 4-Fluoro-2-nitrophenyl Ether (**11a**).

This compound was prepared from **10a** and isolated as an orange oil in 69% yield; ^{1}H nmr (deuteriochloroform): δ 7.73 (1H, dd, J_{HF} = 7.7, J = 3), 7.26 (1H, d, J = 8.6), 7.17 (1H, ddd, J_{HF} = 10, J = 9, 3), 7.08 (2H, d, J = 8.6), 6.77 (1H, m), 6.75 (2H, d, J = 8.6), 6.60 (1H, dd, J = 8.6, 2.5), 6.46 (1H, d, J = 2.5), 4.46 (1H, sept, J = 6), 3.95 (2H, s), 3.76 (3H, s), 1.29 (6H, d, J = 6); eims: m/z 121 (100), 443 (M, 20), 564 (M+121, 10).

Anal. Calcd. for $C_{23}H_{22}FNO_5S$: C, 62.29; H, 5.00; N, 3.16; S, 7.23. Found: C, 62.39; H, 5.01; N, 3.18; S, 7.17.

5-Isopropoxy-2-((methoxymethyl)thio)phenyl 4-Fluoro-2-nitrophenyl Ether (**11b**).

This compound was prepared from **10b** and isolated as an orange oil in 60% yield; ^{1}H nmr (deuteriochloroform): δ 7.72 (1H, dd, J_{HF} = 7.7, J = 3), 7.53 (1H, d, J = 8.6), 7.21 (1H, ddd, J_{HF} = 9, J = 9, 3), 6.90 (1H, dd, J = 9, J_{HF} = 4.5), 6.71 (1H, dd, J = 8.6, 2.6), 6.48 (1H, d, J = 2.6), 4.83 (2H, s), 4.47 (1H, sept, J = 6), 3.36 (3H, s), 1.29 (6H, d, J = 6); eims: m/z 367 (M, 65), 336 (20), 45 (100).

Anal. Calcd. for $C_{17}H_{18}FNO_5S$: C, 55.58; H, 4.94; N, 3.81; S, 8.73. Found: C, 55.66; H, 4.96; N, 3.73; S, 8.83.

4-Fluoro-5-isopropoxy-2-((4-methoxybenzyl)thio)phenyl 4-Fluoro-2-nitrophenyl ether (**11c**).

This compound was prepared from **10c** and isolated as an orange oil in 72% yield; ^{1}H nmr (deuteriochloroform): δ 7.71 (1H, dd, J_{HF} = 8, J = 3), 7.13 (1H, m), 7.11 (1H, d, J_{HF} = 11), 7.09 (2H, d, J = 8.6), 6.76 (2H, d, J = 8.6), 6.65 (1H, d, J_{HF} = 5.7), 6.63 (1H, m), 4.44 (1H, sept, J = 6), 3.97 (2H, s), 3.77 (3H, s), 1.33 (6H, d, J = 6); cims: m/z 121 (100), 160 (84), 461 (M, 2), 582 (M+121, 2).

Anal. Calcd. for $C_{23}H_{21}F_2NO_5S$: C, 59.86; H, 4.59; N, 3.04; S, 6.95. Found: C, 59.96; H, 4.62; N, 3.01; S, 7.03.

2,7-Difluoro-3-isopropoxyphenoxathiin (**7c**) *via* the Smiles Rearrangement of **12**.

A solution of **11c** (95 mg, 0.21 mmole) in trifluoroacetic acid (4.5 ml) was refluxed for 3.5 hours. The solution was concentrated at reduced pressure, and the crude material was dissolved in dimethylformamide (2 ml). The dimethylformamide solution was cooled in an ice bath, and potassium *tert*-butoxide (56 mg, 0.50 mmole) was added *via* spatula. The mixture was warmed to room temperature and then heated at reflux for 2 hours. The dimethylformamide was removed by rotovap, and the crude material was dissoved in ethyl acetate. An aqueous workup followed by flash chromatography on silica gel eluting with 2.5% ethyl acetate/hexanes provided **7c** (37 mg, 0.13 mmole, 61% overall yield) as a colorless oil, which crystallized on standing: mp 56-57°; the spectral data were identical in all respects to that described above for **7c** prepared from **4b** and **5b**.

