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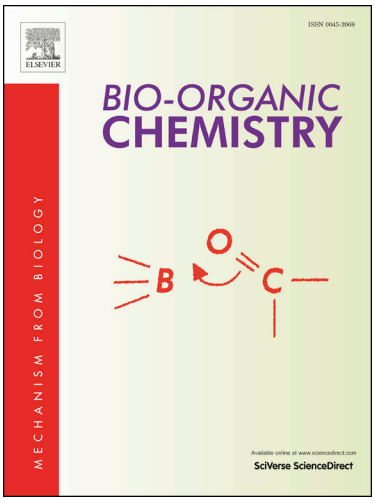

Activity of diphenyl ether benzyl amines against Human African Trypanosomiasis

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Activity of diphenyl ether benzyl amines against Human African Trypanosomiasis.

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Abstract

Insect-borne parasite *Trypanosoma brucei* plagues humans and other animals, eliciting the disease Human African trypanosomiasis, also known as African sleeping sickness. This disease poses the biggest threat to the people in Sub-Saharan Africa. Given the high toxicity and difficulties with administration of currently available drugs, a novel treatment is needed. Building on known Human African trypanosomiasis SAR (structure–activity relationship), we now describe a number of functionally simple diphenyl ether analogs which give low micromolar activity (IC_{50} = 0.16–0.96 μM) against *T. b. rhodesiense*. The best compound shows good selectivity against the L6 cell line (SI = 750) and better selectivity (SI = 1200) against four human cell lines. The data herein provides direction for the ongoing optimization of antitrypanosomal diphenyl ethers.

1. Introduction

In a recent review, Patterson and Wyllie estimate 120,000 annual fatalities from Kinetoplastida genus protazoans (Trypanosomiasis, Chagas, Leishmania).[1] In the case of Human African trypanosomiasis (HAT), the World Health Organization (WHO) estimates approximately 20,000 annual cases with 65 million people at risk.[2] The transmission of this disease is caused primarily by the bite of the tsetse fly, which passes the parasitic protozoan species *Trypanosoma brucei* (T. b.) from its saliva to the blood-stream of the human. In humans, HAT is caused by two trypanosomal sub-species, *T. b. gambiense* in Central and Western Africa and *T. b. rhodesiense* in Western Africa. HAT infections are characterized by two stages. In the first stage, trypanosomes multiply in the circulatory system causing symptoms such as fever, headaches, and joint pain. In the second stage, the parasites cross the blood brain barrier and affect the central nervous system. This results in behavioral changes, sleep disturbances, coma, and eventually death.

Currently, five drugs are used to treat HAT (Figure 1). Problems with these drugs are myriad with some of the most serious being drug-resistance, impractical administration protocols, and high toxicity. Treatment options for *T. b. rhodesiense* infections are suramin for stage I and melarsoprol for stage II of the disease. Arsenic-based melarsoprol is highly toxic.[3] Available treatments for *T. b. gambiense* infections include pentamidine for stage I and melarsoprol and eflornithine for stage II. In recent years, the first line treatment of stage II *T. b. gambiense* infections has been nifurtimox-eflornithine combination therapy (NECT).[4] Trypanosomal drug resistance has been observed with the leading treatment drugs melarsoprol and eflornithine.[4,5] Given these facts, novel orally active compounds are in high demand for HAT and related neglected tropical diseases.[6,7] Much work has focused on second generation pentamidine analogs (Figure 1).[8,9,10,11] Furamidine and an orally administered pro-drug pafuramidine (Figure 2) have shown promise.[12] Unfortunately, phase III clinical trials of pafuramidine were discontinued due to liver and kidney toxicity.[13]

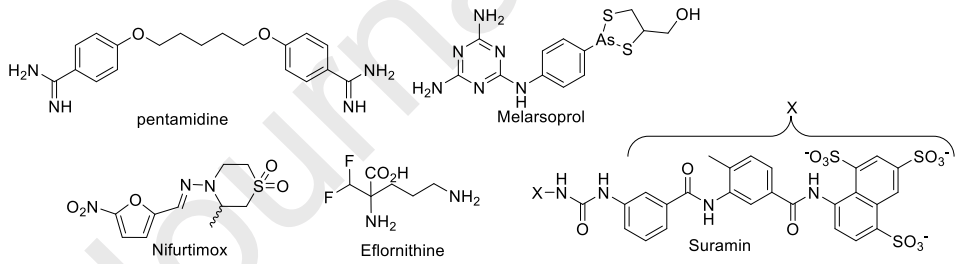


Figure 1. Current drugs registered for treatment of HAT.

Attention has also been focused on nitroaromatic compounds that might improve upon nifurtimox (Figure 1), and indeed fexinidazole (Figure 2) has passed late stage human trials[14,15,16] and has been approved for human use by the European Medicines Agency. Bruhn et al. have reported new pentacyclic nitrofurans active at low nanomolar levels against a nifurtimox-resistant *T. brucei brucei* strain.[17] Another nitroaromatic shows promise in early screens (Hwang et al.).[18] Papadopoulou et al. have recently

reported nitroaryl *N*-(diarylether)-amides that are active against HAT but more active against *T. cruzi* and *L. donovani*.[19] Nitroaromatic compounds have been associated with mutagenicity and an ideal drug candidate might best avoid this moiety. A promising bis-amidine with an *N*-arylbenzamide core (Wang et al., Figure 2) showed good antitrypanosomal activity and low cytotoxicity in early screens, but was toxic to mice.[20] The *N*-aryl benzamide core is a feature of oxaborole[21,22] which has entered clinical trials.[23] Graca et al. have reported symmetrical bisnaphthalimidopropyl derivatives against *T. brucei brucei* with low nanomolar IC_{50}, acceptable toxicity, and metabolic stability.[24] Unfortunately, the pharmacologic properties of these compounds were less than satisfactory.

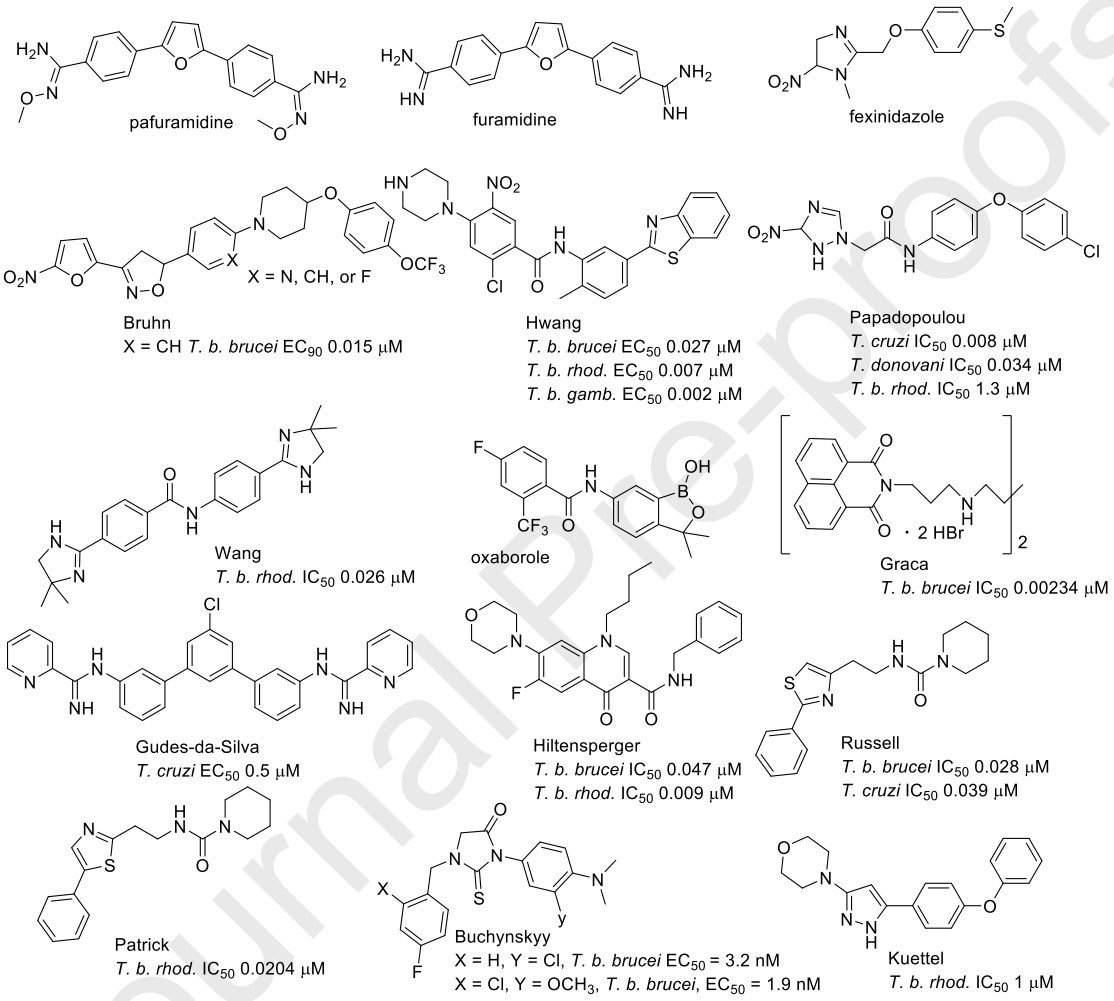


Figure 2. A survey of lead compounds active against HAT.

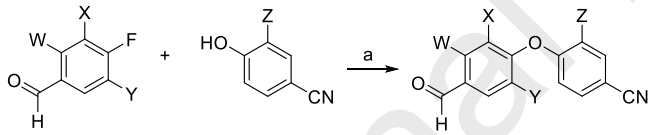
Low micromolar IC_{50} against *T. cruzi* has been reported by Gudes-da-Silva et al. in a series of bis-amidines.[25] Quinolone amides have shown good activity *in vivo* (Hiltensperger et al.).[26] Recently two groups have reported good anti-trypanosome activity and low toxicity in a series of thiazole derivatives that contain *N*-piperidinyl urea moieties, a structural motif that represents a notable departure from the *N*-arylbenzamide and nitroaryl themes. The lead reported by Patrick et al.[27] is the transpositional isomer of the compound reported by Russell et al.[28] with a very similar low nanomolar IC_{50} against trypanosomes. Both studies reported that oxidation of the thiazole moiety by cytochrome P450 impairs their metabolic stability and complicates the development of these

promising leads. Buchynskyy et al.[29] have reported good activity against *T. brucei* in thiohydantoin derivatives. Finally, Kuettel et al. reported 1.0 μM activity for a morpholine diphenylether derivative and proposed a mechanism of action where it binds and hyperactivates the *T. b. rhodesiense* adenosine kinase.[30]

We have found that two diphenylether benzyl amines (**3b** and **4**) without nitroaryl, benzamide, alkylurea or amidine functionality exhibited low micromolar IC_{50} against *T. b. rhodesiense* (Table 1). We now report results from a structure-activity study of these two lead compounds. We started by varying the length and oxidation states of the side chain (Table 1). Next, we examined a family of bis-benzylic amines (Table 2) and introduced other variations to the core structure. (Table 3 and 4). We replaced the benzylic amine of the leads with larger moieties (Table 5 and 6). Finally, we investigated the effects of halogen substituents (Table 7).

2. Chemistry and Results

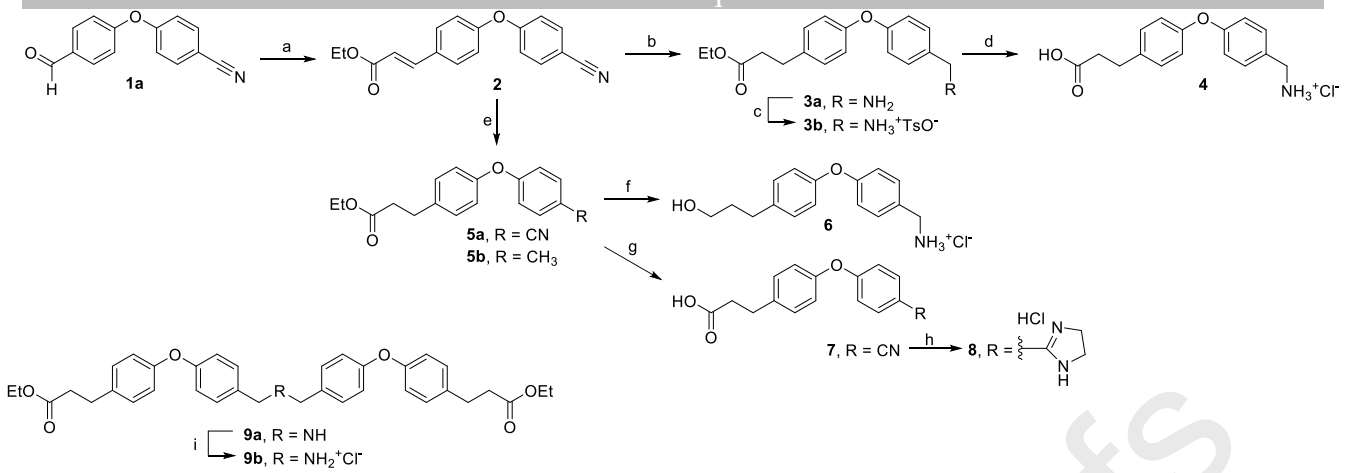
Aldehydes **1a–1g** were prepared by nucleophilic aromatic substitution (Scheme I). The syntheses of target compounds **3b**, **4**, and **6** through **8** are shown in Scheme 2. Aldehyde **1a**[31] was converted by Wadsworth-Horner-Emmons reaction with triethylphosphonoacetate to the cyanopropenoate **2**. Hydrogenation over palladium on carbon gave the propanoate amine **3a** which was then converted to the tosylate salt **3b**.



1a W, X, Y, Z = H
1b W, Y, Z = H, X = Cl
1c W = Cl, X, Y, Z = H
1d W, Y, Z = H, X = F
1e W, Y, Z = H, X = Br
1f W, Z = H, X, Y = F
1g W, Y = H, X = Cl, Z = F

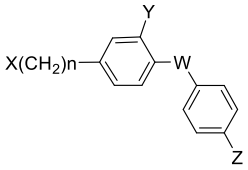
Scheme 1. Synthesis of cyanobiphenyl aldehyde intermediates **1a–1g**. Reagents and conditions: (a) K_2CO_3, DMA, 100–120 °C, 29–91%*. *See experimental section for individual reaction yields.

Hydrolysis of **3a** gave the carboxylic acid ammonium salt **4**. Hydrogenation of **2** over platinum on carbon gave the cyanopropanoate **5a** and byproducts due to hydrogenolysis and amine alkylation (**5b** and **9a**). Reduction of **5a** with a superhydride system led to alcohol ammonium salt **6**. Hydrolysis of **5a** gave carboxylic acid **7** which was converted into the imidazolidinium derivative **8**.



Scheme 2. Synthesis of acyclic aliphatic side chain derivatives from cyanobiphenyl aldehdye intermediates. Reagents, conditions, and yields: (a) triethyl phosphonoacetate, NaH, THF, 0 to 62 °C, 72%; (b) H_2, Pd/C, EtOH, rt, 75%; (c) TsOH, Et_2O, rt, 77%; (d) from **3a**, 2N NaOH, EtOH, H_2O, rt, then conc HCl, 47%; (e) H_2, 60 psi, Pt/C, rt, 50% for **5a**, 4% for **5b**; (f) from **5a**, $LiBH_4$, $LiEt_3BH$, THF, rt; 2N NaOH, then 1N HCl, 93%; (g) from **5a**, 2N NaOH, EtOH, rt, then conc HCl, 77%; (h) ethylenediamine, NaHS, DMA, 120 °C, then conc HCl, 82%; (i) 1N HCl/EtOAc, rt, 69%.

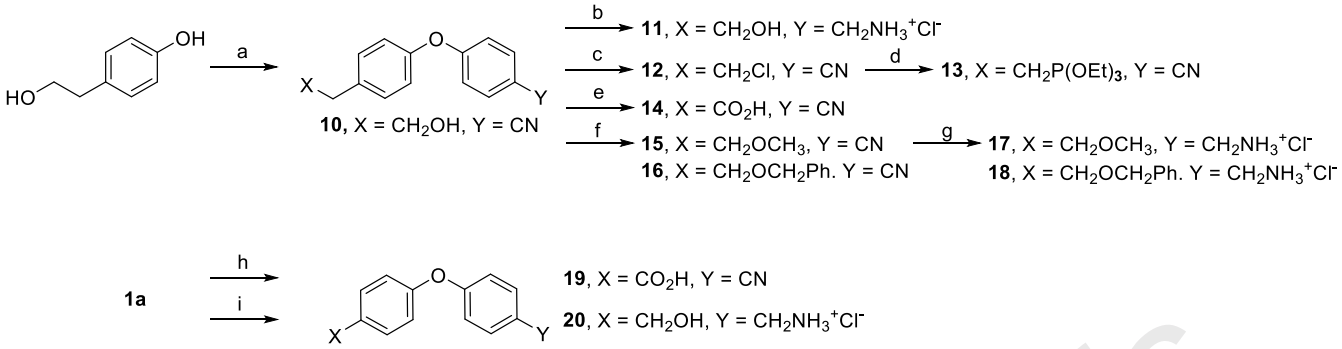
Table 1. Alkyl side chain derivatives and the resulting *in-vitro* activity against *T. b. rhod* and cytotoxicity against the L6 cell line.



Compound	X	n	Y	Z	W	T. b. rhod. IC_{50} (μM) [SI]	L6 cytotoxicity IC_{50} (μM)
3b	EtO_2C	2	H	CH_2NH_2·HOTs	O	1.4 [79]	110
4	HO_2C	2	H	CH_2NH_2·HCl	O	2.0 [150]	>300
6	HO	3	H	CH_2NH_2·HCl	O	0.96 [177]	170
7	HO_2C	2	H	CN	O	160	>370
8	HO_2C	2	H	$C{=}NCH_2CH_2NH$·HCl	O	180	>290
10	HO	2	H	CN	O	71	20
11	HO	2	H	CH_2NH_2·HCl	O	6.6 [18]	120
13[a]	$(EtO)_2PO$	2	H	CN	O	16	10
14	HO_2C	1	H	CN	O	130	280
15	CH_3O	2	H	CN	O	7.0	120
16	BnO	2	H	CN	O	7.5	290
17	CH_3O	2	H	CH_2NH_2·HCl	O	4.1 [44]	180
18	BnO	2	H	CH_2NH_2·HCl	O	2.9 [18]	51
19	HO_2C	0	H	CN	O	120	340
20	HO	1	H	CH_2NH_2·HCl	O	5.7 [35]	200
23	HO	1	H	CH_2NH_2·HCl	S	2.8 [57]	160
26	HO	3	Cl	CH_2NH_2·HCl	O	0.49 [100]	49
27	H_2NCO	2	H	$CONH_2$	O	160	227

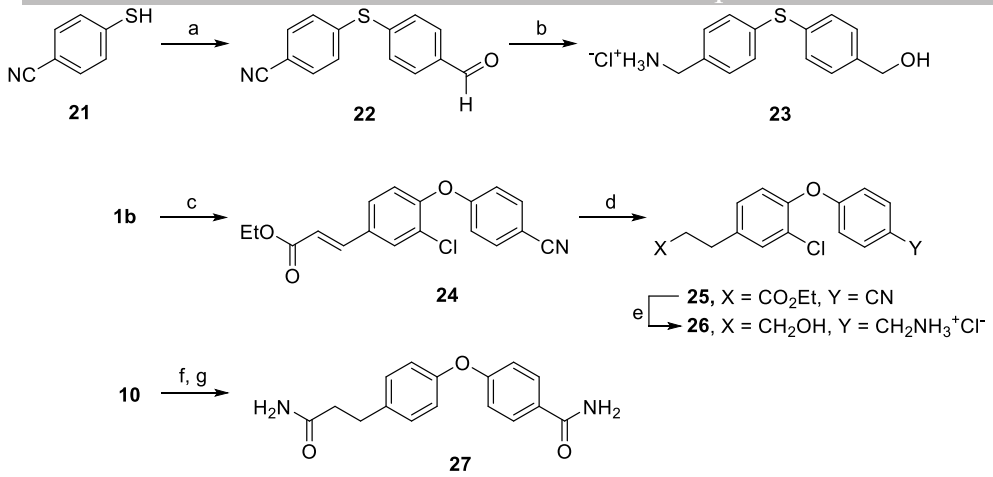
[a]Active against *L. don*. 2.3 μM

As shown in Scheme 3, **10** through **13** were prepared from tyrosol and 4-fluorobenzonitrile by nucleophilic aromatic substitution to form nitrile alcohol **10**. Reduction of **10** with superhydride followed by acidification gave alcohol ammonium salt **11**. Treatment of **10** with thionyl chloride followed by Arbuzov reaction with triethylphosphite produced nitrile phosphonate **13**.



Scheme 3. Synthesis of alkyl side chain phenoxy ether derivatives **13** through **20**. Reagents, conditions, and yields: (a) 4-fluorobenzonitrile, K_2CO_3, DMA, 120 °C, 63%; (b) $LiBH_4$, $LiEt_3BH$, THF/Et_2O, rt; 3N NaOH then conc HCl, 65%; (c) $SOCl_2$, reflux, 78%; (d) $P(OEt)_3$, NaI, reflux, 87%; (e) Jones reagent, acetone, 0 °C to rt; 2N NaOH then conc HCl, 28%; (f) KOH, CH_3I or BnCl, DMSO, rt, 98%; (g) $LiEt_3BH$, THF, rt; 3N NaOH then EtOAc/conc HCl, 48%; (h) Jones reagent, acetone, 0 °C to rt; 2N NaOH then conc HCl, 66%; (i) $LiBH_4$, $LiEt_3BH$, THF/Et_2O, rt; 3N NaOH then conc HCl, 95%.

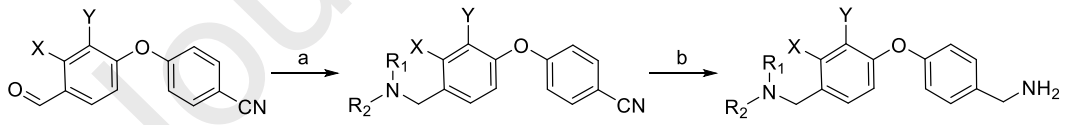
Oxidation of **10** with Jones reagent gave cyano acid **14**. Jones oxidation of **1a** gave the cyano acid **19** while reduction of **1a** with superhydride gave amino alcohol **20**. Cyano acids **14** and **19** were reduced with superhydride, however no pure product could be isolated. Compounds **17** and **18** were made by alkylation of **10** followed by superhydride reduction. Compound **23** was made as shown in Scheme 4. Known **21**[32] and 4-fluorobenzaldehdye gave cyano aldehyde **22**. Subsequent reduction of **22** with superhydride gave alcohol ammonium salt **23**.



