Supporting Information

Synthesis of 2,3-dichloro-4-(2-thienylcarbonyl)anisole (1)

Thiophene-2-carbonyl chloride (10.4 g, 81.2 mmols) was dissolved in 100 mL of CH_2Cl_2 in a 500 mL round bottom flask and stirred on an ice bath. To this solution, 9.43 g (71.0 mmols) of $AlCl_3$ was added portion-wise. The suspension was stirred for 30 min as it gradually changed to a clear solution. A solution of 12.3 g (70.0 mmols) of 2,3-dichloroanisole dissolved in 50 mL of CH_2Cl_2 was added over 10 min. TLC analysis (silica plates, 95% chloroform/5% hexane, UV detection) indicated that approximately 50% of the 2,3-dichloroanisole (R_f~0.9) had been consumed after 2 h. The reaction was then heated to reflux for an additional 3 h, after which TLC analysis indicated that the 2,3-dichloroanisole had been completely consumed. The reaction was quenched at r.t. by the cautious addition of ice pieces followed by the addition of 100 mL of aqueous 5% HCl to facilitate dissolution of precipitated aluminum salts. The phases were separated and diluted with 50 mL of CH_2Cl_2. The organic layer was removed, and the aqueous layer was extracted with 3x50 mL volumes of CH_2Cl_2. The organic extracts were pooled and washed successively with 2×100 mL of de-ionized (DI) H_2O, 2×100 mL of aqueous 5% KOH, 1×100 mL DI H_2O followed by 100 mL of saturated NaCl. The organic layer was dried over anhydrous Na_2SO_4. The CH_2Cl_2 was removed by rotary evaporation to yield a faint amber residue which spontaneously crystallized. After recrystallization from chloroform and hexane, 16.7 grams of 2,3-dichloro-4-(2-thienylcarbonyl) anisole (1) was obtained in 86% theoretical yield relative to limiting 2,3-dichloroanisole. MS: M+H=287; ^{1}H NMR (ppm) (500 MHz, $CDCl_3$-TMS); 7.76, $H^{5'}$ (d, J=4.3 Hz, 1H), 7.43 H (d, J=2.9 Hz, 1H), 7.37 (d, J=8.5 Hz, 1H), 7.13 (t, J=4.3 Hz, 1H), 6.93 (d, J=8.5 Hz, 1H), 3.99 (s, 3H)

Synthesis of 2,3-dichloro-4-(2-thienylcarbonyl)phenol (2)

Compound (1) (16.1 g (56.2 mmols)) dissolved in 150 mL of CH_2Cl_2 in a 500 mL round bottom flask which was cooled in a salt/ice bath. To this solution ~26 g (~100 mmol) of BBr_3 were added dropwise over 10 min to produce an exothermic reaction and deep orange color. The reaction mixture was sealed and allowed to stir overnight at r.t. On the following day, TLC analysis (silica plates, $CHCl_3$, R_f~0.6, UV-detection) indicated there was no starting material remaining. The reaction was quenched slowly with 150 mL of H_2O creating a white precipitate. The CH_2Cl_2 layer was separated and the aqueous phase was further extracted with 2×100 mL portions of ethyl acetate. The CH_2Cl_2 and ethyl acetate extracts were evaporated separately, and the residues were combined. The crude mixture weighing 14.9 grams (99% yield) was dissolved in 150 mL of ethyl acetate and washed twice with 5% aqueous HCl , twice with DI H_2O followed by 100 mL of saturated NaCl. The organic layer was removed and dried over anhydrous Na_2SO_4. The solution was filtered and the solvent removed under vacuum to yield a clear oil that spontaneously crystallized to yield 11.5 g (70% yield) of 2,3-dichloro-4-(2-thienylcarbonyl) phenol (2). MS: 273 (M+H), 271 (M-H): ^{1}H NMR ppm (500 MHz, $CDCl_3$-TMS); 7.77 ppm (d, 4.3 Hz, 1H), 7.44 ppm (d, 3.0 Hz, 1H), 7.33 ppm (d, 8.5 Hz, 1H), 7.14 ppm (t, 4.3 Hz, 1H), 7.04 ppm (d, 8.5 Hz, 1H), 6.40 ppm (s, 1H phenol)

Synthesis of 2,3-dichloro-4-(2-thienylcarbonyl)phenoxyacetic acid, tienilic Acid (TA)