Thio-protected 2-Aminophenyl 2-Thiophenyl Ethers **13**.

The nitro diaryl ether **11** (0.2 mmole) was dissolved in a mixture of methanol (1.5 ml), tetrahydrofuran (1 ml), water (0.5 ml) and glacial acetic acid (0.3 ml). Zinc dust (3 mmoles) was added, and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was filtered and concentrated, and the crude material was partitioned between dichloromethane and 1*M* sodium hydroxide. The organic layer was dried over magnesium sulfate, filtered, and concentrated to provide the corresponding amine in analytically pure form.

5-Fluoro-2-(5-isopropoxy-2-((4-methoxybenzyl)thio)phenoxy)-aniline (**13a**).

This compound was prepared from **11a** and isolated as a colorless oil in 100% yield; ^{1}H nmr (deuteriochloroform): δ 7.26 (1H, d, J = 8.4), 7.14 (2H, d, J = 8.7), 6.78 (2H, d, J = 8.7), 6.74 (1H, dd, J = 9, J_{HF} = 5.6), 6.50 (1H, dd, J = 8.4, 2.3), 6.49 (1H, dd, J_{HF} = 9.9, J = 2.9), 6.37 (1H, ddd, J_{HF} = 9, J = 9, 2.9), 6.28 (1H, d, J = 2.3), 4.40 (1H, sept, J = 6), 3.99 (2H, s), 3.88 (2H, br), 3.77 (3H, s), 1.26 (6H, d, J = 6); cims: m/z 121 (100), 413 (M, 6), 534 (M+121, 4).

Anal. Calcd. for $C_{23}H_{24}FNO_3S$: C, 66.81; H, 5.85; N, 3.39; S, 7.75. Found: C, 66.85; H, 5.87; N, 3.37; S, 7.82.

5-Fluoro-2-(5-isopropoxy-2-((methoxymethyl)thio)phenoxy)aniline (**13b**).

This compound was prepared from **11b** and isolated as a colorless oil in 93% yield; ^{1}H nmr (deuteriochloroform): δ 7.47 (1H, d, J = 8.6), 6.84 (1H, dd, J = 8.7, J_{HF} = 5.4), 6.55 (1H, dd, J = 8.6, 2.7), 6.50 (1H, dd, J_{HF} = 10, J = 2.9), 6.39 (1H, ddd, J_{HF} = 8.7, J = 8.6, 2.9), 6.25 (1H, d, J = 2.7), 4.88 (2H, s), 4.40 (1H, sept, J = 6), 4.02 (2H, br), 3.43 (3H, s), 1.26 (6H, d, J = 6); ^{19}F nmr (deuteriochloroform): δ –39.1 (1F, ddd, J_{FH} ~ 9, 9, 6); cims: m/z 337 (M, 30), 272 (30), 262 (35), 228 (30), 154 (40), 45 (100).

Anal. Calcd. for $C_{17}H_{20}FNO_3S$: C, 60.52; H, 5.97; N, 4.15; S, 9.50. Found: C, 60.46; H, 5.96; N, 4.09; S, 9.59.

5-Fluoro-2-(4-fluoro-5-isopropoxy-2-((4-methoxybenzyl)-thio)phenoxy)aniline (**13c**).

This compound was prepared from **11c** and isolated as a colorless oil in 98% yield; ^{1}H nmr (deuteriochloroform): δ 7.15 (2H, d, J = 8.7), 7.08 (1H, d, J_{HF} = 11), 6.79 (2H, d, J = 8.7), 6.61 (1H, dd, J = 8.7, J_{HF} = 5.3), 6.50 (1H, dd, J_{HF} = 9.7, J = 2.9), 6.43 (1H, d, J_{HF} = 7.3), 6.34 (1H, ddd, J_{HF} = 8.7, J = 8.7, 2.9), 4.35 (1H, sept, J = 6), 3.99 (2H, s), 3.89 (2H, br), 3.78 (3H, s), 1.27 (6H, d, J = 6); cims: m/z 432 (M+1, 8), 431 (M, 8), 220 (67), 205 (57), 121 (100).