Scheme 4. Synthesis of diphenyl thioether and ether derivatives **23**, **26**, and **27**. Reagents, conditions, and yields: (a) 4-fluorobenzonitrile, K_2CO_3, DMA, 120 °C, 57%; (b) $LiBH_4$, $LiEt_3BH$, THF/Et_2O, rt; 2N NaOH then Et_2O/conc HCl, 37%; (c) triethyl phosphonoacetate, NaH, THF, 0 to 55 °C, 52%; (d) $Cu(OAc)_2 \cdot H_2O$, 1,2-BDP, PMHS, *t*-BuOH, toluene, rt, 49%; (e) $LiBH_4$, $LiEt_3BH$, THF, rt; 10% NaOH then CH_3OH/0.5 M HCl, 69%; (f) $SOCl_2$, reflux, 67%; (g) NaI, acetone, reflux, then KCN, DMF, rt; K_2CO_3, then 30% H_2O_2, DMSO, 0 °C to rt, 13%.

The synthesis of **26** required a modification of the method shown in Scheme 2. Ester **24** appeared to undergo loss of chlorine in reductions involving zinc/acetic acid or hydrogenation. A Lipshutz modification of a Stryker reagent[33] gave clean reduction to **25**. Superhydride reduction gave the chlorinated alcohol **26**. Bis-amide **27** was made (Scheme 4) to test the need for both benzylic amines. Following literature precedent[34,35] the bis-nitrile was made by conversion of **10** to the chloride, then the iodide, then the nitrile. Basic hydrogen peroxide gave the bis-amide **27**.

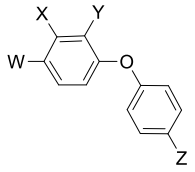
Compounds **28** through **41** in Table 2 were made by reductive amination followed by nitrile reduction with superhydride as shown in Scheme 5.

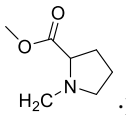
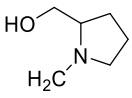
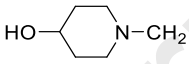
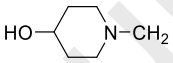
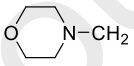
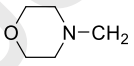
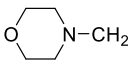
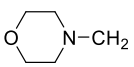


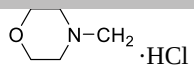
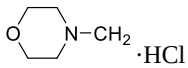
1a X, Y = H
1b X = H, Y = Cl
1c X = Cl, Y = H

Scheme 5. Synthesis of diphenyl ether analogs **28** through **47**. Reagents, conditions, and yields: (a) amine, $NaHB(OAc)_3$, DCM or DCE, rt*; (b) $LiBH_4$, $LiEt_3BH$, THF, rt*. *See experimental section for individual reaction yields.

Table 2. *T. b. rhod.* activity and L6 cell cytotoxicity of diphenyl ether derivatives **28**–**41**.

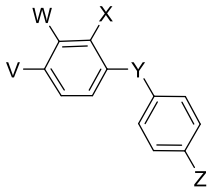


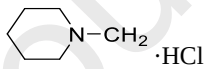
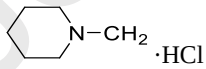
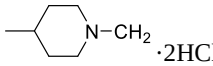
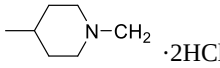
Compound	W	X, Y	Z	T. b. rhod. IC_{50} (μM) [SI]	L6 cytotoxicity IC_{50} (μM)
28	$EtO_2CCH_2NHCH_2$·HCl	H, Cl	CN	110	110
29	$HO_2CCH_2NHCH_2$·HCl	H, Cl	CN	110	210
30	$HO_2CCH_2NHCH_2$·HCl	H, Cl	CH_2NH_2·HCl	4.3	>250
31	$HOCH_2CH_2NHCH_2$·HCl	H, Cl	CH_2NH_2·HCl	3.12	52
32	 ·HCl	H, Cl	CN	140	48
33	 ·HCl	H, Cl	CH_2NH_2·HCl	2.9	38
34		H, Cl	CN	5.4 [18]	97
35		H, Cl	CH_2NH_2	12 [4]	53
36	 ·HCl	H, Cl	CN	>270	70
37	 ·HCl	H, Cl	CH_2NH_2·HCl	0.53 [152]	81
38	 ·HCl	Cl, H	CN	12	43
39	 ·HCl	Cl, H,	CH_2NH_2·HCl	1.1	45

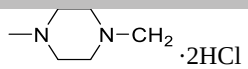
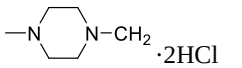
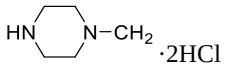
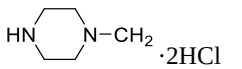
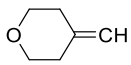
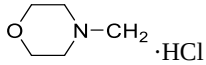
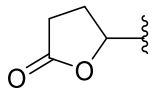
40		H, H	CN	7.5	110
41		H, H	CH_2NH_2·HCl	1.4 [86]	120

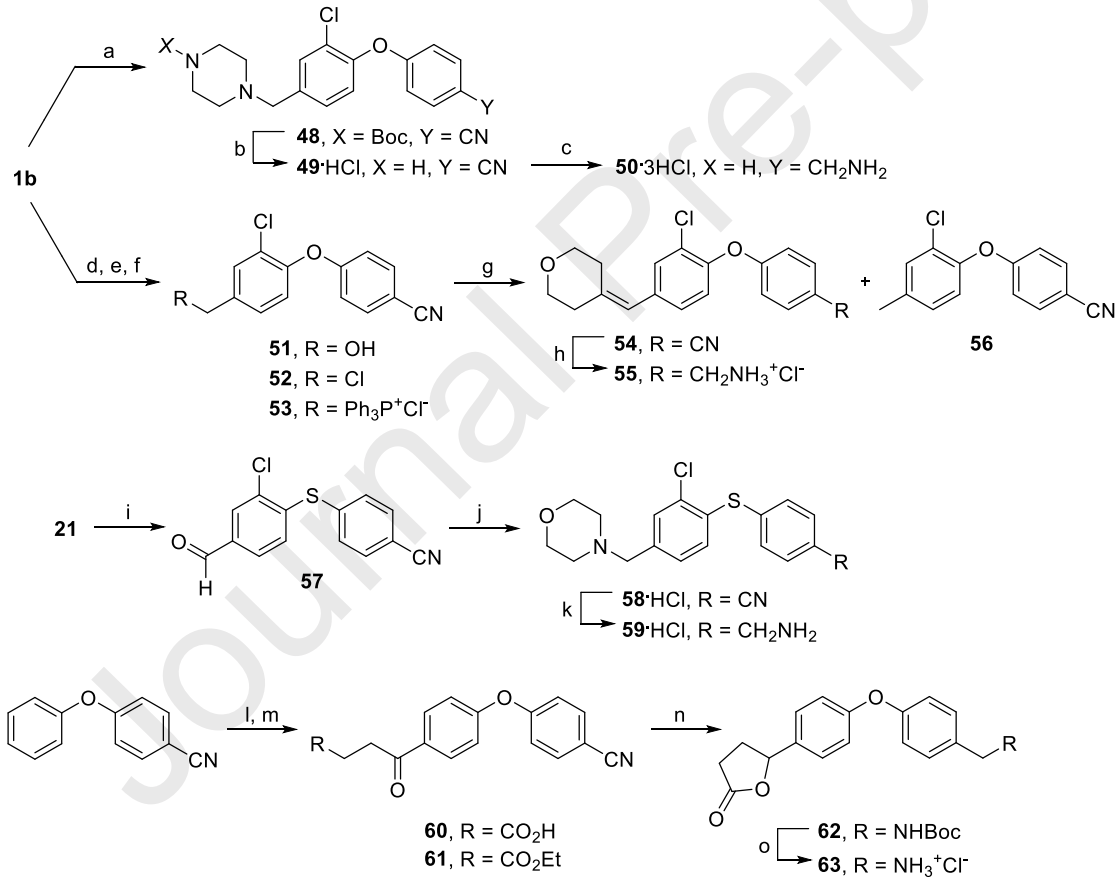
Variation of the aliphatic group of the molecule is shown in Table 3 and Scheme 6. The preparation of a diphenylsulfide, **59**, is also shown. Piperidine and N-methylpiperazine derivatives (**42** through **47**) were made by reductive amination of **1b**. The derivatives, **49** and **50** (Scheme 6) were prepared from Boc protected piperazine. The 4-tetrahydropyranidine compound **55** was formed by reduction of **1b** to **51** followed by treatment with concentrated HCl under phase transfer conditions to give the benzylic chloride **52**. Displacement of chlorine with triphenylphosphine produced salt **53**. Wittig olefination of **53** gave **54** and the hydrolysis product **56.** Subsequent superhydride reduction of **54** led to **55**. Treatment of 3-chloro-4-fluorobenzaldehyde with 4-mercaptobenzonitrile gave **57**. Reductive amination gave **58**. Superhydride reduction produced **59**. Compound **60** was derived from 4-phenoxybenzonitrile by Friedel Crafts reaction with succinic anhydride. Esterification of **60** gave **61** which was converted to the Boc protected amino lactone **62** by simultaneous reduction of the ketone and nitrile groups in a nickel catalyzed sodium borohydride system. Treatment with HCl/EtOAc produced the racemic lactone salt **63.**

Table 3. *T. b. rhod.* activity and L6 cell cytotoxicity of diphenyl ether derivatives with variable aliphatic ring variation.



Compound	V	W, X, Y	Z	T. b. rhod. IC_{50} (μM) [SI]	L6 cytotoxicity IC_{50} (μM)
42		H, Cl, O	CN	3.0	42
43		H, Cl, O	CH_2NH_2·HCl	0.92 [14]	13
44		H, H, O	CN	8.6	85
45		H, H, O	CH_2NH_2·3HCl	1.2 [63]	76

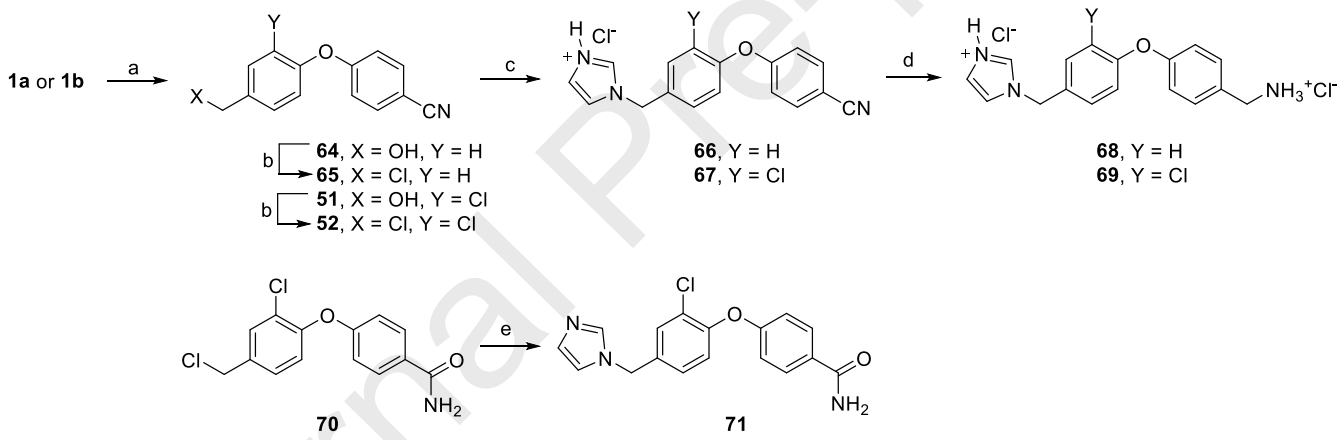
46	 ·2HCl	H, Cl, O	CN	3.4	36
47	 ·2HCl	H, Cl, O	CH_2NH_2·HCl	1.9	33
49	 ·2HCl	H, Cl, O	CN	1.5	37
50	 ·2HCl	H, Cl, O	CH_2NH_2·HCl	1.8	40
55		H, Cl, O	CH_2NH_2·HCl	0.43 [51]	22
59	 ·HCl	H, Cl, S	CH_2NH_2·HCl	0.33 [30]	10
63		H, H, O	CH_2NH_2·HCl	6.7[18]	120



Scheme 6. Methods for the synthesis of chemical intermediates and alicyclic ring derivatives. Reagents, conditions, and yields: (a) 1-boc-piperazine, $NaHB(OAc)_3$, DCE, rt, 1N NaOH, then CH_3OH/0.5 M HCl and Et_2O, 75%; (b) MsOH, THF, rt, then 10%

NaOH; CH_3OH/0.5 M HCl, 30%; (c) $LiBH_4$, $LiHBEt_3$, THF, rt, then 2N NaOH; CH_3OH/0.5 M HCl and Et_2O, 34%; (d) $NaBH_4$, EtOH, rt, then 2N NaOH, 97%; (e) conc HCl, *t*-Bu_4NHSO_4, rt, 93%; (f) Ph_3P, toluene, reflux, 18%; (g) LDA, tetrahydro-4*H*-pyran-4-one, THF, -78 °C, 46%; (h) $LiBH_4$, $LiHBEt_3$, THF, then 1N NaOH; EtOAc/CH_3OH/O.5 M HCl, 61%; (i) 3-chloro-4-fluorobenzaldehyde, K_2CO_3, DMA, 115 °C, 68%; (j) morpholine, $NaHB(OAc)_3$, CH_2Cl_2, rt, 60%; (k) $LiBH_4$, $LiHBEt_3$, THF, then 1N NaOH; EtOAc/O.5 M HCl in CH_3OH, 46%; (l) succinic anhydride, $AlCl_3$, 1,1,2,2-tetrachloroethane, 50 °C, 3M HCl then 2N NaOH, 46%; (m) CH_3COCl, EtOH, reflux, 97%; (n) Boc_2O, $NiCl_2$·6 H2O, $NaBH_4$, diethylenetriamine, CH_3OH, 0 °C, 60%; conc HCl, EtOAc, rt, 71%.

A series of imidazole derivatives (Table 4) were made as shown in Scheme 7. Reduction of aldehydes **1a** and **1b** gave the corresponding alcohols **51** and **64**. The alcohols were treated with concentrated HCl under phase transfer conditions to produce the benzylic chlorides **52** and **65**. Treatment of **64** with concentrated HCl gave **65** cleanly; however, **51** with the same reagent gave **52,** recovered starting material, and a small quantity of **70**. Treatment of **65**, **52** or **70** with imidazole in toluene gave **66**, **67**, and **71** respectively. Superhydride reduction of **66** and **67** generated analogs **68** and **69**.



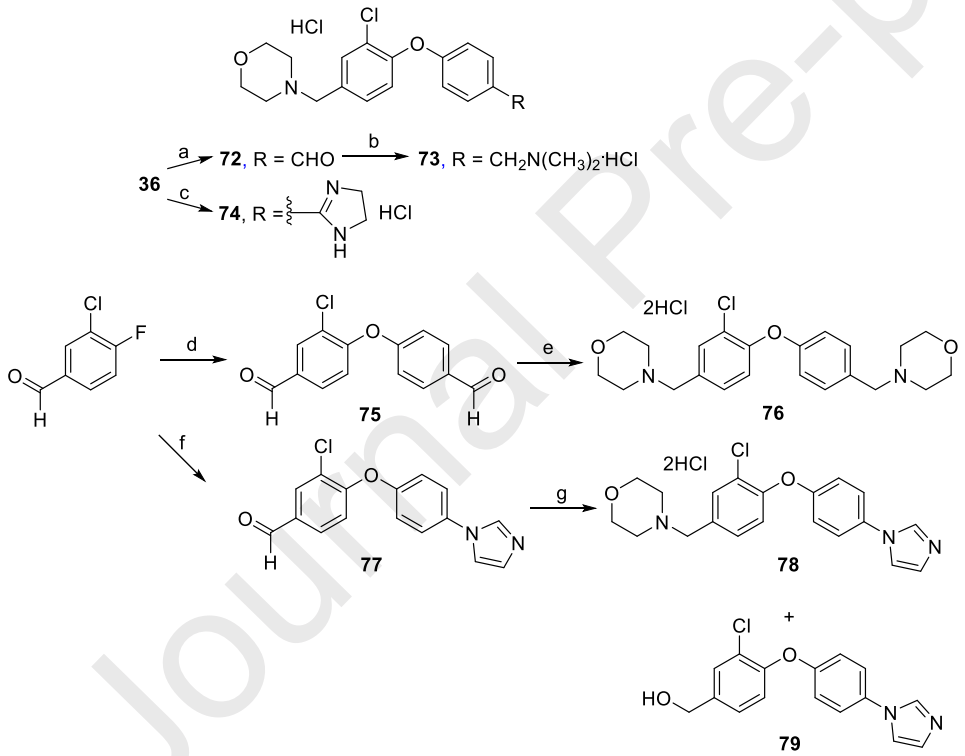
Scheme 7. Synthesis of diphenyl ether imidazole derivatives **66**–**69**, and **71**. Reagents, conditions, and yields: (a) $NaBH_4$, EtOH, rt, 36–93%*; (b) conc HCl, *t*-Bu_4NHSO_4, rt, 93–97%*; (c) imidazole, toluene, 83 °C, then EtOAc/HCl, 79–92%*; (d) $LiHB(Et)_3$, $LiBH_4$, THF, 20 °C, then 1N NaOH; then 0.5 M HCl in CH_3OH, 20–70%*; (e) imidazole, toluene, 90 °C, 49%. *See experimental section for individual reaction yields.

Table 4. *T. b. rhod.* activity and L6 cell cytotoxicity of diphenyl ether imidazole derivatives.

Compound	T. b. rhod.	L6 cytotoxicity
	IC_{50} (μM) [SI]	IC_{50} (μM)
66	13	82

67	12	12.5
68	4.3	12.4
69	2.7 [22]	59
71	5.55	15

Variations of the benzylic amine were synthesized as shown in Scheme 8. Potency and cytotoxicity results are shown in Table 5. DIBAL-H reduction of the nitrile **36** followed by reductive amination with dimethylamine hydrochloride gave **73**. Nitrile **36** was converted to imidazoline **74** upon treatment with ethylenediamine. Nucleophilic aromatic substitution of 4-fluoro-3-chloro-benzaldehyde with 4-hydroxybenzaldehyde gave **75**. Reductive amination with morpholine produced **76**. The imidazole derivative **77** was made from 3-chloro-4-fluorobenzaldehyde and 4-(1H-imidazol-1-yl)-phenol via nucleophilic substitution. Reductive amination with morpholine gave compound **78**. During the reductive amination of **77**, aldehyde reduction to **79** occurred to a small extent. Alcohol **79** was not significantly active against *T. b. rhodesiense*.



Scheme 8. Synthetic route for diphenyl ether derivatives with variation of the benzylic amine fragment. Reagents, conditions, and yields: (a) DIBAL-H, CH_2Cl_2, -45 °C, 89%; (b) $NaHB(OAc)_3$, DCE, rt, then 1N NaOH, then CH_3OH/0.5 M HCl and EtOAc, 42%; (c) ethylenediamine, NaHS, DMA, 120 °C, then conc HCl, 88%; (d) 4-hydroxybenzaldehyde, K_2CO_3, DMA, 115 °C, 86%; (e)

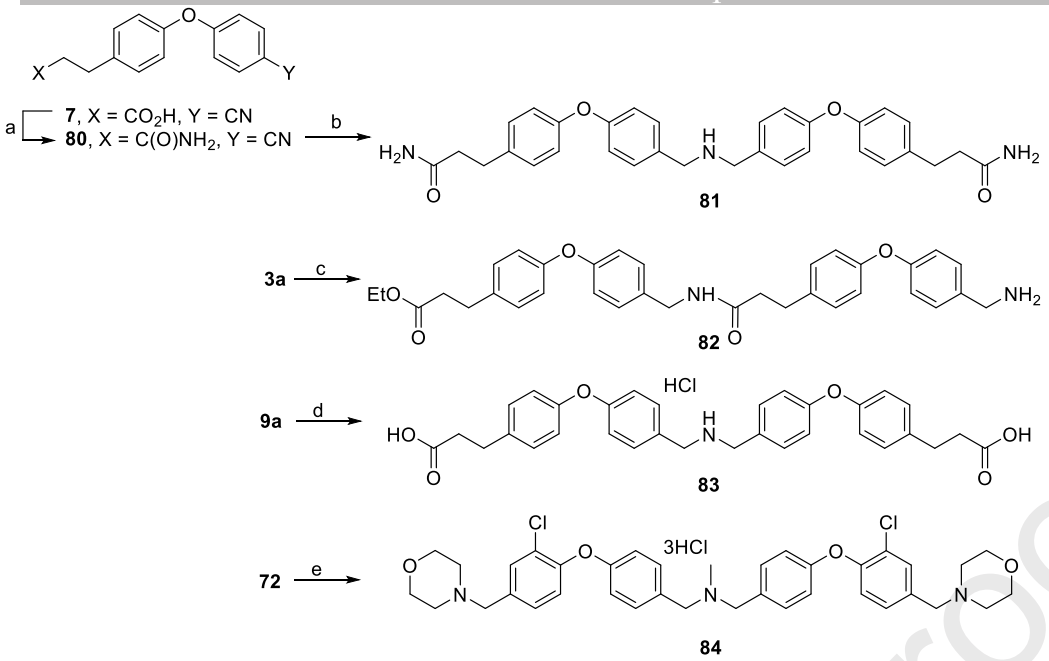
NaHB(OAc)$_3$, DCE, rt, 1N NaOH, then CH_3OH/0.5 M HCl and Et_2O, 72%; (f) 4-(1*H*-imidazol-1-yl)phenol, K_2CO_3, DMA, 115 ^oC, 65%; (g) NaHB(OAc)$_3$, DCE, rt, then 1N NaOH, then CH_3OH/0.5 M HCl and EtOAc, 26%.

Table 5. *T. b. rhod.* activity and L6 cell cytotoxicity of diphenyl ether derivatives with variation of the benzylic amine portion.