Compound (2), 11.4 grams (42.0 mmols), was dissolved in 100 mL of toluene in a 500 mL round bottom flask followed by the addition of 9.5 g (67.0 mmols) of anhydrous K_2CO_3 generating a thick white slurry to which 7 mL of DMSO were added. The slurry turned bright yellow in color and was allowed to stir for 20 min. Then 4.6 g (28.9 mmols) of chloroacetic acid

anhydride was added and the mixture was stirred at reflux for 18 h. The yellow color had faded and the slurry became faint brown. The intermediate tienilic acid anhydride was hydrolyzed by the addition of 100 mL of DI H_2O followed by 5 mL of 50% KOH. Reflux was maintained for 2 h, after which an amber-colored biphasic mixture was obtained. The aqueous layer was removed and acidified generating a precipitant that was made soluble by adding an equal volume of toluene and refluxing for 2 h. The aqueous layer was removed and the clear toluene solution was cooled overnight in a refrigerator. Upon cooling, the product crystallized and was suction filtered. The crystals were then re-dissolved in hot toluene and dried with anhydrous $MgSO_4$.This was removed by filtration and the product was allowed to crystallize again. The crystals were then collected by vacuum filtration followed by oven drying for 24 h to yield TA weighing 9.5 grams (68% yield). HRMS 330.9550 (M+H)=($C_{13}H_9Cl_2O_4S$) Calculated = 346.9548: ^{1}H NMR (500 MHz, acetone-d_6) 8.05 (dd, 4.8 hz and 1 hz, 1H) 7.52 ppm (d, 8.4 hz, 1H), 7.51 ppm (dd, 4.8 hz and 1 hz, 2h), 7.25 ppm (dd, 4 hz and 1 hz, 1H) 7.23 ppm (d, 8.4 hz, 1H), 5.01 (s, 2H) .

Synthesis of thiophene-3-carbonyl chloride

Thionyl chloride (8.9 g, 68 mmols) was added to a solution of 7.0 g (54.6 mmols) of thiophene-3-carboxylic acid in 50 mL of $CHCl_3$. This was followed by the addition of 5 drops of DMF. The slurry was stirred at room temperature for 4 h during which there was an evolution of gas bubbles and complete dissolution of thiophene-3-carboxylic acid. To this solution, 20 mL of hexane were added and the mixture was allowed to stand for 5 min, sufficient time for most of the DMF and some impurities to separate out as an oily layer. The slightly cloudy solution was decanted into a round bottom flask. The solvents and excess thionyl chloride were removed under vacuum at room temperature to produce a clear crystalline mass of thiophene-3-carbonyl

chloride weighing 7.36 g (99% yield) and this was used directly for the next step without purification.

Synthesis of 2,3-dichloro-4-(3-thienylcarbonyl)anisole

Procedures for this step were performed identically to procedures described for the synthesis of compound 1. This compound was obtained in 65% yield: MS M+H 287 ^{1}H NMR (500 MHz, $CDCl_3$+TMS); 7.83 ppm (s 1H), 7.56 ppm (d, 4.93 Hz 1H), 7.36 ppm (dd, 5.0 Hz, 1H), 7.34 ppm (d, 8.5 Hz 1H),6.93 ppm (d, 8.5 Hz 1H), 3.99 ppm (s, 3H)

Synthesis of 2,3-dichloro-4-(3-thienylcarbonyl)phenol

Procedures for this step were performed identically to procedures described for the synthesis of compound 2 with a 90% yield. Care must be taken to not use excessive heat in the presence of strong base as this compound is unstable under these conditions: MS; M+H 273, M-H 271 ^{1}H NMR (500 MHz, $CDCl_3$+TMS) 7.84 ppm (s, 1H), 7.56 (d, 4.8 Hz 1H), 7.38 (dd, 2.8 and 5.0 Hz 1H), 7.34 ppm (d, 8.5 Hz 1H), 7.043 ppm (d, 8.5 Hz 1H), 6.195 ppm (s, 1H, phenol broad)

Synthesis of 2,3-dichloro-4-(3-thienylcarbonyl)phenoxyacetic acid

Procedures for this step were performed identically to the procedures described for the synthesis of compound 3 with 63% yield. HRMS, 330.9596 M+H=($C_{13}H_9Cl_2O_4S$) ^{1}H NMR (500MHz, acetone-d_6); 8.04 ppm (s, 1H), 7.59 ppm (dd, 5.0 Hz and 2.9 Hz, 1H), 7.50 ppm (d, 5.0 Hz, 1H), 7.42 ppm (d, 8.5 Hz 1H), 7.17 ppm (d, 8.5 Hz 1H), 4.96 ppm (s, 2H)