Anal. Calcd. for $C_{23}H_{23}F_2NO_3S$: C, 64.02; H, 5.37; N, 3.25; S, 7.43. Found: C, 64.10; H, 5.39; N, 3.19; S, 7.37.

Phenoxathiins **14**.

A solution of isoamyl nitrite (0.6 mmole) in ethyl acetate (1 ml) was added dropwise to a stirring solution of **13** (0.3 mmole)

in ethyl acetate (11 ml) at room temperature. The solution was maintained at 55° for 2-4 hours. When the reaction was complete, the solution was concentrated and the crude material was purified by flash chromatography on silica gel eluting with 0-5% ethyl acetate/hexanes.

2-Fluoro-7-isopropoxyphenoxathiin (**14a**).

This compound was prepared from **13a** and **13c** and isolated as a white solid in 41 and 59% yields, respectively, mp 64-65°; ^{1}H nmr (deuteriochloroform): δ 6.96 (1H, d, J = 9), 6.94 (1H, m), 6.80 (2H, m), 6.60 (1H, dd, J = 9, 2.4), 6.59 (1H, d, J = 2.4), 4.48 (1H, sept, J = 6), 1.32 (6H, d, J = 6); cims: m/z 277 (M+1, 100), 235 (44); ^{19}F nmr (deuteriochloroform): δ –40.7 (1F, m).

Anal. Calcd. for $C_{15}H_{13}FO_2S$: C, 65.20; H, 4.74; S, 11.60. Found: C, 65.29; H, 4.75; S, 11.50.

2,8-Difluoro-7-isopropoxyphenoxathiin (**14b**).

This compound was prepared from **13b** and isolated as a nearly colorless oil in 46% yield; ^{1}H nmr (deuteriochloroform): δ 6.94 (1H, m), 6.83 (3H, m), 6.69 (1H, d, J_{HF} = 7.3), 4.48 (1H, sept, J = 6), 1.36 (6H, d, J = 6); ^{19}F nmr (deuteriochloroform): δ –40.2 (1F, ddd, J_{FH} ~ 8, 8, 4.9), –59.3 (1F, dd, J_{FH} = 9.8, 7.4); >98% purity by hplc, solvent system A [10], K' = 5.44; hrms: Calcd. for $C_{15}H_{12}F_2O_2S$: 294.0527. Found: 294.0552.

Phenoxathiin 10,10-Dioxides **15**.

These compounds were prepared in 41-73% yields by methods identical to those described above for the preparation of **8**.

2-Fluoro-7-isopropoxyphenoxathiin 10,10-Dioxide (**15a**).

This compound was prepared from **14a** and isolated as a white solid in 41% yield, mp 135-136°; ^{1}H nmr (deuteriochloroform): δ 7.91 (1H, d, J = 8.9), 7.72 (1H, br d, J_{HF} ~ 7), 7.35 (2H, m), 6.91 (1H, dd, J = 9, 2), 6.78 (1H, d, J = 2) 4.64 (1H, sept, J = 6), 1.39 (6H, d, J = 6); ^{19}F nmr (deuteriochloroform): δ –37.0 (1F, q, J_{FH} ~ 6); cims: m/z 309 (M+1, 100).

Anal. Calcd. for $C_{15}H_{13}FO_4S$: C, 58.43; H, 4.25; S, 10.40. Found: C, 58.51; H, 4.27; S, 10.32.

2,8-Difluoro-3-isopropoxyphenoxathiin 10,10-Dioxide (**15b**).

This compound was prepared from **14b** and isolated as an off-white solid in 73% yield, mp 164-165°; ^{1}H nmr (deuteriochloroform): δ 7.72 (1H, m), 7.68 (1H, d, J_{HF} = 9.6), 7.36 (2H, m), 6.89 (1H, d, J_{HF} = 6.4), 4.68 (1H, sept, J = 6), 1.45 (6H, d, J = 6); ^{19}F nmr (deuteriochloroform): δ –35.9 (1F, q, J_{FH} ~ 6), –55.7 (1F, t, J_{FH} ~ 8); hrms: Calcd. for $C_{15}H_{12}F_2O_4S$: 326.0425. Found: 326.0441.

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§ Current address: Krenitsky Pharmaceuticals Inc., 4 University Place, 4611 University Drive, Durham, NC 27707.

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