Compound	T. b. rhod.	L6 cytotoxicity
	IC_{50} (μM)	IC_{50} (μM)
73	13.7	123
74	4.5	53
76	11	56
78	18	26
79	43	ND[a]

[a]Not determined

A number of bulky amines (Table 6) were isolated during the course of this study. Reaction of **9a** with HCl in EtOAc gave **9b** (Scheme 1). Cyano amide **80** was made from **7** via ammonia attack on the succinoyl active ester (Scheme 9). Amino diamide **81** was isolated as a byproduct from hydrogenation of cyano amide **80**. Amine **82** formed over a long period of time at room temperature from neat amino ester **3a**. The dicarboxylic acid ammonium salt **83** was obtained by hydrolysis of **9a**, which itself was a byproduct of hydrogenation of **2** (Schemes 2 and 9). Tertiary amine **84** was formed from **72** via reductive amination.

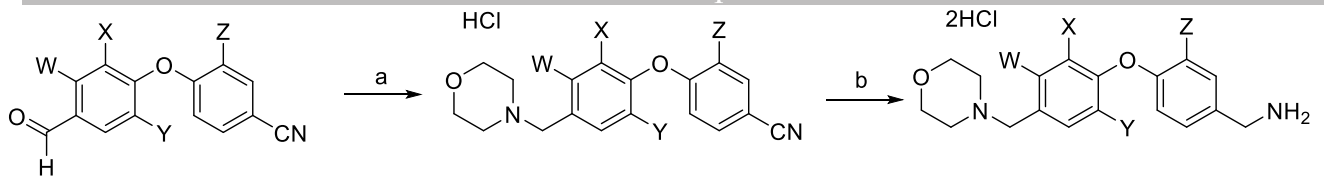


Scheme 9. Synthesis of bulky byproduct amines **81**–**84**. Reagents, conditions, and yields: (a) N-hydroxysuccimide/CH_3CN, then EDCI, then H_2O, then conc NH_3 (aq), rt, 78%; (b) conc NH_3 (aq), H_2, EtOH, rt, 6%; (c) formed as a byproduct of **3a** after 6 months, 9%; (d) 2 N NaOH, EtOH, rt, then conc HCl, 79%; (e) $NaHB(OAc)_3$, DCE, rt, then CH_2Cl_2/0.5 M HCl and Et_2O, 38%.

Table 6. *T. b. rhod.* activity and L6 cell cytotoxicity of large diphenyl ether amine dimers.

Compound	T.b.rhod.	L6 cytotoxicity
	IC_{50} (μM)	IC_{50} (μM)
9b	12	27
81	14	>190
82	2.4	38
83	83	>180
84	2.6	13

The halogenated derivatives of Table 7 were generated from compounds **1b**, **1d**, **1e**, **1f**, and **1g** by reductive amination with morpholine followed by superhydride reduction (Scheme 10).



1b, W, Y, Z = H, X = Cl
1d, W, Y, Z = H, X = F
1e, W, Y, Z = H, X = Br
1f, W, Z = H, X, Y = F
1g, W, Y = H, X = Cl, Z = F

36, W, Y, Z = H, X = Cl
85, W, Y, Z = H, X = F
87, W, Y, Z = H, X = Br
89, W, Y = H, X = Cl, Z = F
91, W, Z = H, X, Y = F

37, W, Y, Z = H, X = Cl
86, W, Y, Z = H, X = F
88, W, Y, Z = H, X = Br
90, W, Y = H, X = Cl, Z = F
92, W, Z = H, X, Y = F

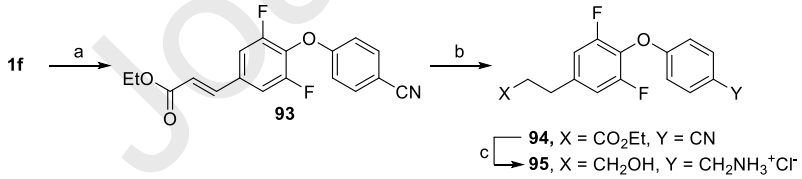
Scheme 10. Synthesis of halogenated cyanobiphenyl ether morpholines from cyanobiphenyl aldehdye intermediates followed by reductive amination to give benzyl amine products. Reagents, conditions, and yields: (a) morpholine, $NaHB(OAc)_3$, DCE, rt, 51–96%*; (b) $LiHB(Et)_3$, $LiBH_4$, THF, rt , 41–81%*. *See experimental section for individual reaction yields.

Table 7. *T. b. rhod.* activity and L6 cell cytotoxicity of halogenated morpholine derivatives and alcohol derivative **95**.

Compound	*T. b. rhod.*	L6 cytotoxicity
	IC_{50} (μM) [SI]	IC_{50} (μM)
37	0.53 [150]	81
86	0.71 [180]	124
88	1.24 [64]	80
90	0.88 [22]	19
92	0.16 [750]	120
95	11.0	ND[a]

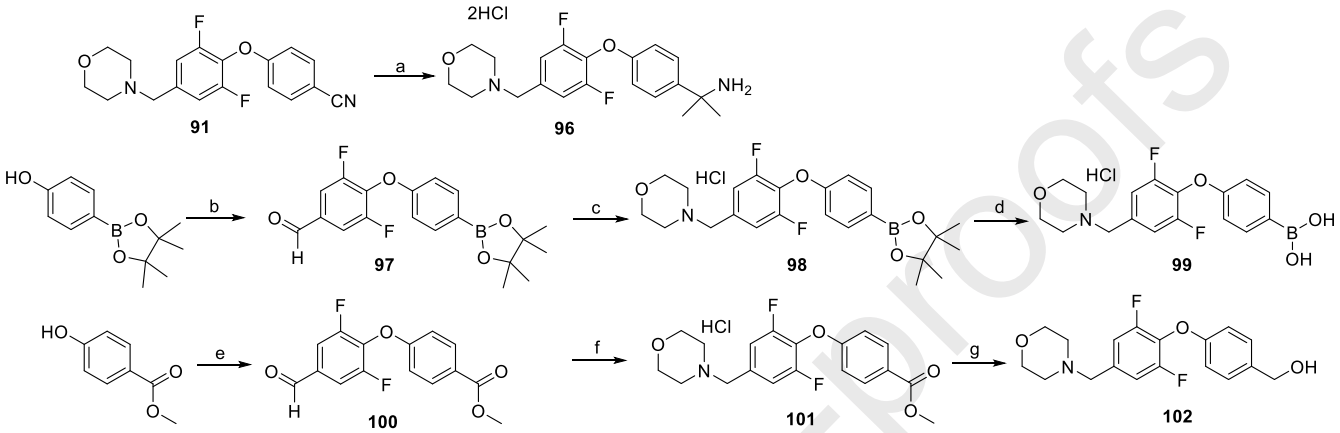
[a]Not determined

In light of the improved activity seen with difluorination in the morpholinyl series, **95**, the difluoro variant of the mono-chlorinated hydroxpropyl **26**, was prepared using the same sequence used to make **26** (Scheme 11).



Scheme 11. Three step synthesis of difluoro benzyl amine **95** from **1f**. Reagents, conditions, and yields: (a) triethyl phosphonoacetate, NaH, THF, 60 °C, 37%; (b) $Cu(OAc)_2{\cdot}H_2O$, 1,2-BDP, PMHS, *t*-BuOH, toluene, rt, 59%; (c) $LiBH_4$, $LiEt_3BH$, THF, rt, then 10% NaOH, then CH_3OH/ 0.5 M HCl, 20%.

An additional group of difluoro compounds is reported in Table 8. These compounds were made according to Scheme 12. The geminal dimethylamine **96** was prepared by reaction of **91** with an organocerium reagent followed by hydrolysis. The boronate ester **97** was prepared from **1f** and a known phenolic boronate by nucleophilic aromatic substitution. Reductive amination of **97** with morpholine gave **98**. This boronate ester was cleaved by brief reaction with $NaIO_4$ to form boronic acid **99**. Methyl 4-hydroxybenzoate and **1f** gave **100** by nucleophilic aromatic substitution. Reductive amination of **100** with morpholine gave morpholine salt **101**. Reduction of **101** with $LiAlH_4$ and subsequent basification generated alcohol **102**.



Scheme 12. Synthetic route for difluoro diphenyl ether morpholine derivatives **96**, **99**, and **102**. Reagents, conditions, and yields: (a) $CeCl_3$, MeLi, THF, -78 °C, then rt 3 days, then 0.5 M HCl/MeOH; 62 %;(b) **1f**, K_2CO_3, DMF, 80 °C 11 h, then 93 °C, 6 h; 70% (c) morpholine, $NaHB(OAc)_3$, DCM, rt, 2 h, then 0.5 M HCl/MeOH, 72%; (d) $NaIO_4$, 1 M HCl (aq), THF, rt, 11 min, then 0.5 M HCl, 75%; (e) **1f**, K_2CO_3, DMF, 80 °C, 11 h, then 93 °C, 3.5 h, 80%; (f) morpholine, $NaHB(OAc)_3$, DCM, rt, 1 h, then 0.5 M HCl/MeOH, 68%; (g) $LiAlH_4$, THF, reflux, 1.5 h, 100%.

Table 8. *T. b. rhod.* activity and L6 cell cytotoxicity of difluoro diphenyl ether morpholine derivatives **96**, **99,** and **102**.

Compound	*T. b. rhod.* IC_{50} (μM)	L6 cytotoxicity IC_{50} (μM)
96	5.6	110
99	22	22
102	127	160

3. Discussion

A set of alkyl side chain derivatives (Table 1) revealed activity for various benzylic ammonium salts. The three-carbon alcoholic side chain in **6** gave maximum activity in this series. The corresponding ester **3b** and carboxylic acid **4** were somewhat less active. The dihydroimidazoline **8** was much less active than **4**, a fact of some interest since amidines are a feature of pentamidine and have appeared in much published work as reviewed above. Analogues **20** and **23** with one carbon alcohol-terminated side

chains, retain some activity with the sulfide **23** somewhat more active than **20**. The two-carbon alcohol-terminated **11** is less active than either **20** or **23**. The methyl ether **17**, made from **11**, shows somewhat improved activity and is less toxic than **11**. Ether **17** shows better selectivity than **20** or **23**. The benzyl ether, **18**, is also more active than **11** but is more toxic. The most cytotoxic material in this series was the cyanophosphonate **13**. Chlorinated **26** gave improved activity compared to **6** albeit with increased toxicity. The bis-amide **27** was not active and indicated that a benzylic amine is needed on the right side of the molecule for activity.

A series of diamino compounds is shown in Table 2. Once again, the benzylic ammonium salts show better activity than their nitrile precursors with one exception. The nitrile **34** with a 4-hydroxypiperidine terminus is unusual in showing more activity than the free amine **35**. Of the benzylic ammonium salts the best activity, 0.53 μM, occurs with the morpholine derivative **37** which represents an improvement compared to the 0.96 μM activity of **6** in Table 1. However, **37** shows less selectivity than **6**. The isomeric morpholine **39** and the non-chlorinated derivative **41** are also active but less so than **37**. Interestingly, the cyano precursors to these amines, **38** and **40**, show better activity than is typical in this series with the exception of **34**.

Structural modifications to the aliphatic ring of the molecule are shown in Table 3. The 4-tetrahydropyranilidiene group **55** gave improved activity but increased toxicity significantly compared to the acyclic analogue **6**. The piperidine, pyrazine, and N-methylpyrazine variations (**42** through **50**) did not give more active compounds and were more toxic than **37**. The sulfur analogue of **34** reported here (**59**) is more active but shows the greatest toxicity in the series. Lactone **63** showed modest activity against *T. b. rhodesiense*.

The imidazole analogues of Table 4 did not show improvement in activity. The best of these, **69**, with 2.7 μM activity (SI = 22) has a chloro substituent ortho to the aryl ether and is a benzylic amine. Table 5 shows compounds in which the benzyl amine is replaced by an amidine or tertiary amines. An increase in size of the amine gives uniformly reduced activity. Table 6 shows a collection of larger amines. Two of these, **81** and **83**, are not significantly active, but **82** shows modest 2.4 μM activity.

Since the presence of chlorine gave improved activity in both the acyclic alcohol **26** and the morpholinyl derivative **37** compared to the halogen free parent compounds, and since saturated cyclic moieties seemed to improve activity, we prepared another series of halogenated compounds. The activities of these compounds are compared to **37** in Table 7. When fluorine was substituted for chlorine (**86)** the selectivity increased. However, bromine substitution for chlorine (**88)** gave reduced selectivity. Fluoro substitution on the opposite ring (**90**) was deleterious to selectivity. Difluoro substitution (**92**) gave significant improvement in activity with less toxicity (SI = 750 against the L6 cell line).

Unfortunately, the activity of the difluoro variant **95** (11 μM) was considerably reduced compared to that of our original 3-hydroxypropyl lead **6 (**0.49 μM). This loss of activity in **95** is surprising if one presumes some binding interaction around the fluorine atoms. Perhaps the better activity that the fluorine substituents impart to **92** might be due simply to decreased basicity at the morpholine nitrogen.

We made difluoronated morpholino compounds with and without the benzyl amine (Table 8). Dimethylation at the benzylic position drops activity significantly (**96)**. Replacing the benzylic amine entirely with a boronic acid group (**99)** or with the corresponding alcohol **(102)** dropped the activity even more.

The most active compounds were submitted to toxicity tests against four different human cells (Table 9). The best compound shows an SI of 750 against rat myoblast L6 and an SI >1000 against these human cell lines. Our more active compounds against *T. b. rhodesiense* are compared to other protozoans in Table 10 and to *Toxoplasma gondii*. All compounds in Table 10 are less active against *T. cruzi*, *L. donovani* and *P. falciparum* than against *T. b. rhodesiense*. Against *T. gondii*, **92** also showed the best activity but negligible activity against *L. donovani* amastigotes. This may indicate possible stage specificity which bears further investigation.

Table 9. Effect of lead compounds tested for toxicity against four human cell lines and corresponding SI values.

Compound	*T. b. rhod.* IC_{50} (μM)	HFF IC_{50} (μM) [SI]	U-2 OS IC_{50} (μM) [SI]	HC-04 IC_{50} (μM) [SI]	HEK293 IC_{50} (μM) [SI]
6	0.96	NR [>420]	NR [>420]	NR [>420]	
26	0.49	>200 [410]	>200 [410]	>200 [410]	150 [300]
37	0.53	400 [750]	320 [600]	300 [570]	
39	1.1	400 [360]	NR [> 360]	NR [> 360]	
41	1.4	NR [>290]	NR [>290]	NR [>290]	
55	0.42	>200 [480]	184.7 [440]	178.0 [424]	150 [360]
59	0.33	184.8 [560]	149.0 [450]	128.0 [390]	148 [55]
68	2.7	NR [>150]	NR [>150]	NR [>150]	
92	0.16	>200 [1200]	>200 [1200]	>200 [1200]	160 [1000]

NR= Not Reached at Concentrations up to 400μM
HFF: human foreskin fibroblasts
HC-04: human liver cell line
U-2 OS: human bone marrow cell line
HEK293 (Human Embryonic Kidney Cell Line)

Table 10. Activity of lead compounds compared with a panel of other parasitic protozoans.

Compound	*T. b. rhod.* IC_{50} (μM)	*T. cruzi* IC_{50} (μM)	*L. don. ax am* IC_{50} (μM)	*P. falc NF54* IC_{50} (μM)	L6 IC_{50} (μM)	RH-dTom IC_{50} (μM)
6	0.96	71	184	11	170	NR
26	0.49	40	201	7.6	49	29.2
37	0.53	72	151	16	81	48.12

39	1.1	62	>247	12	45	NR
41	1.4	129	>269	8.3	120	NR
55	0.42	14	66	8.7	22	31.5
59	0.33	5.2	56	1.2	10	21.0
92	0.16	44	>246	21	120	12.1

RH-dTom: Toxoplasma gondii strain RH

4. Conclusion

We have shown herein an extensive SAR on a series of diphenylethers active against *T.b. rhodesiense* with our best lead compound being the difluorinated double salt **92**. It shows an SI of 750 against rat myoblast L6 and > 1000 against four human cell lines. The monochloro derivative **26** shows poorer selectivity (100) compared to our simple lead **6** (177) against the L6 line. Both show comparable selectivity (~410) against these human cell lines. In contrast, against the L6 line, chlorine substituted **37** shows better selectivity (152) than the unsubstituted compound **41** (86). The greater selectivity of **37** vs. **41** is also seen against human cell lines (~ 600 vs ~ 300 respectively). Selectivity data using the L6 cell line is available for the HAT drugs melarsoprol (5800), pentamidine isethionate (15,000), and suramin (2,100). Our lead **92** falls short by this metric; however, the low toxicity against human cells lines is promising and will guide ongoing identification of more effective antitrypanosomal diphenyl ethers.

5. Experimental

5.1. General.

Melting points are uncorrected. IR were obtained on a Perkin-Elmer Spectrum 100 FT-IR in ATR mode. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AVIII-HD 400 MHz spectrometer. All chemical shifts are reported in parts per million and are relative to TMS (0.0 ppm, 77.0 ppm) for proton and carbon spectra respectively in chloroform-d_1 and to DMSO- d_6 for proton (2.50 ppm) and carbon NMR (39.52 ppm). GC-MS analysis was conducted on an Agilent 7890A-GC with 5975C VL MSD. Target compounds show 95% or greater purity by combustion analyses or by NMR. Combustion analyses were done by M-H-W Laboratories. High resolution mass spectra were obtained from the Midwest Center for Mass Spectrometry. Preparative chromatography was done using the flash method[36] or by Biotage preparative chromatography. Unless otherwise noted, reagents were purchased from Acros Organics and used as obtained.

5.2. Protozoan panel

In vitro antiprotozoal activity was measured using the STIB 900 strain of *T. brucei rhodesiense* (trypomastigotes stage), the MHOM-ET-67/L82 strain of *L. donovani* (axenic grown amastigotes), the *Tulahuen* C4 strain of *T. cruzi* (amastigotes stage), and the NF54 strain of *Plasmodium falciparum* (IEF stage).

5.2.1 Activity against Trypanosoma brucei rhodesiense STIB900. This stock was isolated in 1982 from a human patient in Tanzania and after several mouse passages cloned and adapted to axenic culture conditions.[37] Minimum Essential Medium (50 µl) supplemented with 25 mM HEPES, 1g/l additional glucose, 1% MEM non-essential amino acids (100x), 0.2 mM 2-mercaptoethanol, 1mM Na-pyruvate and 15% heat inactivated horse serum was added to each well of a 96-well microtiter plate. Serial drug dilutions of eleven 3-fold dilution steps covering a range from 100 to 0.002 µg/ml were prepared. Then 4x103 bloodstream forms of *T. b. rhodesiense* STIB 900 in 50 µl was added to each well and the plate incubated at 37 °C under a 5% CO_2 atmosphere for 70 h. 10 µl Alamar Blue (resazurin, 12.5 mg in 100 ml double-distilled water) was then added to each well and incubation continued for a further 2–4 h.[38] Then the plates were read with a Spectramax Gemini XS microplate fluorometer (Molecular Devices Cooperation, Sunnyvale, CA, USA) using an excitation wave length of 536 nm and an emission wave length of 588 nm. Data were analyzed with the graphic programme Softmax Pro (Molecular Devices Cooperation, Sunnyvale, CA, USA), which calculated IC_{50} values by linear regression[39] and 4-parameter logistic regression from the sigmoidal dose inhibition curves. Melarsoprol (Arsobal Sanofi-Aventis, received from WHO) is used as control.

5.2.2 Activity against T. cruzi. Rat skeletal myoblasts (L-6 cells) were seeded in 96-well microtiter plates at 2000 cells/well in 100 µL RPMI 1640 medium with 10% FBS and 2 mM L-glutamine. After 24 h the medium was removed and replaced by 100 µl per well containing 5000 trypomastigote forms of *T. cruzi* Tulahuen strain C2C4 containing the β-galactosidase (Lac Z) gene.[40] After 48 h the medium was removed from the wells and replaced by 100 µl fresh medium with or without a serial drug dilution of eleven 3-fold dilution steps covering a range from 100 to 0.002 µg/ml. After 96 h of incubation, the plates were inspected under an inverted microscope to assure growth of the controls and sterility. Then the substrate CPRG/Nonidet (50 µl) was added to all wells. A color reaction developed within 2–6 h and could be read photometrically at 540 nm. Data were analyzed with the graphic programme Softmax Pro (Molecular Devices), which calculated IC_{50} values by linear regression (Huber 1993) and 4-parameter logistic regression from the sigmoidal dose inhibition curves. Benznidazole is used as control (IC_{50} 0.5±0.2 µg/ml).

5.2.3 Activity against L. donovani axenic amastigotes. Amastigotes of *L. donovani* strain MHOM/ET/67/L82 are grown in axenic culture at 37 °C in SM medium (Cunnigham et al. 1977) at pH 5.4 supplemented with 10% heat-inactivated fetal bovine serum under an atmosphere of 5% CO_2 in air. 100 µl of culture medium with 10^5 amastigotes from axenic culture with or without a serial

drug dilution are seeded in 96-well microtiter plates. Serial drug dilutions of eleven 3-fold dilution steps covering a range from 100 to 0.002 µg/ml are prepared. After 70 h of incubation the plates are inspected under an inverted microscope to assure growth of the controls and sterile conditions. 10 µl of Alamar Blue (12.5 mg resazurin dissolved in 100 ml distilled water) are then added to each well and the plates incubated for another 2 h. Then the plates are read with a Spectramax Gemini XS microplate fluorometer (Molecular Devices Cooperation, Sunnyvale, CA, USA) using an excitation wave length of 536 nm and an emission wave length of 588 nm. Data are analyzed using the software Softmax Pro (Molecular Devices Cooperation, Sunnyvale, CA, USA). Decrease of fluorescence (= inhibition) is expressed as percentage of the fluorescence of control cultures and plotted against the drug concentrations. From the sigmoidal inhibition curves the IC_{50} values are calculated.