Synthesis of benzothiophene-*S*-oxide

Benzo-[b]-thiophene (240 mg, 1.79 mmol) was dissolved in 10 mL of CH_2Cl_2 to which 3 equivalents (428 μL) of trifluoroacetic acid and 107 uL of 30% H_2O_2 were added. The reaction was allowed to stir overnight after which 10 mL of a 5% $KHCO_3$ solution was added. The organic layer was removed and dried over $MgSO_4$. A mass spectrum indicated that there was a mixture of benzothiophene and benzothiophene-*S*-oxide. MS: 2M+Na= m/z 323. In order address whether or not the 2M+Na ion identified was a dimer formed from a chemical reaction or the product of a reaction in the ESI source, this same solution was passed through a small column of silica gel with CH_2Cl_2 until all the benzothiophene was eluted off. The *S*-oxide was then eluted with ether and evaporated under N_2 gas. ^{1}H NMR (500MHz, $CDCl_3$-TMS) 7.98 ppm (d, J = 7.7 Hz, 1 H), 7.62-7.5 ppm (m, 3 H), 7.31 ppm (d, J = 5.9 Hz, 1 H), 7.12 ppm (d, J = 5.9 Hz, 1 H)

Synthesis of benzothiophene-*S,S*-dioxide

To a solution that consisted of 2 mL of 88% formic acid and 1 mL of H_2O_2 were added to 10 mL of CH_2Cl_2 containing benzothiophene (100 mg, 7.46 mmol). The reaction mixture was stirred for 4 h at r.t. TLC analysis ($CHCl_3$, silica plates, UV detection) indicated that all starting material had been consumed. To this mixture, 10 mL of aqueous 5% $KHCO_3$ was added. The organic layer was removed, dried over $MgSO_4$ and evaporated to yield 103 mg of product (99%). MS (M+H) m/z 169.^{1}H NMR (500MHz , $CDCl_3$-TMS); 7.73 ppm (d, J = 7.0 Hz, 1 H), 7.64 - 7.48 ppm (m, 2 H), 7.37 ppm (d, J = 7.0 Hz, 1 H), 7.23 ppm (d, J = 6.6 Hz, 1 H), 6.73 ppm (d, J = 7.0 Hz, 1 H)

Incubations of benzothiophene-*S*-oxide

A concentrated solution of benzothiophene-*S*-oxide was added to a mixture of RLMs (0.5 mg) in 100 mM kPi buffer in the presence and absence of 1 mM NADPH. After incubation for 1 hour, the mixtures were extracted with $CHCl_3$ and dried under N_2 gas. The samples were then reconstituted in D_2O and ACN and directly injected into a Bruker APEX Qe 47 LTQ-ICR. Results are discussed in the manuscript.

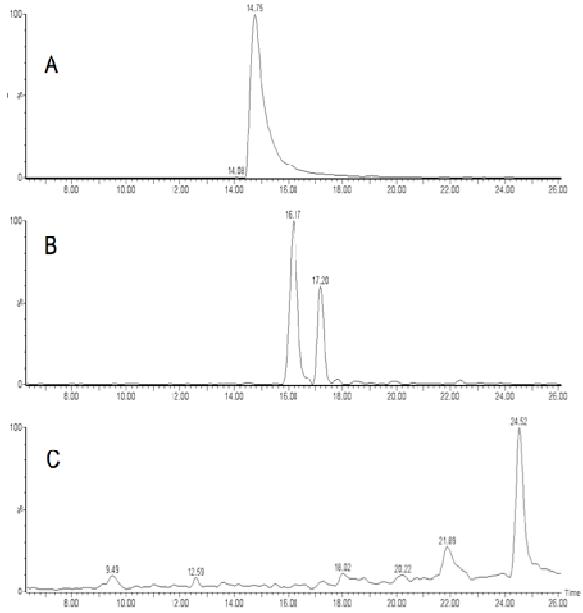

FIGURE S1. XIC's at m/z 347 from incubations with TA (A) and TAI (B) and the XIC at m/z 675 (C) which is the *S*-oxide dimer of TAI.

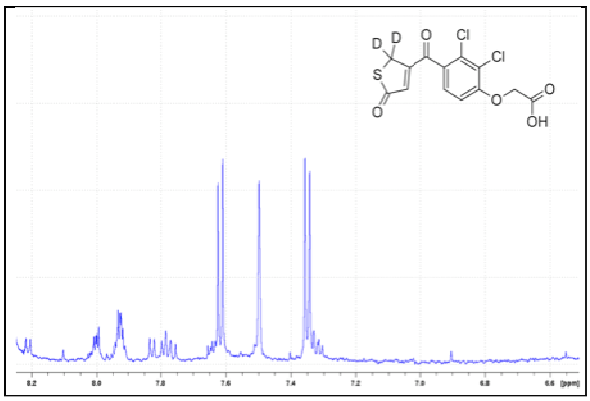

Figure S2: 1D ^{1}H NMR Spectrum expanded to show only the aromatic region of TAI-M1 and TAI-M2 in D_2O a peak at 4.9 ppm was also observed corresponding to the methylene group on the acetic acid moiety.