5.2.4 Activity against P. falciparum. In vitro activity against erythrocytic stages of *P. falciparum* was determined using a 3H-hypoxanthine incorporation assay[41,42], using the drug sensitive NF54 strain[43] and the standard drugs chloroquine (Sigma C6628) and artesunate (Sigma A3731). Compounds were dissolved in DMSO at 10 mg/ml and further diluted in medium before added to parasite cultures incubated in RPMI 1640 medium without hypoxanthine, supplemented with HEPES (5.94 g/l), $NaHCO_3$ (2.1 g/l), neomycin (100 U/ml), AlbumaxR (5 g/l) and washed human red cells A+ at 2.5% haematocrit (0.3% parasitaemia). Serial drug dilutions of eleven 3-fold dilution steps covering a range from 100 to 0.002 µg/ml were prepared. The 96-well plates were incubated in a humidified atmosphere at 37 °C; 4% CO_2, 3% O_2, 93% N_2. After 48 h 50 µl of 3H-hypoxanthine (=0.5 µCi) was added to each well of the plate. The plates were incubated for a further 24 h under the same conditions. The plates were then harvested with a Betaplate™ cell harvester (Wallac, Zurich, Switzerland), and the red blood cells transferred onto a glass fibre filter then washed with distilled water. The dried filters were inserted into a plastic foil with 10 ml of scintillation fluid, and counted in a Betaplate™ liquid scintillation counter (Wallac, Zurich, Switzerland). IC_{50} values were calculated from sigmoidal inhibition curves by linear regression (Huber 1993) using Microsoft Excel. Chloroquine and artemisinin are used as control.

5.3. Cytotoxicity Assay

5.3.1 In vitro cytotoxicity with L-6 cells.[44] Assays were performed in 96-well microtiter plates, each well containing 100 µl of RPMI 1640 medium supplemented with 1% L-glutamine (200mM) and 10% fetal bovine serum, and 4000 L-6 cells (a primary cell line derived from rat skeletal myoblasts).[45,46] Serial drug dilutions of eleven 3-fold dilution steps covering a range from 100 to 0.002 µg/ml were prepared. After 70 hours of incubation the plates were inspected under an inverted microscope to assure growth of the controls and sterile conditions. 10µl of Alamar Blue was then added to each well and the plates incubated for another 2 hours. Then the plates were read with a Spectramax Gemini XS microplate fluorometer (Molecular Devices Cooperation, Sunnyvale, CA, USA)

using an excitation wave length of 536 nm and an emission wave length of 588 nm. The IC_{50} values were calculated by linear regression (Huber 1993) and 4-parameter logistic regression from the sigmoidal dose inhibition curves using SoftmaxPro software (Molecular Devices Cooperation, Sunnyvale, CA, USA). Podophyllotoxin (Sigma P4405) is used as control.

5.3.2 Cytotoxicity IC_{50} Assay on Human Cell Lines: Compounds were screened for toxicity against host cell lines grown in 96 well plates, and assessed for viability with Alamar blue as previously reported (Pubmed ID 29081387). Cultured host cells were human foreskin fibroblasts (HFF), U-2 OS osteosarcoma cells, and HC-04 hepatocytes.

5.4. Toxoplasma IC_{50}

Toxoplasma gondii strain RH IC_{50}'s were assessed with a fluorescent plate reader following infection of foreskin fibroblast cells in 96 well plates, as previously described (Pubmed ID 29081387).

5.5. General Procedures for nitrile reductions

5.5.1. Method A. Nitrile ammonium salt reduction. To the nitrile salt (0.676 mmol) in anhydrous THF (2 mL) under nitrogen with stirring was added a 4 M THF solution of $LiBH_4$ (0.21 mL, 0.831 mmol), and then after 5 min a 1.7 M THF solution of $LiHBEt_3$ (0.89 mL, 1.51 mmol). After 2 days at rt 2 M NaOH (6 mL) was added and the solution was then stirred for 45 minutes. The solution was then extracted with EtOAc (3 x 25 mL). The organic phase was washed with brine, dried over $MgSO_4$, filtered, and then the solvent removed by rotary evaporation.

5.5.2. Method B. Hydroxy nitrile reduction. To a solution of the hydroxy nitrile(1.43 mmol) in anhydrous ether (2.5 mL, Fischer) and anhydrous THF (0.5 mL, Aldrich) under a nitrogen atmosphere was added 4 M LiBH4 in THF (0.726 mL, 2.90 mmol) followed by 1 M lithium $LiHBEt_3$ in THF (1.72 mL, 1.72 mmol, Alfa Aesar). The resulting mixture was stirred at rt for 24 hours before a second addition of 1 M $LiHBEt_3$ in THF (1.15 mL, 1.15 mmol) was added. The reaction was allowed to stir for another 24 hours at rt. Then the mixture was diluted with ether (15 mL), NaOH (3M, 2.5 mL) was added and the mixture then was stirred for 30 minutes. More NaOH (2.5 mL) was added and the two layers were separated. The organic layer was then washed with distilled water (2 x 2.5 mL) followed by brine (2 x 2.5 mL). The organic layer was dried with $MgSO_4$ and filtered. The filtrate was acidified with 12 M HCl. This solution was concentrated by rotary evaporation until a white precipitate formed which was collected by filtration.

5.5.3. Method C. Ester nitrile reduction. To the ester nitrile (1.00 mmol) under nitrogen was added anhydrous THF (4 mL), a 4 M solution of $LiBH_4$ in THF (0.55 mL, 2.20 mmol) and a 1.7 M solution of $LiHBEt_3$ in THF (0.3 mL, 0.500 mmol). After 4.5 h of stirring at rt additional $LiHBEt_3$ (1.2 mL, 2 mmol) was added. After an additional 19.5 h of stirring 2 M NaOH (6 mL) was added.

After 1 h of stirring the mixture was diluted with water (14 mL), extracted with DCM (3 x 20 mL), and then dried over Mg_2SO_4. The solution was filtered and then the solvent removed by rotary evaporation to give the crude amine.

5.5.4. Method D. for hydroxy nitrile ammonium salt substrates Method B was followed with one additional mole equivalent of $LiBH_4$.

5.5.5. Method E. for ester nitrile ammonium salt substrates Method C was followed with one additional mole equivalent of $LiBH_4$.

General Procedures for Reductive Aminations

5.5.6. Method F. for neutral amine substrates. The direct amination procedure (Method l) of Abdel-Magid et al. was followed using either DCM or DCE as solvent.[47]

5.5.7. Method G. for hydrochloride substrates. Method F was followed with one equivalent of triethylamine added before addition of the reductant.

5.6 Procedures and Spectral Data

5.6.1. 4-(4-Formylphenoxy)benzonitrile **1a**.

A literature procedure was followed (Li et al.) IR (neat, cm^{-1}): 3100, 2854, 2747, 1693, 1584, 1493, 1109, 831, 854. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.28 (AA', 2H), 7.30 (AA', 2H), 7.93 (BB', 2H), 8.00 (BB', 2H), 9.99 (s, 1H); ^{13}C NMR (100 MHz, $CHCl_3$-d_1) δ 107.5, 118.3, 119.3, 119.5, 132.0, 132.6, 134.3, 159.4, 160.4, 190.5; GS-MS t_r, = 10.50 m/z = 121.0.

5.6.2. 4-(2-Chloro-4-formylphenoxy)benzonitrile **1b**.

A variation of a literature procedure was employed.[48] A mixture of 4-hydroxybenzonitrile (5.00 g, 0.042 mol), 3-chloro-4-fluoro-benzaldehyde (6.433 g, 0.0406 mol), and anhydrous K_2CO_3 (5.805 g, 0.042 mol) were heated to 110 °C in DMA (30 mL) for 10 h. The reaction mixture was poured into 10% NaOH (6 mL) containing 25 g of ice. The residual material was transferred with water giving a solution volume of 75 mL. A solid formed while the mixture was stirred. Suction filtration produced a dull yellow crude solid (9.369 g, 91%). mp 83.0–85.0 °C (lit 85.1–87.3 °C). The spectra matched the literature and the compound was used without further purification.

5.6.3. 4-(3-Chloro-4-formylphenoxy)benzonitrile **1c**.

The compound is reported in a patent.[49] A mixture of 4-hydroxybenzonitrile (5.00 g, 0.042 mol), 2-chloro-4-fluorobenzaldehyde (6.347 g, 0.040 mol), and anhydrous K_2CO_3 (5.805 g, 0.042 mol) was heated in DMA (30 mL) in an oil bath (133–155 °C) for 2.5 h. When cool, the reaction was transferred to a 400 mL beaker with 2.5 M NaOH (70 mL). To this mixture was added water (50 mL) and ice (50 g). After stirring the light tan solid was collected by suction filtration. After drying in a vacuum oven a brown-orange solid (10.1g, 98%) was obtained. Purification of a 2 g sample by Kugelrohr distillation (190-243 °C, 0.05 mm Hg) gave mostly white solid with some yellow contamination (1.82 g, 89%) and a black residue (0.174 g). Recrystallization from DCM or

EtOH did not significantly improve the purity. mp (from EtOH) 105.5−107.1 °C. IR (neat, cm^{-1}) 3098, 3064, 3047, 2893, 2233, 1681, 1607, 1587, 1502, 1481, 1225, 921, 850, 821, 790. ^{1}H NMR (400 MHz, $CHCl_3$-d_1) δ 7.02 (ddd, J = 8.6, 3.4, 0.75 Hz, 1H), 7.03 (d, J = 2.3 Hz, 1H), 7.15 (AA', 2H), 7.72 (BB', 2H), 7.97 (d, J = 8.6 Hz, 1H), 10.4 (d, J = 0.77 Hz, 1H); ^{13}C NMR (100 MHz, (400 MHz, $CHCl_3$-d_1) δ 108.2, 117.6, 118.1, 120.1, 128.7, 131.4, 134.2, 134.7, 158.7, 160.8, 188.2 The product was used without further purification.

5.6.4. 4-(2-Fluoro-4-formylphenoxy)benzonitrile **1d.**

A mixture of 3,4-difluorobenzaldehyde (5.68 g, 0.040 mol), 4-hydroxybenzonitrile (5.00 g, 0.042 mol), and K_2CO_3 (5.805 g, 0.042 mol) in DMA (31 mL) under nitrogen was heated with stirring at 115 °C for 5 h. The mixture was poured onto ice (25 g) and NaOH (10%, 6 mL). With stirring a solid appeared which was isolated and washed with water (7.245 g). The crude material was recrystallized from ethanol/water (6.38 g, 66%). mp 91−92 °C. IR (neat, cm^{-1}) 3069, 2842, 2738, 2228, 1696, 1614, 1595, 1497, 1274, 1226, 1168, 969, 949, 863, 836, 781, 747. ^{1}H NMR (400 MHz, $CHCl_3$-d_1): δ 7.03 (AA', 2H), 7.26 (t, J = 7.8 Hz, 1H), 7.68 (BB', 2H), 7.72 (ddd, J = 8.2, 1.9, 1.0 Hz, 1H), 7.76 (dd, J = 10.2, 1.9 Hz, 1H), 9.97 (d, J = 1.9 Hz, 1H). ^{13}C NMR (100 MHz, $CHCl_3$-d_1): δ 107.7, 117.4, 117.6, 118.0, 118.3, 122.2, 127.3, 127.4. 134.3, 134.4, 147.4, 147.5, 153.1, 155.6, 159.7, 189.4. Anal. Calcd for $C14H_8FNO2$: C, 69.71; H, 3.34; N, 5.81. Found: C, 69.90; H, 3.65; N 5.65.

*5.6.5. 4-(2-Bromo-4-formylphenoxy)benzonitrile **1e.***

Under nitrogen with stirring 3-bromo-4-fluorobenzaldehyde (8.12 g, 0.040 mol), 4-hydroxybenzonitrile (5.00 g 0.042 mol), and K_2CO_3 (5.805 g, 0.042 mol), in DMA (31 mL) were heated for 10 h. The mixture was poured into ice (25 g) and 10% NaOH (6 mL). EtOAc was added. The organic phase was extracted with water (3 x 30 mL) and then dried over MgSO4. After rotary evaporation a yellow oil (11.4 g) was obtained. The compound was recrystallized from EtOH/water to give the product (9.78 g, 81%). mp 79.5−80.0 °C. IR (neat, cm^{-1}) 3065, 3095, 2855, 2232, 1683, 1587, 1563, 1498, 1265, 150, 1165, 1038, 906, 896, 862, 811. ^{1}H NMR (400 MHz, $CHCl_3$-d_1): δ 7.07 (AA', 2H), 7.14 (d, J = 8.3 Hz, 1H), 7.69 (BB', 2H), 7.86 (dd, J = 8.3, 1.9 Hz, 1H), 8.21 (d, J = 1.9 Hz, 1H), 9.96 (s, 1H). ^{13}C NMR (100 MHz, $CHCl_3$-d_1): δ 107.8, 116.1, 118.3, 118.7, 121.0, 130.4, 134.2, 134.4, 135.6, 156.9, 159.3, 189.2. Anal. Calcd for $C14H_8BrNO2$: C, 55.66; H, 2.67; Br, 26.45; N 4.64. Found: C, 55.52; H, 2.80; Br, 26.55; N, 4.42.

5.6.6. 4-(2,6-Difluoro-4-formylphenoxy)benzonitrile **1f.**

3,4,5-trifluorobenzaldehye (5.395 g, 0.0337 mol, Oakwood Chemical), 4-cyanophenol (4.009 g, 0.0337 mol) and anhydrous K_2CO_3 (4.644 g, 0.0337 mol) were dissolved in DMF (26 mL) and then heated to 80 °C (oil bath temperature) with stirring under nitrogen. After 1.5 hours of stirring, the reaction mixture was cooled and then poured onto 16 g of ice containing NaOH (2.5 M, 1 mL). The precipitate was collected by suction filtration and washed with water. The solid dissolved in EtOAc (100 mL), extracted with water (3 x 60 mL), and then the organic phase was dried with $MgSO_4$. Filtration and removal of the solvent by rotary evaporation gave a white slightly tacky product (5.344 g, 61%). Longer reaction times or higher temperatures reduced the yield. An analytical sample

was prepared by Kugelrohr distillation (175–185°C at 0.02 mm Hg) followed by recrystallization with EtOAc/Hexane. mp 129.8–130.2 °C. IR (cm^{-1}) 3059, 2888, 2228, 1694, 1594, 1504, 1446, 1240, 1203, 984, 878, 863, 839. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.05 (AA', 2H), 7.61 (BB' from fluorine coupling, 2H), 7.66 (BB', 2H), 9.95 (t, J = 1.8 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 107.5, 113.7, 115.9, 116.3, 118.3, 133.9, 135.3, 157.4, 159.8, 188.3. Anal. Calcd for $C_{14}H_7F_2NO_2$: C, 64.87; H, 2.72; N, 5.40. Found: C, 64.53; H, 2.99; N, 5.09.

*5.6.7. 4-(2-Chloro-4-formylphenoxy)-3-fluorobenzonitrile **1g.***

3-Chloro-4-fluorobenzaldehyde (2.0 g, 0.012 mol, Oakwood Chemical), 4-cyanophenol (1.73 g, 0.0126 mol, Oakwood Chemical) and anhydrous K_2CO_3 (1.65 g, 0.012 mol) were mixed in DMA (9.0 mL) and heated to 100 °C (oil bath temperature). After 12 hours of stirring, the reaction mixture was cooled producing a dark red-brown viscous oil. NaOH (2 M, 4 mL) and 25 g ice were added at rt. The reaction mixture was refrigerated for over 24 hours. A dark red-brown solid precipitated. This was then filtered and purified via Kugelrohr distillation (73.1–76.9 °C at 0.04 mm Hg) followed by recrystallization from diethyl ether/hexane to give a white powder (1.004 g, 29%). mp 76.6−78.2 °C. IR (cm^{-1}) 3090, 3059, 2852, 2745, 2237, 1690, 1508, 1236, 1205, 963, 844, 736, 646. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.07 (m, 2H), 7.48 (dt, J = 1.6, 8.8 Hz, 1H), 7.55 (dd, J = 1.6, 9.6 Hz, 1H), 7.79 (dd, J = 2, 8.4 Hz, 1H), 7.92 (d, J = 9.3 Hz, 1H), 9.96 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 108.9, 117.0, 119.3, 121.2, 126.3, 129.59, 129.63, 129.77, 132.3, 133.8, 146.97, 151.7, 154.2, 155.8, 189.3. Anal. Calcd for C14H7ClFNO2: C, 61.00; H, 2.56; N, 5.08. Found: C, 61.18; H, 2.75; N, 4.92.

5.6.8. (E)-Ethyl 3-[4-(4-cyanophenoxy)phenyl]propenoate **2**.

To a 250 mL 3-neck round bottom flask, fitted with a condenser, mechanical stirrer, a Newman funnel, and a nitrogen inlet, in an ice bath, was added sodium hydride (1.276 g, 53.17 mmol) and then hexane (20 mL). After agitation the hexane was removed. THF (23 mL) was then added, followed by dropwise addition of triethylphosphonoacetate (distilled, 4.82 g, 21.5 mmol). Then 4-(4-formylphenoxy)benzonitrile (4.80 g, 21.5 mmol) was added in one portion. The flask was stirred for 30 min and then warmed at 60 °C for 10 minutes with an oil bath. The reaction mixture was poured over ice and then the tan solid isolated by vacuum filtration. Kugelrohr distillation gave colorless solid (4.282 g, 68%). In another run the crude brown product (6.91 g) was recrystallized from ethanol (95%, 20 mL) to give a beige solid (4.568 g, 72%). mp 87.0–89.6 °C. IR (neat, cm^{-1}) 3064, 2983, 2228, 1707, 1629, 1590, 1508, 1499, 1474, 1245, 1171, 1110, 1007, 884, 876, 855, 834, 823. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.27 (t, 3H), 4.20 (q, 2H), 6.62 (d, 1H), 7.16 (AA', 2H), 7.18 (AA', 2H) 7.68 (d, 1H), 7.83 (BB', 2H), 7.88 (BB', 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 14.2, 60.0, 105.8, 117.9, 118.6, 118.8, 120.1, 130.6, 130.8, 134.8, 143.4, 156.4, 160.3, 166.2. GC-MS t_r = 9.00 m/z = 293.1. HRMS-TOF MS EI$^+$ (*m/z*): [M$^+$] calcd for $C_{18}H_{15}NO_3$ 293.1052; found 293.1045. Anal. Calcd for $C_{18}H_{15}NO_3$: C, 73.71; H, 5.15; N, 4.78. Found: C, 73.80, H, 5.13; N, 4.64.

5.6.9. 4-(4-(2-Carboxyethyl)phenoxy)phenyl)methanaminium chloride **4**.

To ethyl 3-[4-(4-aminomethylphenoxy)phenyl]propanoate (0.252 g, 0.842 mmol) in 95% ethanol (3.5 mL) was added 2 M NaOH (1.1 mL). After 4 h of stirring at rt water (3.5 mL) and then 12 M HCl was added until the pH = 1. The solid formed was collected by suction filtration and then recrystallized from methanol/acetonitrile (0.123 g, 47%). mp 238−240 °C dec with gas evolution. IR (neat, cm^{-1}) 2972, 2876, 2583, 1701, 1602, 1579, 1505, 1445, 1259, 1223, 1200, 1173, 940, 878, 826. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.54 (t, J = 7.8 Hz, 2H), 2.82 (t, J = 7.6 Hz, 2H), 3.98 (q, J = 5.8 Hz, 2H), 6.93 (AA', 2H), 7.01 (AA', 2H) 7.26 (BB', 2H), 7.50 (BB', 2H), 8.41 (bs, 3H), 12.12 (bs, 1H). ^{13}C (100 MHz, DMSO-d_6) δ 29.6, 35.3, 41.6, 118.2, 118.8, 128.7, 129.8, 130.9, 136.4, 154.4, 157.2, 173.7. HRMS-TOF MS EI$^+$ in sodium acetate (m/z): [M + Na]$^+$ calcd for $C_{16}H_{18}ClNO_3$ ^{23}Na 294.1106; found 294.1114.

5.6.10. Ethyl 3-[4-(4-methylphenoxy)phenyl]propanoate **5b**. Ethyl 3-[4-(4-aminomethylphenoxy)phenyl]propanoate **3a**.

To 5% Pd on carbon with 55% water (42 mg) was added conjugated ester **2** (0.412 g, 1.40 mmol) in 95% ethanol (35 mL). Parr hydrogenation (61 psi) at rt for 14.5 h was followed by filtration through celite and solvent removal giving a mixture of products (0.408 g). The mixture was subjected to flash chromatography with 30% EtOAc/hexane eluent giving the hydrogenolysis product **5b** (0.053 g, 13%). Elution with 100% EtOAc (100 mL) gave no significant amount of material. Subsequent elution with methanol (75 mL) gave the primary amine **3a** (0.313 g, 75%).

*Hydrogenolysis product **5b***: oil. IR (neat, cm^{-1}) 3036, 2924, 2855, 1736, 1604, 1500, 1238, 1168, 874, 846, 817. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.16 (t, J = 7.1 Hz, 3H), 2.28 (s, 3H), 2.59 (t, J = 7.6 Hz, 2H), 2.82 (t, J = 7.6 Hz, 2H), 4.035 (q, J = 7.1 Hz, 2H), 6.37 (AA', 4H), 7.18 (BB', 4H), ^{13}C NMR (100 MHz, DMSO-d_6) δ 14.1, 20.2, 29.5, 35.2, 59.8, 118.1, 118.6, 129.7, 130.3, 132.4, 135.2, 154.4, 155.4, 172.1. GC-MS t_r = 5.80 min, m/z = 284.1. HRMS-TOF MS EI$^+$ (m/z): [M$^+$] calcd for $C_{18}H_{20}O_3$ 284.1412; found 284.1408.

3a: oil. IR (neat, cm^{-1}) 3350, 2982, 1729, 1601, 1499, 1232, 1168, 873, 827. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.15 (t, J = 7.1 Hz, 3H), 2.60 (t, J = 7.6 Hz, 2H), 2.59 (t, 2H), 2.82 (t, J = 7.6 Hz, 2H), 3.69 (s, 2H), 4.04 (q, J = 7.1 Hz, 2H), 6.89 (AA', 2H), 6.92 (AA', 2H) 7.22 (BB', 2H), 7.31 (BB', 2H); ^{13}C (100 MHz, DMSO-d_6) δ 14.1, 29.5, 35.2, 45.0, 59.8, 118.2, 118.3, 128.5, 129.7, 135.3, 139.4, 155.0, 155.3, 172.1. GC-MS t_r = 5.00 min, m/z = 299.1. HRMS-TOF MS EI$^+$ (m/z): [M$^+$] calcd for $C_{18}H_{21}NO_3$ 299.1521; found. 299.1522.

5.6.11. Ethyl 3-[4-(4-aminomethylphenoxy)phenyl] propanoate tosylate **3b**.

To **3a** (0.095 g, 0.32 mmol in ether was added tosic acid (0.060 g, 0.32 mmol) in ether. The white solid formed was collected by vacuum filtration and dried (0.116 g, 77%). mp 163.5−165.5 °C. IR (neat, cm^{-1}) 3066, 2976, 1727, 1716, 1604, 1505, 1483, 1245, 1164, 1123, 1106, 1034, 1010, 878, 831, 813, 683. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.16 (t, J = 7.2 Hz, 3H), 2.29 (s, 3H), 2.62 (t, J = 7.6 Hz, 2H), 4.01 (q, J = 6.0 Hz, 2H) 4.05 (q, J = 7.2 Hz, 2H), 6.93, (AA', 2H), 7.02 (BB', 2H), 7.12 (AA', 2H), 7.27 (BB', 2H), 7.46 (AA', 2H) 7.48 (BB', 2H), 8.08 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 14.6, 21.2, 30.0, 35.6, 42.2, 60.3, 118.7,

119.3, 126.0, 128.5, 129.1, 130.4, 131.3, 136.5, 138.0, 146.2, 155.0, 157.8, 172.6. Anal. Calcd for $C_{25}H_{29}NO_6S$: C, 63.68; H, 6.20; N, 2.97; S, 6.80. Found: C, 63.76; H, 6.12; N, 2.74; S, 6.63.

5.6.12. Ethyl 3-(4-(4-cyanophenoxy)phenyl)propanoate **5a** and Diethyl 3,3'-((((azanediylbis(methylene))bis(4,1-phenylene))bis(oxy))bis(4,1-phenylene)) dipropionate **9a**.

Ester **2** (0.779 g, 2.66 mmol) in EtOH (25 mL) was hydrogenated (Parr) in the presence of 5% platinum on carbon catalyst (0.048 g) at 60 psi for 21 h. Filtration through celite and rotary evaporation of solvent gave a mixture of products (0.671 g). The crude products were separated by flash chromatography using 10% EtOAc/hexane and then 20% EtOAc/hexane giving the hydrogenolysis product **5b** (0.028 g, 4%) and then cyanoester **5a** (0.393 g, 50%). Subsequent elution with 100% EtOAc give the secondary amine **9a** (0.184 g, 12%).

5a: oil. IR (neat, cm^{-1}) 3063, 2984, 2937, 2227, 1730, 1597, 1497, 1245, 1201, 1168, 874, 852, 837. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.16 (t, *J* = 7.1 Hz, 3H), 2.63 (t, *J* = 7.6 Hz, 2H), 2.87 (t, *J* = 7.6 Hz, 2H), 4.05 (q, *J* = 7.1 Hz, 2H), 7.04 (AA', 2H), 7.07 (AA', 2H), 7.32 (BB', 2H), 7.82 (BB', 2H). ^{13}C (100 MHz, DMSO-d_6) δ 14.1, 29.6, 35.0, 59.8, 104.8, 117.7, 118.7, 120.2, 130.2, 134.6, 137.5, 152.6, 161.3, 172.1. GC-MS t_r = 5.80 min, m/z = 295.1. HRMS-TOF MS EI$^+$ (*m/z*): [M$^+$] calcd for $C_{18}H_{17}NO_3$ 295.1208; found 295.1235.

9a: oil. IR (neat, cm^{-1}) 2982, 1731, 1602, 1499, 1232, 1167, 1099, 1043, 1015, 874, 827. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.14 (t, *J* = 7.1 Hz, 3H), 2.58 (t, *J* = 7.6 Hz, 2H), 2.81 (t, *J* = 7.5 Hz, 2H), 3.63 (s, 2H), 4.03 (q, *J* = 7.2 Hz, 2H), 6.88 (AA', 2H), 6.91 (AA', 2H), 7.21 (BB', 4H), 7.32 (BB', 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 14.2, 29.6, 35.3, 51.7, 60.0, 118.4, 118.5, 129.6, 129.9, 135.6, 135.9, 155.3, 155.6, 172.4. HRMS-TOF MS EI$^+$ (*m/z*): [M$^+$] calcd for $C_{36}H_{40}NO_6$ 582.2856; found 582.2833.

5.6.13. Bis(4-(4-(3-ethoxy-3-oxopropyl)phenoxy)benzyl)ammonium chloride **9b**.

To **7** (0.184 g, 0.316 mmol) was added 1 M HCl/EtOAc (0.6 mL, 0.6 mmol). Vacuum filtration gave the salt ***9b*** (0.135 g, 69%). mp 211–212 °C. IR (neat, cm^{-1}) 3063, 3032, 2993, 2909, 2788, 2734, 2601, 1728, 1606, 1503, 1238, 1167, 874, 857, 829, 812. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.15 (t, *J* = 7.1 Hz, 6H), 2.61 (t, *J* = 7.5 Hz, 4H), 2.84 (t, *J* = 7.6 Hz, 4H), 4.04 (q, *J* = 7.1 Hz, 4H), 4.11 (s, 4H), 6.94 (AA', 2H), 7.00 (AA', 2H), 7.26 (BB', 2H), 7.52 (BB', 2H), 9.47 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 14.1, 19.6, 35.1, 49.2, 59.8, 118.1, 119.0, 126.5, 132.0, 136.2, 154.3, 157.6, 172.2. Anal. Calcd for $C_{36}H_{40}ClNO_6$: C, 69.92; H, 6.52; Cl, 5.73; N, 2.27. Found: C, 70.00; H, 6.32; Cl, 5.55; N, 2.28.

5.6.14. (4-(4-(3-Hydroxypropyl)phenoxy)phenyl)methanaminium chloride **6**.

By Method C **5a** (0.295 g, 1.00 mmol) was converted to **6** (0.333 g). The impure oil was dissolved in EtOAc (5 mL) and 1 M HCl in EtOAc (2 mL) was added dropwise. Filtration gave **6** (0.272 g, 93 %). mp 177–179 °C dec. IR (neat, cm^{-1}) 3250, 2921, 2758, 2706, 2623, 1641, 1615, 1415, 1599, 1501, 1455, 1388, 1248, 1200, 1170, 1056, 1032, 877, 849, 837. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.71 (m, 2H), 2.60 (t, J = 7.7 Hz), 3.42 (t, J = 6.5 Hz, 2H), 4.00 (m, 2H), 6.93 (AA', 2H), 7.02 (AA', 2H), 7.24 (BB', 2H), 7.48 (BB', 2H), 8.30 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 30.9, 34.3, 41.6, 60.0, 118.1, 118.9, 128.6, 129.8, 130.9, 137.7,

154.1, 157.6. Anal. Calcd for $C_{16}H_{20}ClNO_2 + 2H_2O$: C, 58.09; H, 7.62. Found: C, 58.17; H, 7.03. HRMS-TOF MS ES^+ (*m/z*): $[M^+]$ calcd for $C_{16}H_{17}O_2$: 241.1229; found: 241.1228. This sole ion in the HRMS electrospray spectrum does not match the parent or any likely fragmentation. Due to this odd elemental analysis and HRMS data, the free amine was prepared from this salt by treatment with 2 M NaOH followed by extraction with DCM. mp (DCM/hexane) 73−75 °C. IR (neat, cm^{-1}) 3353, 3289, 3032, 2932, 2861, 1601, 1500, 1238, 875, 834, 813. ^1H NMR (400 MHz, $CHCl_3$-d_1) δ 1.56 (bs, 3.7H, overlapping water), 1.88 (pseudo-quintet, 2H), 2.69 (t, *J* = 7.7 Hz, 2H), 3.68 (t, *J* = 6.4 Hz 2H), 3.84 (s, 2H), 6.92 (AA', 2H), 6.96 (AA', 2H, 7.26 (m, 4H). ^{13}C NMR (100 MHz, $CHCl_3$-d_1) δ 31.3, 34.3, 45.9, 62.1, 118.7, 118.8, 128.4, 129.6, 136.7, 137.9, 155.4, 156.3. HRMS-TOF MS EI^+ (*m/z*): $[M^+]$ calcd for $C_{16}H_{19}NO_2$: 257.1416; found 257.1411. Anal. Calcd for $C_{16}H_{19}NO$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.51; H, 7.55; N, 5.21.

5.6.15. 3-[4-(4-Cyanophenoxy)phenyl]propanoic acid **7**.

To ethyl [4-(4-cyanophenoxy)phenyl]propenoate (0.121 g, 0.410 mmol) and 95% ethanol (1.5 mL) was added 2N NaOH (0.5 mL). After stirring at rt for 3 h 12 M HCl was added until pH = 1. Two volumes of water were added and then the solid was collected by vacuum filtration and then recrystallized from ether/hexane (0.084 g, 77%). mp 149.0−150.0 °C. IR (neat, cm^{-1}) 2929, 2222, 1700, 1597, 1498, 1240, 1200, 1167, 873, 851, 832. ^1H NMR (400 MHz, DMSO-d_6) δ 2.56 (t, *J* = 7.6 2H) 2.84 (t, *J* = 7.6, 2H) 7.05 (AA', 2H), 7.07 (AA', 2H), 7.33 (BB', 2H), 7.82 (BB', 2H), 12.16 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 29.6, 35.2, 104.8, 117.7, 118.8, 120.2, 130.2, 134.6, 137.9, 152.5, 161.4, 173.7. HRMS TOF MS EI^+ (*m/z*): $[M^+]$ calcd for $C_{16}H_{13}NO_3$ 267.0865; found 267.0865. Anal. Calcd for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.24. Found: C, 71.93; H, 5.19; N, 5.29.

5.6.16. 2-(4-(4-(2-Carboxyethyl)benzyl)phenyl)-4,5-dihydro-1H-imidazol-3-ium chloride **8**.

To **11** (0.545 g, 2.00 mmol) in DMA (2 mL) was added ethylenediamine (2 mL, 30 mmol) and NaHS hydrate (14.1 mg). The mixture was heated at 120 °C (oil bath temperature) for 2 h and then poured into water (20 mL). After 1 h the mixture was cooled in an ice water bath and 12 M HCl (6.5 mL) was added slowly dropwise until the pH = 1. The yellow solid obtained was recrystallized from water (8 mL) to give colorless **8** (0.572 g, 82%). mp 205−207 °C (sealed tube) dec with gas evolution. IR (neat, cm^{-1}) 3357, 3273, 3206, 3129, 2981, 2905, 2455, 1936, 1713, 1605, 1563, 1498, 1248, 1173, 869, 832. ^1H NMR (400 MHz, DMSO-d_6) δ 2.58 (t, *J* = 7.6 Hz, 2H), 2.85 (t, *J* = 7.6 Hz, 2H), 3.97 (s, 4H), 7.07 (AA', 2H), 7.15 (AA', 2H) 7.33 (BB', 2H), 8.02 (BB', 2H), 10.58 (s 2H), 12.16 (s, 1H). ^{13}C (100 MHz, DMSO-d_6) δ 29.6, 35.2, 44.2, 116.0, 117.3, 120.2, 130.2, 131.2, 138.0, 152.5, 162.5, 164.1, 173.7. HRMS TOF MS ES^+ in sodium acetate (*m/z*): $[M + Na]^+$ calcd for $C_{18}H_{18}N_2O_3{}^{23}Na$ 333.1215; found 333.1204.

5.6.17. 4-(4-(2-Hydroxyethyl)phenoxy)benzonitrile **10**.

4-(2-hydroxyethyl)phenol (10.000 g, 72.4 mmol, TCI America), 4-fluorobenzonitrile (9.980 g, 82.4 mmol, Oakwood Chemical) and anhydrous K_2CO_3 (10.017 g, 72.5 mmol) were mixed in DMA (82.1 mL) and heated to 120 °C (oil bath temperature). After 46 hours of stirring the reaction mixture was cooled and poured into cold NaOH (2N, 300 mL) and distilled water (400 mL). The mix-

ture was refrigerated overnight to precipitate the product. The crude brown product was collected by filtration and purified by Kugelrohr (166-179 °C at 0.05 torr) to give a white solid (10.936 g, 63 % yield). mp 62.6–63.6 °C. IR (neat, cm^{-1}) 3371, 2944, 2226, 1597, 1495, 1417, 1288, 1244, 1201, 1168, 1106, 1045, 1016, 873, 834. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.83 (BB', 2H), 7.32 (AA', 2H), 7.06 (m, 4H), 4.66 (t, J = 5.2, 1H), 3.63 (td, J = 7.0, 5.2, 2H), 2.75 (t, J = 7.0, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.0, 152.9, 137.2, 135.1, 131.2, 120.6, 119.2, 118.2, 105.2, 62.5, 38.7. Anal. Calcd for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N; 5.85. Found: C, 75.46; H, 5.64; N; 5.68.

5.6.18. (4-(4-(2-Hydroxyethyl)phenoxy)phenyl)methanaminium chloride **11**.

By Method B **10** (0.353 g, 1.43 mmol) was converted to **11** (0.260 g, 65%). mp 206–208 °C. IR (neat, cm^{-1}) 3280, 3028, 2928, 2618, 1602, 1502, 1466, 1407, 1387, 1339, 1251, 1167, 1119, 1102, 1081, 1054, 1011, 976, 874, 851, 832, 822, 810, 761. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.18 (bs, 3H), 7.46 (BB', 2H), 7.25 (BB', 2H), 7.01 (AA', 2H), 6.92 (AA', 2H), 4.65 (t, J = 5.181, 1H), 3.99 (s, 2H), 3.60 (td, J = 7.0, 5.2, 2H), 2.71 (t, J = 7.00, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.3, 154.3, 135.2, 130.9, 130.4, 128.6, 18.8, 118.1, 62.1, 41.6, 38.2. Anal. Calcd for $C_{15}H_{18}ClNO_2$: C, 64.40; H, 6.49; N, 5.01; Cl, 12.67. Found: C, 64.36; H, 6.30; N, 4.91; Cl, 12.48.

5.6.19. 4-(4-(2-Chloroethyl)phenoxy)benzonitrile **12**.[50]

Thionyl chloride (5 mL, Sigma-Aldrich) was carefully added to 4-(4-(2-hydroxyethyl)phenoxy)benzonitrile (301 mg, 1.26 mmol). The mixture was heated to reflux for 19 h. Excess $SOCl_2$ was distilled off and the residue was dissolved in ether and cautiously neutralized with saturated Na_2CO_3 followed by water. The ether was extracted and dried with $MgSO_4$. The solvent was then removed by rotary evaporation to produce a brownish yellow oil. Kugelrohr distillation (160-200 °C at 0.10 torr) gave a white solid (252 mg, 78%). mp 57.5–59.0 °C. IR (neat, cm^{-1}) 3065, 2932, 2868, 2226, 1910, 1594, 1496, 1453, 1440, 1416, 1327, 1298, 1245, 1200, 1166, 1109, 1037, 1020, 949, 875, 853, 840, 813, 776, 744, 710, 682. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.84 (AA', 2H), 7.39 (AA', 2H), 7.09 (m, 4H), 3.88 (t, J = 7.2, 2H), 3.06 (t, J = 7.0, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.2, 153.0, 135.2, 134.6, 130.9, 120.2, 118.7, 117.8, 104.9, 45.3, 37.4. Anal. Calcd for $C_{15}H_{12}ClNO$: C, 69.91; H, 4.69; N, 5.44; Cl, 13.76. Found: C, 70.16; H, 4.80; N, 5.28; Cl, 13.55.

5.6.20. Diethyl (4-(4-cyanophenoxy)phenethyl)phosphonate **13**.

A literature procedure was modified.[51] Triethyl phosphite (2 mL) was added to 4-(4-(2-chloroethyl)phenoxy)benzonitrile (575 mg, 2.23 mmol) and NaI (15 mg, 0.1 mmol). Under a nitrogen atmosphere, the reaction was heated to reflux for 36 h. Excess triethyl phosphite was removed by water aspiration while heating to 130 °C. The crude product was isolated by Kugelrohr distillation (215–235 °C at 0.025 torr) leaving a colorless liquid (695 mg, 86.7%). IR (neat, cm^{-1}) 3470, 3040, 2984, 2936, 2912, 2226, 1712, 1597, 1497, 1445, 1392, 1246, 1203, 1168, 1098, 1055, 1028, 965, 875, 836. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.84 (BB', 2H), 7.37

(AA', 2H), 7.07 (m, 4H), 3.99 (m, 4H), 2.81 (m, 2H), 2.08 (m, 2H), 1.23 (t, J = 7.02, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.4, 152.6, 137.9, 134.6, 130.9, 130.1, 120.3, 118.7, 117.7, 104.8, 60.9, 27.4, 26.8, 25.4, 16.3.

5.6.21. 2-(4-(4-Cyanophenoxy)phenyl)acetic acid **14**.

To a solution of 4-(4-(2-hydroxyethyl)phenoxy)benzonitrile (500 mg, 2.08 mmol) in acetone (15 mL, Fischer) at 0 °C was added Jones reagent. Jones reagent was prepared by dissolving chromium trioxide (25 g) in distilled water (500 mL) followed by addition of concentrated sulfuric acid (25 mL) with stirring. The Jones reagent was added to the reaction mixture until the orange color persisted. After stirring at 0 °C for 3 h more Jones reagent was added before removing the ice bath. The reaction was stirred at rt for an additional 1.5 h. The reaction was quenched via isopropanol with subsequent addition of water (10 mL) and ether (10 mL). The layers were separated and the organic layer was washed with 2 M NaOH (3 x 10 mL). The aqueous layer was then acidified with 12 M HCl until pH reached 1 and then washed with ether (3 x 30 mL). The ether was dried with $MgSO_4$ then removed by rotary evaporation to give a crude brown product which was then recrystallized with ether/hexanes to give a light beige powder (150 mg, 28%). mp 126–127 °C. IR (neat, cm^{-1}) 3102, 2237, 1732, 1732, 1596, 1494, 1417, 1386, 1286, 1252, 1202, 1162, 1102, 1016, 877, 825, 781, 727, 663. ^{1}H NMR (400 MHz, d_6-DMSO) δ 12.38 (bs, 1H), 7.83 (AA', 2H), 7.36 (AA', 2H), 7.09 (m, 4H), 3.61 (s, 2H). ^{13}C NMR (100 MHz, d_6-DMSO) δ 172.6, 161.3, 153.0, 134.6, 132.0, 131.4, 120.1, 118.7, 117.9, 104.9, 39.9. Anal. Calcd for $C_{15}H_{11}NO_3$: C, 71.14; H, 4.38; N, 5.53. Found: C, 71.34; H, 4.42; N, 5.31.

5.6.22. 4-(4-(2-Methoxyethyl)phenoxy)benzonitrile[52] **15.**

To DMSO (8.4 mL) was added powdered KOH (938 mg, 16.72 mmol). After stirring for 5 min, the substrate (1.000 g, 4.180 mmol) was added, followed immediately by methyl iodide (0.52 mL, 8.360 mmol). Stirring was continued for 1 h, after which the mixture was poured into water (30 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic extracts were washed with water (5 x 15 mL). Rotary evaporation gave a colorless oil which still contained small amounts of DMSO. The product was further purified by Kugelrohr (172–176 °C at 0.05 torr) to give a white solid (1.043 g, 98 %). mp 45–47 °C. IR (neat, cm-1) 3066, 2981, 2938, 2867, 2831, 2222, 1595, 1497, 1252, 1199, 1169, 1104, 968, 877, 850, 835, 818, 772, 715. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.83 (AA', 2H), 7.33 (AA', 2H), 7.05 (m, 4H), 3.55 (t, J = 6.8 Hz, 2H), 3.26 (s, 3H), 2.83 (t, J = 6.8 Hz, 2H). ^{13}C NMR (400 MHz, DMSO-d_6) δ 161.4, 152.5, 136.2, 134.6, 130.7, 120.1, 118.7, 117.7, 104.8, 72.6, 57.8, 34.6. Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.73; H, 6.12; N, 5.57.

5.6.23. 4-(4-(2-(Benzyloxy)ethyl)phenoxy)benzonitrile ***16.***

To DMSO (8.4 mL) was added powdered KOH (938 mg, 16.72 mmol). After stirring for 5 min, the substrate (1.000 g, 4.180 mmol) was added, followed immediately by benzyl chloride (0.96 mL, 8.360 mmol). Stirring was continued for 1, after which the mixture was poured into water (30 mL) and placed in a refrigerator for 2 d. A white precipitate had formed and was collected by filtration. Kugelrohr distillation (222–230 °C at 0.05 torr) gave a white solid. The white solid was recrystallized with methanol to give the product (0.630 g, 47 %). mp 79–81 °C. IR (neat, cm^{-1}) 3062, 2947, 2931, 2870, 2842, 2788, 2227, 1592,

1578, 1491.1, 1454.5, 1361.7, 1320.9, 1290.2, 1250.8, 1200.1, 1170.9, 1105.7, 1073.9, 1005.9, 874, 857, 833, 697. ^{1}H NMR (400 MHz, $CHCl_3$-d_1) δ 7.59 (AA', 2H), 7.31 (m, 7H), 6.99 (m, 4H), 4.55 (s, 2H), 3.71 (t, *J* = 6.9 Hz, 2H), 2.95 (t, *J* = 6.9 Hz, 2H). ^{13}C NMR (400 MHz, $CHCl_3$-d_1) δ 161.4, 153.1, 138.3, 136.2, 134.1, 130.7, 128.4, 127.6, 127.6, 120.4, 118.9, 117.7, 105.6, 73.0, 70.9, 35.7. Anal. Calcd for $C_{22}H_{19}NO_2$: C, 80.22; H, 5.81; N, 4.25. Found: C, 79.99; H, 5.61; N, 4.25.

5.6.24. 4-(4-(2-Methoxyethyl)phenoxy)phenyl)methanaminium chloride ***17.***

To a solution of 4-(4-(2-methoxyethyl)phenoxy)benzonitrile (500 mg, 1.97 mmol) in anhydrous THF (2 mL, Sigma-Aldrich) under a nitrogen atmosphere was added 1.7 M $LiHBEt_3$ in THF (2.55 mL, 4.33 mmol). The resulting mixture was stirred at rt for 24 hours then 3M NaOH (6 mL) was added. After 1 h the solution was then extracted with EtOAc (3 x 30 mL). The organic layer was then washed with distilled water (2 x 30 mL) followed by brine (2 x 30 mL). The organic layer was acidified with 12 M HCl which gave a turbid solution. The solution was concentrated using a rotary evaporation until a white precipitate formed (280 mg, 48% yield). mp 169−172 °C. IR (neat, cm^{-1}) 2866, 2594, 1599, 1502, 1380, 1251, 1171, 1109, 957, 878, 850, 831. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.36 (bs, 3H), 7.49 (AA', 2H), 7.27 (AA', 2H), 7.02 (BB', 2H), 6.93 (BB', 2H), 3.99 (s, 2H), 3.53 (t, *J* = 6.9 Hz, 2H), 3.25 (s, 3H), 2.80 (t, *J* = 6.9 Hz, 2H). ^{13}C NMR (400 MHz, DMSO-d_6) δ 157.2, 154.5, 134.7, 130.9, 130.4, 128.7, 118.8, 118.2, 72.7, 57.8, 41.6, 34.6. Anal. Calcd for $C_{16}H_{20}ClNO_2$: C, 65.41; H, 6.86; N, 4.77; Cl, 12.07. Found: C, 65.30; H, 7.00; N, 4.79; Cl, 11.91.

5.6.25. (4-(4-(2-(Benzyloxy)ethyl)phenoxy)phenyl)methanaminium chloride ***18.***

To a solution of 4-(4-(2-(benzyloxy)ethyl)phenoxy)benzonitrile (450 mg, 1.37 mmol) in anhydrous THF (2 mL Sigma-Aldrich) under a nitrogen atmosphere was added 1.7 M $LiHBEt_3$ in THF (1.77 mL, 3.01 mmol). The resulting mixture was stirred at rt for 24 hours then 3M NaOH (6 mL) was added. After stirring for 1 hour the solution was then extracted with diethyl ether (3 x 30 mL). The organic layer was then washed with distilled water (2 x 30 mL) followed by brine (2 x 30 mL). The organic layer was acidified with 12 M HCl until a white precipitate formed which was collected by filtration. The precipitate was pure product (339 mg, 62% yield). mp 167−168 °C. IR (neat, cm^{-1}) 2963, 2575, 1598, 1502, 1480, 1465, 1359, 1245, 1168, 1082, 975, 857, 744. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.41 (bs, 3H), 7.50 (AA', 2H), 7.30 (m, 6H), 7.01 (BB', 2H), 6.94 (BB', 2H), 4.49 (s, 2H), 3.99 (q, *J* = 5.7 Hz, 2H), 3.65 (t, *J* = 6.9 Hz, 2H), 2.86 (t, *J* = 6.9 Hz, 2H). ^{13}C NMR (400 MHz, DMSO-d_6) δ 157.3, 154.5, 138.5, 134.7, 130.9, 130.4, 128.7, 128.2, 127.4, 127.4, 118.8, 118.1, 71.7, 70.5, 41.6, 34.8. Anal. Calcd for $C_{22}H_{24}ClNO_2$: C, 71.44; H, 6.54; N, 3.79; Cl, 9.58. Found: C, 71.07; H, 6.61; N, 3.66; Cl, 9.42.

5.6.26. 4-(4-Cyanophenoxy)benzoic acid ***19***.[53]

To a solution of 4-(4-formylphenoxy)benzonitrile (135 mg, 0.605 mmol) in acetone (10 mL, Fischer) was added Jones reagent. Jones reagent was prepared as above for **14**. Jones reagent was added to the reaction mixture until the orange color persisted and allowed to stir for 18 h. The reaction was quenched with isopropanol then water (10 mL) and ether (10

mL) were added. The layers were separated and the organic layer was washed with 2 M NaOH (3 x 10 mL). The aqueous layer was then acidified with 12 M HCl until pH reached 1 and subsequently washed with ether (3 x 30 mL). The organic layer was dried with $MgSO_4$ and evaporated to give a brown product. The crude product was then dissolved in a 1:1 hexane:ether solvent pair then concentrated by rotary evaporation to give a light tan precipitate (95 mg, 66%). mp 145−146 °C. IR (neat, cm^{-1}) 2994, 2851, 2667, 2554, 2225, 1924, 1671, 1611, 1591, 1495 1429, 1291, 1239, 1171, 1159, 1127, 1102, 1010, 968, 930, 876, 864, 845, 770, 729, 689, 659. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.94 (bs, 1H), 8.02 (BB', 2H), 7.91 (AA', 2H), 7.22 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.1, 160.2, 159.2, 135.3, 132.3, 127.5, 119.9, 119.6, 119.0, 106.7. Anal. Calcd for $C_{14}H_9NO_3$: C, 70.29; H, 3.79; N, 5.86. Found: C, 70.07; H, 3.93; N, 5.63.

5.6.27. (4-(4-(Hydroxymethyl)-2-methylphenoxy)phenyl)methanaminium chloride **20**.

4-(4-Formylphenoxy)benzonitrile (0.319 g, 1.43 mmol) was added to anhydrous ethyl ether (2.5 mL) and THF (0.5 mL) under nitrogen. $LiBH_4$ (4 M) in THF (0.715 mL, 2.86 mmol), was added drop-wise to the solution and then superhydride (1 M) in THF (0.715 mL, 0.715 moles) was added. The solution was stirred at rt under nitrogen overnight at which time additional superhydride (0.715 mL) was added. After 26 h EtOAc (15 mL) was added and then NaOH (5 mL). After stirring at rt for 30 min the solution was extracted with water (3 x 2.5 mL) and then washed with brine (5 mL). A solution of 1 M HCl in EtOAc was added dropwise until turbid and the pH was 1. The solvent was removed by rotary evaporation to give a slightly ivory colored solid (0.313 g, 95.4%). The product was recrystallized using 95% ethanol and ethyl acetate. mp 295°C dec. IR (neat, cm^{-1}) 3821, 3743, 3259, 2952, 2604, 1602, 1501, 1477, 1385, 1248, 1199, 1169, 1117, 1082, 1036, 1015, 1001, 876, 833, 820, 809. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.98 (s, 2H), 4.48 (d, J = 5.3 Hz, 2H), 5.22 (t, J = 5.6Hz, 1H), 6.97 (AA', 2H), 7.01 (AA', 2H), 7.36 (BB', 2H), 7.49 (BB', 2H), 8.37 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 41.7, 62.3, 118.2, 118.7, 128.3, 128.7, 130.9, 138.1, 154.9, 157.3. HRMS-TOF MS EI$^+$ of the free amine (*m/z*): [M$^+$] calcd for $C_{14}H_{15}NO_2$ 229.1103; found 229.1097.

5.6.28. 4-((4-Formylphenyl)thio)benzonitrile **22**.[54]

To a solution of 4-mercaptobenzonitrile (4.645 g, 34.36 mmol) dissolved in DMA (180 mL) was added 4-fluorobenzaldehyde (3.7 mL, 34.49 mmol) and anhydrous K_2CO_3 (5.364 g, 38.81 mmol). The mixture was heated at 120 °C for 19 h and then poured into distilled water and then extracted with EtOAc (2 x 25 mL). The combined organic layers were washed with 5% aqueous K_2CO_3 (2 x 30 mL), water (40 mL), and brine (50 mL). The organic layer was then dried using Na_2SO_4 and filtered. The solvent was removed by rotary evaporation to obtain an orange gel. Kugelrohr distillation (135 °C, 0.10 torr) gave a white solid (8.175 g, 57%). mp 107.0–108.4 °C. IR (neat, cm^{-1}) 3081, 2837, 2226, 1700, 15867, 15623, 1485, 1388, 1307, 1284, 1218, 1172, 1080, 1015, 908, 835, 823, 729, 695. ^{1}H NMR (400 MHz, $CHCl_3$-d_1) δ 7.44 (AA', 2H), 7.52 (BB', 2H), 7.63 (AA', 2H), 7.88 (BB', 2H), 10.03 (s, 1H). ^{13}C NMR (100 MHz, $CHCl_3$-d_1) δ 91.0, 111.1, 118.3, 130.6, 130.8, 131.3, 132.9, 135.5, 141.4, 141.7. The data matched the literature and the compound was used without further purification.

5.6.29. (4-((4-(Hydroxymethyl)phenyl)thio)phenyl)methanaminium chloride **23**.

By Method C **22** (0.335, 1.53 mmol) was converted to the free base. To the free base in ether was added 12 M HCl dropwise to precipitate the amine salt as a white solid (0.158 g, 37%). mp 300 °C dec. IR (neat, cm^{-1}) 3411, 2255, 1659, 1023, 1000, 823, 761. ^1H NMR (400 MHz, DMSO-d_6) δ 3.99 (s, 2H), 4.51 (d, J = 5.60 Hz, 2H), 5.31 (m, 1H), 7.28 (AA', 2H), 7.36 (AA'BB', 4H), 7.46 (BB', 2H), 8.40 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 42.2, 62.8, 128.2, 130.0, 130.5, 131.9, 132.4, 133.2, 137.0. Anal. Calcd for $C_{14}H_{16}ClNOS$: C, 59.67; H, 5.72; N, 4.97; S, 11.38; Cl, 12.58. Found: C, 59.46; H, 5.92; N, 5.03; S, 11.11; Cl, 12.30.

*5.6.30. Ethyl (E)-3-(3-chloro-4-(4-cyanophenoxy)phenyl)acrylate **24.***

To a 3-neck round bottom flask fitted with a mechanical stirrer, a Newman funnel and a nitrogen inlet was added through a powder funnel NaH (1.68 g, 70.1 mmol) and hexanes (20 mL). The hexanes were removed by syringe. THF (23 mL) was added to the flask. The mixture was cooled in an ice bath and then triethyl phosphonoacetate (3.05 g, 13.6 mmol) was added dropwise via the Newman funnel. When hydrogen evolution ceased 4-(2-Chloro-4-formylphenoxy)benzonitrile (3.51 g, 13.6 mmol) was added in one portion. The solution was warmed to 55 °C for 10 min. The mixture was poured into ice water. After the tan colored solid appeared it was collected by filtration (2.178 g, 6.66 mmol, 52 % yield). mp 96.6–97.5 °C. Kugelrohr distillation at 0.04 mm Hg at 214–225 °C gave a white solid. IR (neat, cm^{-1}) 3066, 3000, 2973, 2929, 2904, 2868, 2224, 1704, 1636, 1668,1636, 1607, 1591, 1567, 1490, 1285, 1213, 1247, 1198, 1168, 1143, 1110, 1096, 981, 952, 914, 873, 853, 832, 754, 732, 713, 687, 673. ^1H NMR (400 MHz, $CHCl_3$-d_1) δ 1.35 (t, J = 7.2 Hz, 3H), 4.28 (q, J = 7.2 Hz, 2H), 6.42 (d, J = 16 Hz, 1H), 6.99 (AA', 2H), 7.11 (d, J = 8.4 Hz, 1H, 7.45 (d, J = 8.4 Hz, 1H), 7.61 (d, J = 16 Hz, 1H), 7.64 (BB', 2H), 7.67 (s, 1H). ^{13}C NMR (100 MHz, $CHCl_3$-d_1) δ 14.23, 60.8, 106.8, 117.5, 118.5, 119.6, 122.5, 127.4, 128.0, 130.4, 133.1, 134.23, 141.8, 151.6, 160.3, 166.4. HRMS TOF MS ES^+ (*m/z*): [M+] calcd for $C_{18}H_{14}ClNO_3$ 327.0662; found 327.0660.

*5.6.31. Ethyl 3-chloro-4-(4-cyanophenoxy)phenylpropanoate **25.***

To a 10 mL round bottom flask was added $Cu(OAc)_2 \cdot H_2O$ (0.104 g, 0.521 mmol), 1,2-bis(diphenylphospin0)benzene (0.012 g, 0.0269 mmol), freshly distilled toluene (1.7 mL) and then warm degassed *tert*-butyl alcohol (370 µL, 0.00392 mmol) via a syringe. The mixture turned blue. After stirring for 20 min under argon pressure, polymethylhydrosiloxane (264 µL, 0.148 µmol) was added, causing the color to change from blue to dark green. This mixture was then transferred by syringe to another flask containing solid (*E*)-Ethyl 3-[4(4-cyanophenoxy) phenyl]propenoate (0.463 g, 1.41 mmol), causing the color to change to black. Everything dissolved within 20 min. The reaction mixture was stirred at rt under argon for 5 days, with additional degassed, distilled toluene (2.0 mL, total 3.7 mL) added to maintain stirring as necessary. The mixture was then diluted with EtOAc (25-30 mL) and NaOH (1 M, 10 mL). After separating the base the solution was then extracted with HCl (1 M, 10 mL), dried over MgSO4 and then concentrated by rotary evaporation to give the product (0.439 g, 1.33 mmol). The product was obtained by Biotage chromatography (hexane/ethyl acetate, Snap ultra 10 g) as a colorless oil (0.229 g, 0.694 mmol, 49 %). IR (neat, cm^{-1}) 3098, 3069, 2981, 2938, 2867, 2226, 1729, 1608, 1595, 1503, 1487, 1445, 1407, 1373, 1350, 1297, 1249, 1186, 1166, 1058, 836. ^1H NMR (400 MHz, $CHCl_3$-d_1) δ 1.26 (t, J = 7.2,

3H), 2.65 (t, *J* = 7.6, 2H), 2.96 (t, *J* = 7.6, 2H), 4.15 (q, *J* = 7.2, 2H), 6.92 (AA', 2H), 7.05 (d, 1H), 7.15 (d, 1H), 7.35 (d, 1H), 7.60 (BB', 2H). ^{13}C NMR (50 MHz, $CHCl_3$-d_1) δ 14.2, 30.0, 35.5, 60.6, 106.0, 116.9, 118.7, 122.8, 126.8, 128.4, 130.9, 134.1, 139.6, 148.3, 161.0, 172.3. HRMS TOF MS ES$^+$ (*m/z*): [M+] calcd for $C_{18}H_{16}ClNO_3$ 329.0819; found 329.0811.

5.6.32. (4-(2-Chloro-4-(3-hydroxypropyl)phenoxy)phenyl)methanaminium chloride **26**.

To a 25 mL round bottom flask under argon was added **25** (0.229 g, 0.694 mmol), anhydrous THF (2.0 mL), $LiBH_4$ (4 M, 0.66 mL, 2.64 mmol), and $LiHB(C_2H_5)_3$ (1.7 M, 1.02 mL, 1.735 mmol), after which the color changed to light yellow. After 3 days 10% NaOH (7.5 mL) was added, which produced gas evolution. After 30 min H_2O (10 mL) was added, the solution then extracted with DCM (3 x 20 mL), and then dried over $MgSO_4$. Rotary evaporation gave a light yellow oil (0.280 g). The salt was prepared by dissolving the oil in EtOAc (10 mL) then adding methanolic HCl (0.5M, 3 mL) followed by partial removal of solvent by rotary evaporation to give a white solid (0.151 g, 69% yield). mp 194−195 °C. IR (neat, cm^{-1}) 3313, 2883, 2635, 1612, 1509, 1489, 1247, 1209, 1171, 1137, 1058, 850, 829. ^{1}H NMR (400 MHz, $CHCl_3$-d_1) δ 1.72 (m, 2H), 2.63 (t, 2H), 3.42 (td, *J* = 6.3, 5.1 Hz, 2H), 3.97 (s, 2H), 4.54 (t, *J* = 5.1 Hz, 1H), 1H), 6.92 (AA', 2H), 7.05 (d, *J* = 8.2 Hz, 1H), 7.23 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.44 (d, *J* = 2.0 Hz, 1H), 7.48 (BB', 2H), 8.34 (s, 3H). ^{13}C NMR (50 MHz, $CHCl_3$-d_1) δ 30.6, 33.9, 42.6, 59.8, 116.6, 121.8, 124.8, 128.6, 128.8, 130.4, 131.0, 140.5, 148.6, 157.1. Anal. Calcd for $C_{16}H_{19}Cl_2NO_2$: C, 58.55; H, 5.83; Cl, 21.60; N, 4.27. Found: C, 58.75; H, 6.00; Cl, 21.76, N, 4.35.

5.6.33. 4-(4-(3-Amino-3-oxopropyl)phenoxy)benzamide **27.**[55,56]

$SOCl_2$ (5 mL Sigma-Aldrich) was carefully added to 4-(4-(2-hydroxyethyl)phenoxy)benzonitrile (1.00, 1.26 mmol). The mixture was heated to reflux for 19 h. Excess $SOCl_2$ was distilled off and the residue was dissolved in ether and cautiously neutralized with concentrated Na_2CO_3 followed by water. The ether was dried with $MgSO_4$. The solvent was then removed by rotary evaporation to produce a dark yellow oil. Kugelrohr distillation (170-180 °C at 0.10 torr) gave 4-(4-(2-chloroethyl)phenoxy)benzonitrile as a white solid (709 mg, 67% yield). To this solid (250 mg, 0.97 mmol) in 2 mL of acetone was added sodium iodide (290 mg, 1.94 mmol). The reaction mixture was refluxed overnight. After filtration, the solvent was evaporated to give crude 4-(4-(2-iodoethyl)phenoxy)benzonitrile as a yellow powder (339 mg). A mixture of this yellow powder (339 mg) and potassium cyanide (189 mg, 2.91 mmol) in anhydrous DMF (5 mL, Sigma-Aldrich) was allowed to stir 3 days at rt. The product was extracted with chloroform (3 x 10 mL) and the solvent was evaporated to give 4-(4-(2-cyanoethyl)phenoxy)benzonitrile as a crude yellow oil (200 mg). Potassium carbonate (144 mg, 1.05 mmol) was added to the oil (200 mg, 0.81 mmol) in DMSO (1.85 mL). The solution was cooled to 0 °C and then 30% H_2O_2 (aq) (0.23 mL, 2.30 mmol) was added dropwise to the reaction. The reaction was allowed to warm to rt and allowed to stir for 3 h. The reaction mixture was then poured into water to give the product as a white precipitate collected by filtration. The product was then purified with flash chromatography to give a pure white powder (35 mg, 13% yield). mp 234−235 °C. IR (neat, cm^{-1}): 3387, 3185, 1646, 1623, 1599, 1506, 1415, 1397, 1243, 1165, 1118, 1014, 856. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.88 (m, 3H), 7.27 (m, 4H), 6.98 (m, 4H), 6.78 (s, 1H), 2.81 (t, *J* = 7.6 Hz, 2H), 2.27 (t, *J* = 7.6 Hz, 2H). ^{13}C

NMR (400 MHz, DMSO-d_6) δ 173.4, 167.3, 159.8, 153.6, 137.6, 129.8, 129.6, 128.7, 119.5, 116.9, 36.7, 30.1. Anal. Calcd for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.87; N, 9.85. Found: C, 67.72; H, 5.85; N, 9.70.

5.6.34. N-(3-Chloro-4-(4-cyanophenoxy)benzyl)-2-ethoxy-2-oxoethan-1-aminium chloride **28**.

By Method G **1b** (0.500 g, 1.94 mmol) was converted to the impure free amine (0.633 g). NMR showed the product with 10–20% of the alcohol from aldehyde reduction at ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.72 (s, 2H), 1.72 (s, 1H). The oil was dissolved in EtOAc (4 mL) and then HCl in EtOAc (30 drops) was added until precipitate no longer formed and the pH = 1. Filtration with a glass fritted Hirsch funnel followed by drying (50 degrees, 4 h) gave the product (0.516 g, 70%). mp 186−187 °C dec. IR (neat, cm^{-1}) 2988, 2935, 2723, 2642, 2620, 2423, 2226, 1749, 1734, 1596, 1488, 1230, 1250, 904, 852, 336. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.24 (t, J = 7.1Hz, 3H), 3.35 (broad s, 2H), 3.96 (s, 2H), 4.20 (q, J = 7.1 Hz, 2H) , 4.21 (broad s, 2H), 7.07 (AA', 2H), 7.38 (d, J = 8.4 Hz, 1H), 7.61 (dd, J = 8.3, 2.1 Hz,), 7.88 (BB', 2H), 7.89 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 13.9, 46.1, 48.6, 61.7, 105.6, 117.3, 118.6, 123.0, 125.4, 130.6, 131.5, 133.0, 134.8, 150.0, 160.2, 166.6. Anal. Calcd for $C_{18}H_{18}Cl_2N_2O_3$: C, 56.71; H, 4.76; Cl, 18.60; N, 7.35. Found: C, 56.49; H, 5.00; Cl, 18.44; N, 7.31.

5.6.35. 1-Carboxy-N-(3-chloro-4-(4-cyanophenoxy)benzyl)methanaminium chloride **29.**

To ester-nitrile **28** (378 mg, 0.991 mmol) in 4 mL of ethanol was added 2 M NaOH (1.75 mL, 3.5 mmol). After 2 h of stirring at rt 12 M HCl (0.31 mL) was added dropwise during which time the pale yellow color disappeared and white precipitate formed with pH = 1. The solid was collected on a glass fritted Hirsch funnel and dried in a vacuum oven to give **29** (0.225 g, 64%). mp 221–223 °C (sealed tube) dec with gas evolution. IR (neat, cm^{-1}) 3560, 3467, 3060, 2934, 2890, 2790, 2648, 2421, 2236, 1744, 1634, 1598, 1493, 1404, 1254, 1209, 1168, 1063, 890, 850, 817. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.53 (s, 2H), 4.07 (s, 2H), 7.06 (AA', 2H), 7.36 (d, J = 8.3 Hz, 1H), 7.53 (dd, J = 8.4 , 2.0 Hz, 1H), 7.79 (d, J = 2.0 Hz, 1H), 7.86 (BB', 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 47.8, 49.1, 105.5, 117.2, 118.6, 122.9, 125.4, 130.6, 132.2, 134.8, 149.4, 160.3, 168.8. Anal. Calcd for $C_{16}H_{14}Cl_2N_2O_3$: C, 54.41; H, 4.00; Cl, 20.07; N, 7.93. Found: C, 54.27; H, 4.26; Cl, 19.84; N, 7.66.

5.6.36. N-(4-(4-(Ammoniomethyl)phenoxy)-3-chlorobenzyl)-1-carboxymethanaminium chloride **30**.

To the acid-nitrile salt **29** (0.225 g, 0.637 mmol) in anhydrous THF (2 mL) was added 4 M $LiBH_4$ in THF (0.398 mL, 1.59 mmol). After gas evolution had stopped, 1.7 M superhydride in THF (0.824 mL, 1.40 mmol) was added. The solution was opaque but most of the solid dissolved. After 24 h NaOH (2 M, 3.9 mL) was added. After 30 mins of rapid stirring, 12 M HCl was added dropwise. The solid obtained was stirred with hot ethanol (10 mL) then, after cooling, was filtered and dried to give a white solid (0.657 g) contaminated with NaCl. The solvent was removed from the filtrate to give a tan solid 0.211 g (not the product). The white solid was recrystallized from water to give the product (0.066 g, 26%). mp > 360 °C (sealed tube) dec. IR (neat, cm^{-1}) 2928, 2796, 2762, 2634, 2597, 2414, 1744, 1600, 1499, 1413, 1267, 1209, 1170, 1061, 919, 860, 845, 817. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.34 (s, 2H? overlaps water), 4.00 (s, 2H), 4.04 (s, 2H), 6.96 (AA', 2H), 7.10 (d, J = 8.3 Hz, 1H), 7.51 (dd, J = 8.3, 2.0 Hz, 1H), 7.55 (BB', 2H) 7.80 (d, J = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 41.4, 48.1, 48.9, 117.2, 121.2, 124.6, 129.6, 130.4, 131.1, 131.6,

132.1, 151.1, 156.5, 168.4. Anal. Calcd for the semihydrate $C_{32}H_{39}C_{l6}N_4O_2$: C, 47.78; H, 4.89, Cl, 26.44; N, 6.97. Found: C, 47.44; H, 4.82; Cl, 26.01; N, 6.75.

5.6.37. N-(4-(4-(Ammoniomethyl)phenoxy)-3-chlorobenzyl)-2-hydroxyethan-1-aminium chloride **31**.

By Method E **28** (0.300 g, 0.787 mmol) was reduced to the free amine (0.298 g). This oil was dissolved in EtOAc (6 mL) and then HCl in EtOAc was added dropwise until precipitation seemed to stop and the pH = 1. The solid was removed by vacuum filtration using a glass fritted Hirsch funnel and then dried in a vacuum oven at 45 °C to give a partly white and yellow solid (0.268 g). The solid was recrystallized from ethanol (15 mL) to give a white solid (0.174 g, 58%). The mother liquor was evaporated to give a tan solid (0.132 g, 44%). mp 277 °C dec. IR (neat, cm^{-1}) 3366, 2916, 1600, 1497, 1268, 1062, 846, 814. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.95 (t, J = 5.4 Hz, 2H) 3.69 (bs, 2H), 4.00 (s, 2H), 4.16 (bs, 2H), 5.25 (bs, shoulders suggest a triplet, 1H), 6.99 (AA', 2H), 7.13 (d, J = 8.4 Hz, 1H), 7.52 (BB', 2H), 7.57 (dd, J = 8.5, 2.0 Hz, 1H), 7.88 (d, J = 2.0 Hz, 1H), 8.68 (bs, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 41.5, 48.5, 48.7, 56.5, 117.3, 121.2, 124.6, 129.2, 129.9, 130.9, 131.1, 132.6, 151.5, 156.4. Anal. Calcd for $C_{16}H_{21}Cl_3N_2O_2$: C, 50.61; H, 5.57; Cl, 28.01; N, 7.38. Found: C, 50.16; H, 5.55; Cl 27.88, N, 7.17.

5.6.38. 1-(3-Chloro-4-(4-cyanophenoxy)benzyl)-2-(methoxycarbonyl)pyrrolidin-1-ium chloride **32**.

By Method G **1b** (0.537 g, 2.084 mmol) was converted to the impure free base (0.637 g, 1.72 mmol, 83%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.85 (m, 2H), 1.96 (m, 1H), 2.18 (m, 1H), 2.42 (q, J = 8.4 Hz, 1H), 3.09 (m, 1H), 3.30 (dd, J = 8.9, 6.2 Hz, 1H), 3.55 (d, J = 13.1Hz, 1H), 3.70 (s, 3H), 3.91 (d, J = 13.1 Hz, 1H), 6.94 (AA', 2H), 7.07 (d, J = 8.3 Hz, 1H), 7.30 (dd, J = 8.2, 2.0 Hz, 1H), 7.51 (d, J = 2.0 Hz, 1H), 7.60 (BB', 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 23.1, 29.3, 51.8, 53.4, 57.8, 65.4, 106.0, 116.9, 118.7, 122.5, 126.7, 128.9, 131.4, 134.1, 138.0, 148.9, 161.0, 174.3. The base was dissolved in EtOAc and a 1 M solution of HCl in EtOAc (2 mL) was added. Methanol was added to dissolve the resulting solid and the solvent volume was reduced by rotary evaporation. More EtOAc was added and the solvent volume was reduced again. This process was repeated until a faint turbidity appeared in the flask during rotary evaporation at which point the flask was removed and the salt was allowed to precipitate as a slushy white solid. The solid was collected by suction filtration and allowed to dry overnight (60 °C, 9 torr) to give the salt (0.662 g, 78% from the aldehyde). mp 159.5–160.0 °C with gas evolved. IR (neat, cm^{-1}) 3087, 2956, 2460, 2227, 1749, 1595, 1580, 1489, 1250, 1213, 1167, 1063, 888, 850, 834. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.93(bm, 1H), 2.07 (bm, 2H), 2.44 (bm, 1H), 3.29 (bm, 1H), 3.54 (bm, 1H), 3.68 (s, 3H), 4.46 (bm, 1H), 4.54 (bm, 2H), 7.07 (AA', 2H), 7.39 (d, J = 8.3 Hz, 1H), 7.62 (d, J = 8.1 Hz, 1H), 7.89 (BB', 2H), 7.91(bs, 1H)), 10.88 (bs, 1H). ^{13}C NMR 100 MHz, DMSO-d_6) δ 21.9, 27.8, 53.0, 54.6, 56.1, 65.1, 105.8, 117.3, 118.5, 123.0, 125.5, 129.6, 131.9, 133.5, 134.8, 150.4, 160.1, 168.5. Anal. Calcd for $C_{20}H_{20}Cl_2N_2O_3$: C, 58.98; H, 4.95; Cl, 17.41; N, 6.88. Found: C, 59.17; H, 4.85; Cl, 17.19; N, 6.71.

5.6.39. 1-(4-(4-(Ammoniomethyl)phenoxy)-3-chlorobenzyl)-2-(hydroxymethyl)pyrrolidin-1-ium chloride **33**.

By Method E **32** (0.407 g, 1.000 mmol) was converted to the impure free base, a yellow glass (0.416 g). The glass contained absorptions in the NMR indicating -BCH_2CH_3 at ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.531 (t, 3H), 0.026 (q, 2H). EtOAc (5 mL) was

added at which point a white solid formed. The mixture was digested in EtOAc and then the solid (0.082 g) was removed by filtration. To the filtrate was added 1 M HCl/EtOAc which gave a pale yellow tacky solid after rotary evaporation of solvent. Overnight drying (70 °C, 9 torr) gave a free flowing but hygroscopic tan solid (0.264 g, 80% from **32**). mp 132–135 °C (sealed tube). IR (neat, cm^{-1}) 3321, 2950, 2877, 2706, 2605, 1560, 1509, 1491, 1250, 1207, 1171, 1060, 892, 852, 832. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.82 (m, 2H), 1.98 (m, 1H), 2.13 (m, 1H), 3.15 (m, 1H), 3.29 (m, 1H), 3.56 (m, 2H), 3.68 (m, 2H), 4.01 (m, 2H), 4.27 (dd, *J* = 13.2, 7.1 Hz, 1H), 4.60 (dd, *J* = 12.8, 4.3 Hz, 1H), 7.02 (AA', 2H), 7.13 (d, J = 8.3 Hz, 1H), 7.53 (BB', 2H), 7.64 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.95 (d, *J* = 2.0 Hz, 1H), 8.39 (s, 3H), 10.42 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.6, 25.9, 41.5, 53.5, 55.6, 59.4, 68.4, 117.6, 121.0, 124.6, 128.6, 129.4, 131.1, 131.7, 133.4, 152.0, 156.2. HRMS-TOF MS ES$^+$ (*m/z*): [M$^+$] calcd for $C_{19}H_{24}N_2O_2{}^{35}Cl$ 347.1526; found 347.1543.

5.6.40. 4-(2-Chloro-4-((4-hydroxypiperidin-1-yl)methyl)phenoxy)benzonitrile **34**.

By Method G **1b** (0.387 g, 1.50 mmol) was converted to an oil (0.483 g) containing about 39% of the alcohol from aldehyde reduction. The oil was dissolved with EtOAc (12 mL) and 1 M HCl in EtOAc was added until the solution was opaque. The mixture was extracted with EtOAc (3 x 25 mL) to remove the alcohol and then neutralized with 2 M NaOH. The solution was again extracted with EtOAc (3 x 25 mL). The combined extracts were dried over $MgSO_4$, filtered, and then the solvent was removed by rotary evaporation to give 0.224 g of the free base as an oil. The base was isolated as a solid from ether/pentane (0.176 g, 34%). mp 92.0–92.5 °C. IR (neat, cm^{-1}) 3400, 2946, 2801, 2757, 2227, 1607, 1594, 1504, 1486, 1247, 1167, 1056, 855, 843, 842. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.54 (bs, 1H), 1.62 (dtd, *J* = 13.2, 9.3, 3.8 Hz, 2H), 1.91 (m, 2H), 2.21 (td, *J* = 10.7, 2.2 Hz, 2H), 2.76 (dt, *J* = 11.7, 4.2 Hz, 2H), 3.48 (s, 2H), 3.74 (septet, *J* = 4.3Hz, 1H), 6.94 (AA', 2H), 7.06 (d, J= 8.2 Hz, 1H), 7.27, (dd, *J* = 8.2, 2.0 Hz, 1H), 7.46 (d, *J* = 2.0 Hz, 1H), 7.60 (BB', 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 34.5, 51.0, 61.7, 67.9, 106.0, 117.0, 118.7, 122.4, 126.7, 128.7, 131.2, 134.1, 138.0, 148.8, 131.0. Anal. Calcd $C_{19}H_{19}ClN_2O_2$: C, 66.57; H, 5.59; Cl, 10.34; N, 8.17. Found: C, 66.49; H, 5.34; Cl, 10.46; N, 7.96.

5.6.41. 1-(4-(4-(Aminomethyl)phenoxy)-3-chlorobenzyl)piperidin-4-ol chloride **35**.

Method D was modified. After **34** (0.229 g, 0.668 mmol) was treated with the reductants and stirred overnight, 6N HCl (4.5 mL) was added. After 30 min of stirring solid NaOH was slowly added to raise the pH to 13. After 1 h of stirring the mixture was extracted with EtOAc (3 x 25 mL) and then dried over Na_2SO_4 overnight. Filtration and rotary evaporation gave the impure free base (0.236 g) which tended to produce small amounts of white solid from chloroform solution. This was removed by filtration and the filtrate was washed with ether. The small additional amount of white solid (11 mg) was removed by filtration. This solid was not soluble in DMSO. The solvent was removed from the filtrate and the residue was taken up into ether. Slow addition of pentane in portions over 8 h gave **35** as a white solid (0.104 g, 0.300 mmol, 45%). mp 106.0–107.0 °C. IR (neat, cm^{-1}) 3292, 2940, 2813, 1596, 1506, 1488, 1245, 1204, 1166, 1056, 826, 783, 733. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.55 (bs, 4H), 1.60 (m, 2H) 1.90 (m, 2H), 2.17 (t, *J* = 10 Hz, 2H), 2.75 (m, 2H), 3.45 (s, 2H), 3.72 (septet, *J* = 4.3 Hz, 1H), 3.84 (s, 2H), 6.91 (d, *J* = 8.3 Hz, 2H), 6.93

(BB', 2H) 7.15 (dd, *J* = 8.3, 2.2 Hz 1H), 7.26 (s, 1H), 7.27 (BB', 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 34.5, 45.9, 51.0, 61.8, 68.0, 118.0, 120.3, 125.5, 128.3, 128.5, 131.0, 135.5, 138.2, 151.4, 155.9. Anal. Calcd for the semihydrate $C_{38}H_{48}Cl_2N_4O_5$: C, 64.13; H, 6.80; Cl, 9.96; N, 7.87. Found: C, 64.04; H, 6.88; Cl, 9.81, N, 7.49.

5.6.42. 4-(3-Chloro-4-(4-cyanophenoxy)benzyl)morpholin-4-ium chloride **36**.

By Method F **1b** (0.392 g, 1.52 mmol) was converted to the free base, a white solid (0.487 g). The solid was dissolved in hot EtOAc (5-6 mL) and filtered. To the filtrate 1 M HCl in EtOAc was added dropwise until turbid. The resulting solid was collected by filtration and dried overnight (60 °C, 9 torr) giving the salt (0.267 g, 48%). mp 220 °C dec. IR (neat, cm^{-1}) 2980, 2869, 2527, 2463, 2227, 1598, 1490, 1251, 1168, 1124, 1082, 1064, 963, 868, 854, 834. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.08 (m, 2H), 3.27 (d, *J* = 12.0 Hz, 2H), 3.82 (t, 11.9 Hz, 2H), 3.95 (d, *J* = 11.7 Hz, 2H), 4.36 (s, 2H), 7.12 (AA', 2H), 7.40 (d, *J* = 8.3 Hz, 1H), 7.69 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.86 (BB', 2H), 8.00 (s, 1H), 11.57 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 50.6, 57.5, 63.1, 105.7, 117.4, 118.6, 122.9, 125.6, 128.3, 132.5, 134.0, 134.8, 150.4, 160.1. Anal. Calcd for $C_{18}H_{18}Cl_2N_2O_2$: C, 59.19; H, 4.97; Cl, 19.41; N, 7.67; O, 8.76. Found: C, 59.30; H, 5.1 6; Cl, 19.29; N, 7.78.

5.6.43. 4-(4-(4-(Ammoniomethyl)phenoxy)-3-chlorobenzyl)morpholin-4-ium chloride **37**.

By Method A **36** (0.247 g, 0.676 mmol) gave an oil (0.233 g). The oil was dissolved with EtOAc/methanol and 1 M HCl in EtOAc was added dropwise slowly with stirring to form the salt. The solid formed was collected by filtration and dried (0.205 g, 75%). mp 241−243 °C dec. IR (neat, cm^{-1}) 3401, 2921, 2694, 2598, 2543, 2471, 1602, 1511, 1500, 1258, 1208, 1172, 1124, 1082, 1065, 967, 870, 833. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.07 (m, 2H), 3.26 (d, *J* = 11.4 Hz, 2H), 3.85 (t, *J* = 12.5 Hz, 2H), 3.95 (m, 2H), 4.00 (q, *J* = 5.6 Hz, 2H), 4.34 (s, 2H), 7.04 (AA', 2H), 7.15 (d, *J* = 8.4 Hz, 1H), 7.53 (BB', 2H), 7.65 (d, *J* = 8.1 Hz, 1H), 7.99 (s, 1H), 8.44 (s, 3H), 11.74 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 41.5, 50.6, 57.5, 63.0, 117.5, 121.2, 124.7, 126.9, 129.4, 131.1, 132.2, 133.9, 152.1, 156.3. Anal. Calcd for $C_{18}H_{23}Cl_3N_2O_2$: C, 53.28; H, 5.71; Cl, 26.21; N, 6.90. Found: C, 53.47; H, 6.00; Cl, 26.43; N, 6.91.

5.6.44. 4-(2-chloro-4-(4-cyanophenoxy)benzyl)morpholin-4-ium chloride **38**.

By Method F **1c** (0.773 g, 3.00 mmol) was converted to the crude free amine (0.918 g). HRMS-TOF MS EI$^+$ (*m/z*): [M$^+$] calcd for $C_{18}H_{17}{}^{35}Cl\ N_2O_2$ 328.0979; found 328.0969. The amine was dissolved in EtOAc (7 mL) and then treated with 1 M HCl/EtOAc (4 mL). After filtration, washing with EtOAc, and drying, a tan solid (0.871 g, 79%) was obtained. The solid was digested with 1:1 acetonitrile and DCE (20 mL). Filtration gave **38** (0.188 g). After partial removal of the solvent a second crop (0.325 g) of similar purity was obtained. A third crop (0.108 g) was slightly less pure by NMR. An analytical sample was prepared by recrystallization from methanol/EtOAc. mp 230−231 °C dec. IR (neat, cm^{-1}) 3044, 3063, 2987, 2954, 2873, 2342, 2220, 1593, 1490, 1263, 1245, 1233, 976, 918, 877, 845, 824. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.23 (m, 2H), 3.33 (s, 2H), 3.90 (m, 4H), 4.48 (s, 2H), 7.23 (AA', 2H), 7. 25 (m, 1H), 7.41 (d, *J* = 2.5 Hz, 1H), 7.91 (BB', 2H), 8.03 (d, *J* = 8.3 Hz, 1H), 11.40 (s, 1H). ^{13}C NMR (100 MHz, DMSO-

d_6) δ 50.8, 55.2, 63.0, 106.3, 118.6, 118.9, 116.0, 120.9, 123.6, 134.8, 135.8, 136.2, 156.4, 159.8. Anal. Calcd for $C_{18}H_{18}Cl_2N_2O_2$: C, 59.19; H, 4.97. Found: C, 60.91; H, 5.55.

5.6.45. 4-(4-(4-(Ammoniomethyl)phenoxy)-2-chlorobenzyl)morpholin-4-ium chloride **39**.

By Method A **38** (0.250 g, 0.684 mmol) was converted to the crude free amine (0.253 g). The amine was dissolved in EtOAc (5 mL) and then 1 M HCl/EtOAc (3 mL) was added. Removal of solvent by rotary evaporation gave a glass that could not be recrystallized. The glass was dissolved in water (10 mL) and 10% NaOH (10 mL) and then extracted into DCM (3 x 20 mL). After drying with $MgSO_4$ and rotary evaporation the free amine was obtained (0.194 g). The amine was again converted to the salt as described above giving a solid which upon filtration gave the hygroscopic salt (0.243 g). An analytical sample was recrystallized from acetonitrile/DCE. mp (sealed tube) 165 °C dec. IR (neat, cm^{-1}) 3405, 2871, 2698, 2464, 1597, 1572, 1509, 1490, 1243, 1210, 1120, 967, 919, 866, 842, 830. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.20 (m, 2H), 3.29 (m, 2H) 3.89 (m, 4H), 4.01 (m, 2H), 4.43 (s, 2H), 7.05 (d, J = 8.0 Hz, 1H), 7.12 (s, 1H), 7.17 (AA', 2H), 7.58 (BB', 2H), 7.97 (s, J = 8.0 Hz, 1H), 8.45 (s, 3H), 11.42 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 41.6, 50.8, 55.2, 63.0, 117.1, 118.6, 119.7, 121.9, 130.5, 131.2, 135.7, 135.9, 155.2, 158.6. The salt (0.243 g) was converted to the free amine with 5% NaOH (20 mL). Extraction with DCM (3 x 20 mL) and drying with $MgSO_4$ gave the free base (0.187 g, 73%). IR (neat, cm^{-1}) 3356, 3298, 3060, 2959, 2854, 2813, 2766, 1597, 1569, 1506, 1484, 1455, 1240, 1115, 916, 865, 820. ^{1}H NMR (400 MHz, $CHCl_3$-d_1) δ 2.51 (m, 4H), 3.57 (s, 2H), 3.72 (m, 4H), 3.87 (s, 2H), 6.87 (dd, J = 8.5, 2.5 Hz, 1H), 6.98 (s, 1H), 6.99 (AA', 2H), 7.30 (BB', 2H), 7.39 (d, J = 8.5 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 45.8, 53.5, 59.1, 67.0, 116.6, 119.0, 119.3, 119.4, 128.4, 128.6, 129.6, 129.8, 131.6, 135.0, 139.0, 155.1, 157.1. HRMS-TOF MS EI^+ (*m/z*): [M^+] calcd for $C_{18}H_{21}ClN_2O_2$ 332.1292; found 332.281.

5.6.46. 4-(4-(4-Cyanophenoxy)benzyl)morpholin-4-ium chloride **40**.

By Method F **1a** (0.670 g, 3.00 mmol) was converted to the free amine (0.837 g). The amine was taken up into EtOAc (8 mL) and 1 M HCl/EtOAc was added until the pH was 1. Filtration gave the salt **(**0.802 g, 81%). An analytical sample was recrystallized from acetonitrile/DCE. mp 228–232 °C. IR (neat, cm^{-1}) 3096, 3035, 2979, 2882, 2518, 2460, 2222, 1594, 1497, 1248, 1206, 1178, 1125, 965, 914, 868, 841, 830. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.09 (m, 2H), 3.25 (m, 2H), 3,76 (m, 2H), 3.93, (m, 2H), 4.34 (m, 2H) 7.15 (AA', 2H), 7.23 (AA', 2H), 7.67 (BB', 2H), 7.87 (BB', 2H), 10.95 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 50.5, 58.2, 63.1, 105.6, 118.5, 118.7, 120.2, 125.9, 133.8, 133.8, 134.7, 155.5, 160.6. Anal. Calcd for the semihydrate $C_{36}H_{40}Cl_2N_4O_6$: C, 63.62; H, 5.93; Cl, 10.43; N, 8.24. Found: C, 63.89; H, 5.94; Cl, 10.06; N, 8.45.

5.6.47. (4-(4-ymot)phenoxy)phenyl)methanamine, 4-(4-(4-(ammoniomethyl)phenoxy)benzyl)morpholin-4-ium chloride **41**.

By Method A **40** (0.250 g, 0.756 mmol) was converted to the crude free base (0.259 g). Addition of 1 M HCl/EtOAc (4 mL) to the free base in EtOAc (5 mL) gave an impure salt (0.267 g). The free amine was regenerated from the salt with 10% NaOH, extracted into DCM (4 x 15 mL), and dried over Na_2SO_4. Filtration and solvent removal gave the free amine as an oil. IR (neat, cm^{-1}) 3361, 3032, 2957, 2855, 2806, 2762, 1601, 1499, 1235, 1115, 915, 866, 838. ^{1}H NMR (400 MHz, $CHCl_3$-d_1) δ 1.57 (bs, 4H), 2.45 (m,

4H), 3.47 (s, 2H), 3.71 (m, 4H), 3.85 (s, 2H), 6.94 (AA', 2H), 6.97 (AA', 2H), 7.27 (BB', 2H), 7.27 (BB', 2H). ^{13}C NMR (100 MHz, $CHCl_3$-d_1) δ 45.9, 53.6, 67.0, 118.4, 119.0, 128.5, 130.5, 132.4, 138.3, 156.0, 156.6. HRMS-TOF MS EI$^+$ (*m/z*): [M$^+$] calcd for $C_{18}H_{22}N_2O_2$ 298.1681; found 298.1673. The amine was again converted to the hygroscopic salt **41** with 1 M HCl/EtOAc. mp (sealed tube) 246–253 °C dec. IR (neat, cm^{-1}) 3399, 2916, 2691, 2530, 2467, 1603, 1505, 1251, 869, 855, 829. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.06 (m, 2H), 3.21 (m, 2H), 3.84 (m, 2H), 3.94 (m, 2H), 4.01 (q, *J* = 5.4 Hz, 2H), 4.30 (d, *J* = 4.3 Hz, 2H), 7.05 (AA',2H), 7.09 (AA', 2H), 7.55 (BB', 2H), 7.67 (BB', 2H), 8.47 (bs, 3H), 11.61 (bs, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 41.6, 50.4, 58.2, 63.0, 118.5, 119.0. 124.3, 129.6, 131.1, 133.5, 156.2, 157.5.

*5.6.48. 1-(3-Chloro-4-(4-cyanophenoxy)benzyl)piperidin-1-ium chloride **42.***

By Method F 4-(3-chloro-4-formylphenoxy)benzonitrile (0.379 g, 1.47 mmol) was converted to the free amine (0.446 g). The free amine was treated with methanolic HCl (0.5 M, 5 mL) to give the salt (0.419 g, 78%). mp 245 °C dec. IR (neat, cm^{-1}) 3091, 3029, 2953, 2619, 2516, 2226, 1609, 1594, 1582, 1502, 1490, 1253, 1170, 947, 895, 852, 844, 825. ^{1}H NMR (400 MHz, DMSO-d_6) *δ* 1.36 (m, 1H), 1.70 (dd, *J* = 13.2, 2.6 Hz, 1H), 1.79 (m, 4H), 2.85 (m, 2H), 3.30 (bs, 2H), 4.28 (d, *J* = 5.3, 2H) 7.12 (AA', 2H) 7.39 (d, *J* = 8.3 Hz, 1H), 7.68 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.87 (BB', 2H), 7.99 (d, *J* = 2.0 Hz, 1H), 10.75 (bs, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) *δ* 24.2, 25.8, 54.5, 62.6, 63.6, 105.9, 106.0, 116.5, 116.9, 118.6. 118.7, 122.3, 122.7, 126.6, 127.0, 128.8, 129.3, 131.3, 134.1, 138.0, 140.1, 148.6, 149.1, 160.9, 161.0. Anal. Calcd for $C_{19}H_{20}Cl_2N_2O$: C, 62.82; H, 5.55; Cl, 19.52, N, 7.71. Found: C, 62.54; H, 5.70; Cl, 19.80 N, 7.23.

*5.6.49. 1-(4-(4-(Ammoniomethyl)phenoxy)-3-chlorobenzyl)piperidin-1-ium chloride **43.***

By method A **42** K8-2 (0.207 g, 0.569 mmol) was converted to the free amine (0.217 g). The free amine was treated with methanolic HCl (0.5 M, 7 mL) and then anhydrous ether (15 mL) in portions. The salt did not precipitate. The solvent was removed by rotary evaporation, the residue dissolved in hot water and methanol, then acetonitrile was added. The solvent was removed giving a hygroscopic glass (0.185 g, 46%). mp 254 °C dec. An analytical sample was recrystallized from CH_3OH/EtOAc. IR (neat, cm^{-1}) 3387, 2946, 2865, 2710, 2627, 2543, 1599, 1510, 1490, 1250, 1206, 1171, 945, 891, 856, 832. ^{1}H NMR (400 MHz, DMSO-d_6) *δ* 1.35 (bs, 1H), 1.68 (bs, 1H), 1.78 (bs, 4H), 2.83 (bs, 2H), 3.28 (s, 2H), 4.00 (s, 2H), 4.24 (s, 2H), 7.04 (AA', 2H), 7.12 (d, *J* = 8.3 Hz, 1H), 7.52 (BB', 2H), 7.62 (d, *J* = 8.4 Hz, 1H), 7.95 (s, 1H) 8.42 (bs, 3H), 10.81 (bs, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) *δ* 21.4, 22.2, 41.5, 51.6, 57.5, 117.6, 121.0, 124.7, 129.4, 131.1, 132.1, 133.7. 156.3. Anal. Calcd for $C_{19}H_{25}Cl_3N_2O$: C, 56.52; H, 6.24; N, 6.94; Cl, 26.34. Calcd for the semihydrate $C_{38}H_{52}Cl_6N_4O_3$: C, 55.29; H, 6.35; Cl 25.76; N, 6.79. Found: C, 55.83; H, 6.61; Cl; N.

*5.6.50. 1-(4-(4-Cyanophenoxy)benzyl)-4-methylpiperazine-1,4-diium chloride **44**.*

To **1a** (0.467 g, 2 mmol) and methyl piperazine (0.22 g, 2 mmol) in DCM (12 mL) was added sodium triacetoxyborohydride (0.590 g, 2.8 mmol). The reaction was heated to 90 °C overnight. The solution was then stirred in 1 M NaOH (25 mL), extracted with DCM (3 x 25 mL), and then dried over magnesium sulfate. Filtration and rotary evaporation gave the free base which

was then treated with 0.5 M HCl in methanol (36 mL) at 0 °C. Ether was added dropwise until precipitation stopped. The solid was then digested in ethyl acetate, filtered ,and then dried overnight at 55 °C (10 torr) (0.367g, 60%). mp 240 °C dec. IR (neat, cm^{-1}) 2969, 2345, 2225, 1596, 1497, 1251, 1173, 877, 849 and 829. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.80 (s, 3H), 3.42 (s, 16 H, overlaps water), 3.59 (bs, 3H) 4.33 (s, 2H), 7.15 (AA', 2H), 7.21 (AA', 2H), 7.71 (BB', 2H), 7.85 (BB', 2H) and 11.78 (bs, 1.4H). ^{13}C NMR (50 MHz, DMSO-d_6) δ 14.1, 20.7, 59.7, 118.4, 118.6, 120.3, 134.7, 170.3. Anal. Calcd for the semihydrate $C_{38}H_{48}Cl_4N_6O_3$: C, 58.62; H, 6.21; Cl, 18.21; N, 10.79. Found: C, 58.78, H, 6.30; Cl, 17.76; N, 10.66.

*5.6.51. 1-(4-(4-(Ammoniomethyl)phenoxy)benzyl)-4-methylpiperazine-1,4-diium chloride **45**.*

To **44** (0.257g, 0.676 mmol) in anhydrous THF (2 mL) under nitrogen was added a THF solution of $LiBH_4$ (4 M, 0.42 mL, 0.831 mmol) while stirring. After 5 min THF solution of $LiHBEt_3$ (1.76 M, 0.89 mL, 1.51 mmol) was added. The reaction was stirred at rt for 48 hours then 2 M NaOH (6 mL) was added. The solution was stirred for 45 min. It was then extracted with ethyl acetate (3 x 25 mL), washed with brine, dried over magnesium sulfate and filtered. The solvent was removed by rotary evaporation. The free base was then dissolved in methanol (1 mL) and 0.5 M HCl in methanol was added. After standing overnight ether was added dropwise, resulting in a white solid. mp 200 °C dec. IR (neat, cm^{-1}) 3400, 2982, 2352, 1603, 1505, 1256, 1173, 949 and 827. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.79 (bs, 3H), 3.59 (bs, 2H), 4.00 (d, J = 5.51 Hz, 2H), 4.36 (s, 2H), 7.04 (AA', 2H), 7.08 (AA', 2H), 7.54 (BB', 2H), 7.65 (BB', 2H) and 8.49 (s, 3H), 11.9 (bs, 1.24H). ^{13}C NMR of the free base (50 MHz, $CHCl_3$-d_1) δ 45.9, 46.0, 53.0, 55.1, 62.4, 118.4, 119.0, 128.4, 130.5. Anal. Calcd for the monohydrate $C_{19}H_{30}Cl_3N_3O_2$: C, 52.01; H, 6.89; Cl, 24.24; N, 9.58; O, 7.29. Found: C, 52.12; H, 6.79; Cl 24.34: N, 9.62.

*5.6.52. 1-(3-Chloro-4-(4-cyanophenoxy)benzyl)-4-methylpiperazine-1,4-diium chloride **46.***

To **1b** (2.00 g, 7.76 mmol) in DCM (12 mL) was added methyl piperizine (0.77g, 7.76 mmol) and sodium triacetoxyborohydride (1.80 g, 8.5 mmol). The reaction was heated overnight at 90 °C and then NaOH was added (1 M, 25 mL). The mixture was extracted with DCM (3 x 25 mL), washed with water (2 x 15mL) and then dried over magnesium sulfate. After filtration and solvent removal via rotary evaporation the free base was treated with 0.5 M HCl in methanol (31 mL) to give the salt. The salt was digested using ethyl acetate and filtered. It was then boiled with DCM and filtered again. The product was dried overnight in the oven at 55 °C. (1.15 g, 57%). mp 230 °C. IR (neat, cm^{-1}) 3498, 3000, 2980, 2944, 2348, 2228, 1596, 1493, 1274, 1263, 1209, 1181, 1167, 1105, 1083, 1064, 952, 925, 905, 889, 859, 851, 836, 824. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.81 (bs, 3H), 3.55 (bs, 17H, overlaps water), 4.31 (bs, 2H), 7.11 (AA', 2H), 7.39 (d, J = 8.2 Hz, 1H), 7.66 (bs, 1H), 7.85 (BB', 2H), 7.95 (bs, 0.7H) and 11.72 (bs, 1.24H). ^{13}C NMR (50 MHz, DMSO-d_6) δ 41.9, 47.4, 49.9, 57.2, 105.7, 117.4, 118.6, 123.1, 125.7, 132.0, 133.6, 134.8, 150.2, 160.2. Anal. Calcd for $C_{19}H_{22}Cl_3N_3O$: C, 55.02; H, 5.35; N, 10.13; Cl, 25.64. Found: C, 54.87; H, 5.42; N, 9.96; Cl, 25.59.

*5.6.53. 1-(4-(4-(Ammoniomethyl)phenoxy)-3-chlorobenzyl)-4-methylpiperazine-1,4-diium chloride **47.***

To (0.280 g, 0.676 mmol) in anhydrous THF (2 mL) under nitrogen was added a 4 M THF solution of $LiBH_4$ (0.42 mL, 0.831 mmol). After 5 minutes $LiHBEt_3$ in THF (1.7 M, 0.89 mL, 1.51 mmol) was added. The reaction was stirred at rt for 48

hours and then stirred with 2 M NaOH (6 mL) for 45 minutes. It was then extracted with ethyl acetate (3 x 25 mL), washed with brine, dried over magnesium sulfate and filtered. The solvent was removed by rotary evaporation. The free base was then dissolved in methanol (1 mL) and 0.5 M HCl in methanol was added. After standing overnight some product precipitated as a white solid. The remaining product was precipitated by dropwise addition of ether. mp 220 °C. IR (neat, cm^{-1}) 3394, 2982, 2375, 1603, 1505, 1463, 1256, 1172, 950, 858 and 826. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.80 (bs, 3H), (3.16, 31H, overlapping signals), 3.53 (bs, 69H, overlaps water), 4.00 (q, J = 5.7 Hz, 2.7H), 4.26 (bs, 2.7H), 7.02 (AA', 2H), 7.14 (d, J = 8.4 Hz, 1H), 7.51 (BB', 2H), 7.60 (d, J = 8.4 Hz, 1H), 7.91 (s, 1 H), 8.37 (s, 3H), 11.65 (bs, 1H). ^{13}C NMR of free base (50 MHz, $CHCl_3$-d_1) δ 46.02, 53.02, 55.1, 61.9, 117.8, 117.9, 120.4, 121.5, 125.5, 128.5, 128.67, 129.8, 131.1, 131.2, 135.2. Anal. Calcd for the semihydrate $C_{38}H_{56}Cl_8N_6O_3$: C, 49.16; H, 6.08; N, 9.05. Found: C, 48.84; H, 5.96; N, 8.63.

5.6.54. Attempted preparation of tert-butyl 4-(3-chloro-4-(4-cyanophenoxy)benzyl)piperazine-1-carboxylate, mesylate salt and 4-(2-chloro-4-(piperazin-1-ylmethyl)phenoxy)benzonitrile ***48.***

By Method F **1b** (0.392 g, 1.52 mmol) and 1-boc-piperazine (Oakwood, 0.283 g, 1.52 mmol) were converted to the crude free amine (0.623 g). The free amine was treated with methanolic HCl (0.5 M, 4 mL) and then anhydrous ether (15 mL) was slowly added to give the salt (0.527 g, 75%). mp 196 °C (sealed tube) dec with effervescence. IR (neat, cm^{-1}) 3008, 2981, 2936, 2515, 2431, 2227, 1695, 1599, 1496, 1255, 1167, 1142, 960, 866, 856, 846, 830. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.42 (s, 9H), 2.99 (m, 2H), 3.27 (m, 4H), 4.02 (d, J = 12.0 Hz, 2H), 4.35 (s, 2H), 7.12 (AA', 2H), 7.40 (d, J = 8.4 Hz, 1H), 7.66 (d, J = 8.3 Hz, 1H), 7.87 (BB', 2H), 7.96 (s, 1H), 11.4 (bs, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 27.9, 50.2, 54.9, 57.2, 79.9, 105.7, 117.4, 118.6, 122.9, 125.6, 128.4, 132.4, 134.0, 134.8, 150.4. 153.4, 160.1. Anal. Calcd for $C_{23}H_{27}Cl_2N_3O_3$: C, 59.49; H, 5.86; Cl, 15.27, N, 9.05. Found: C, 59.48; H, 5.86; Cl, 19.00 N, 8.71. Chlorine remained high in reanalysis consistently. In an attempted preparation of the mesylate salt, treatment of the crude free amine (0.644 g, 1.5 mmol) in EtOAc (2 mL) with methanesulfonic acid (97 μL, 1.5 mmol) at 0 °C followed by anhydrous ether (15 mL) gave the salt (0.469 g, 59%) which was found to have undergone partial loss of Boc. The product (0.469 g) was treated with additional methanesulfonic acid (194 μL, 3 mmol) in anhydrous THF (2 mL) to complete the deprotection. After 7.5 h anhydrous ether (10 mL) was added to precipitate the very hygroscopic salt (0.431 g). The salt was dissolved DCM and NaOH (10%, 4 mL), extracted with DCM (3 x 15 mL), and dried over $MgSO_4$. Filtration and rotary evaporation gave the free base as an oil (0.194 g, 30% based on **1b**). IR (neat, cm^{-1}) 3315, 2942, 2815, 2226, 1607, 1595, 1504, 1487, 1251, 1167, 852, 835, 793. ^{1}H NMR (400 MHz, $CHCl_3$ d_1): δ 1.63 (s, 1H, overlaps water), 2.44 (bs, 4H), 2.91 (t, J = 4.8 Hz, 4H), 3.48 (s, 2H), 6.94 (AA', 2H), 7.07 (d, J = 8.3 Hz, 1H), 7.27 (dd, J = 8.3, 2.0 Hz, 1H, overlaps chloroform), 7.49 (d, J = 2.0 Hz, 1H), 7.60 (BB', 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ. 46.0, 54.4, 62.4, 106.0, 116.9, 118.7, 122.4, 126.7, 128.9, 131.4, 134.1, 137.5, 148.9, 161.0. HRMS-TOF MS EI$^+$ (*m/z*): [M+] calcd for $C_{18}H_{18}N_3OCl$ 327.1138; found 327.1143.

5.6.55. 4-(3-Chloro-4-(4-cyanophenoxy)benzyl)piperazin-1-ium chloride ***49.***

Treatment of **48** with methanolic HCl (0.5M, 3mL) in anhydrous ether (15 mL) at 0 °C gave the salt (0.185 g, 0.46 mmol) assumed to be the monochloride. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.40 (bs, 32H, overlaps water), 4.36 (s, 2H), 7.11 (AA', 2H), 7.40 (d, J = 8.3 Hz, 1H), 7.70 (d, J = 8.3 Hz, 1H), 7.86 (BB', 2H), 8.00 (s, 1H), 9.67 (bs, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 47.4, 57.3, 105.7, 117.4, 118.6, 123.0. 125.6, 132.3, 133.8, 134.8, 150.3, 160.1. The salt was reduced without further purification.

5.6.56. (4-(2-Chloro-4-(piperazin-1-ylmethyl)phenoxy)phenyl)methanamine, 1-(4-(4-(Ammoniomethyl)phenoxy)-3-chlorobenzyl)piperazine-1,4-diium trichloride ***50*****.**

By Method A **49** (0.170 g, 0.467 mmol) was converted to the crude free amine (0.070 g). IR (neat, cm^{-1}) 3347, 3052, 2945, 2828, 1597, 1568, 1506, 1490, 1251, 1167, 858, 830. ^{1}H NMR (400 MHz, $CHCl_3$-d_1) δ 1.62 (s, 7H, overlaps water), 2.43 (s, 4H), 2.90 (t, J = 4.8 Hz, 4H), 3.45 (s, 2H), 3.85 (s, 2H), 6.92 (m, 3H), 7.16 (dd, J = 8.3, 2.0 Hz, 1H), 7.27 (2H, overlaps chloroform), 7.44 (d, J = 2.0 Hz, 1H). ^{13}C NMR (100 MHz, $CHCl_3$-d_1) δ 45.9, 46.0, 54.4, 62.5, 117.9, 120.4, 125.5, 131.1, 135.1, 138.2, 151.4, 155.9. HRMS-TOF MS EI$^+$ (*m/z*): [M+] calcd for $C_{18}H_{22}N_3OCl$ 331.1451; found 331.1451. To the amine in anhydrous ether (4 mL) at 0 °C was added methanolic HCl (0.5 M, 1.5 mL) to give the salt (0.066 g, 0.16 mmol, 34%) assumed to be the trihydrochloride. mp 277 °C dec. IR (neat, cm^{-1}) 3373, 2970, 2684, 2387, 1739, 1599, 1509, 1495, 1259, 1217, 1206, 1170, 1064, 960, 892, 849, 827. ^{1}HNMR (400 MHz, DMSO-d_6) δ 3.37 (s, 8H?, overlaps water), 2.35 (q, J = 6.0 Hz, 2H), 4.30 (bs, 3H), 7.02 (AA', 2H), 7.14 (d, J = 8.4 Hz, 1H), 7.51 (BB', 2H), 7.60 (bs, 1H), 7.93 (bs, 1H), 8.37 (bs, 3H), 9.62 (bs, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 41.53, 47.21, 57.2, 117.5, 118.6, 119.0, 121.3, 121.3, 124.8, 129.4, 129.6, 131.1, 132.2, 133.6, 133.8, 152.1, 156.3. Anal. Calcd for $C_{18}H_{25}Cl_4N_3O$: C, 49.00; H, 5.71; Cl, 32.14; N, 9.52. Found: C, 49.02; H, 5.87; Cl, 32.56; N, 9.54.

5.6.57. 4-(2-Chloro-4-(hydroxymethyl)phenoxy)benzonitrile **51.**

To **1b** (o.258 g, 2.57 mmol) in ethanol (7 mL) was added $NaBH_4$ (0.038 g, 2.57 mmol). After stirring at rt for 1 h 2 M NaOH (5 mL) was added. After stirring for 0.5 h the water (20 mL) was added and the phases were separated. The water phase was extracted with DCM (2 x 20 mL), dried over $MgSO_4$ and then filtered. Rotary evaporation gave 0.645 g which was purified by Kugelrohr distillation (205–220 °C / 0.05 torr) giving a colorless oil (0.641 g, 96%) which then solidified. The material was carried on without further purification. mp 73–77 °C. IR (neat, cm^{-1}) 3407, 3099, 3067, 2929, 2877, 2227, 1610, 1595, 1503, 1486, 1246, 1166, 833. ^{1}H NMR (400 MHz, $CHCl_3$-d_1) δ 1.90 (bs, 1H), 4.73 (s, 2H), 6.94, (AA', 2H), 7.12 (d, J = 8.3 Hz, 1H), 7.32 (dd, J = 8.3, 2.0 Hz, 1H), 7.54 (d, J = 2.0 Hz, 1H), 7.60 (BB', 2H). ^{13}C NMR (100 MHz, $CHCl_3$-d_1) δ 64.0, 106.1, 117.0, 118.7, 122.8, 126.7, 127.1, 129.5, 134.2, 139.8, 149.3, 160.9. HRMS-TOF MS EI$^+$ (*m/z*): [M$^+$] calcd for $C_{14}H_{10}NO_2Cl$ 259.0400; found 259.0390. The product was carried on without further purification.

5.6.58. 4-(2-Chloro-4-(chloromethyl)phenoxy)benzonitrile **52** and 4-(2-chloro-4-(chloromethyl)phenoxy)benzamide **70.**

To **51** (0.641 g, 2.47 mmol) in DCM (20 mL) was added 12 M HCl (15 mL) and *tert*-butylammonium hydrogen sulfate (0.084 g, 0.247 mmol). After stirring overnight starting material was still present in equilibrium with the product. Refluxing the mixture for 4 h did not change the ratio. The layers were separated and the DCM phase was washed with water (20 mL), saturated $NaHCO_3$

(20 mL), and then dried over $MgSO_4$. Rotary evaporation gave an oil (0.616 g) which was purified by Biotage (ethyl acetate/hexane step gradient, Snap ultra 25 g) to give three fractions: **52** (0.454 g, 66%), a mixed fraction of **51** and **52** (0.101 g), and **70** (0.020 g, 2.5%).

52: mp 67–68.5 °C. IR (neat, cm^{-1}) 3077, 2231, 1610, 1600, 1581, 1505, 1487, 1254, 1167, 830, 687. ^{1}H NMR (400 MHz, $CHCl_3$-d_1) δ 4.58 (s, 2H), 6.97 (AA', 2H) 7.11 (d, *J* = 8.1 Hz, 1H), 7.34 (dd, *J* = 8.1, 2.3 Hz, 1H), 7.55 (d, *J* = 2.2 Hz, 1H), 7.62 (BB', 2H). ^{13}C NMR (100 MHz, $CHCl_3$-d_1) δ 44.63, 106.5, 117.2, 118.6, 122.7, 127.1, 128.6, 131.3, 134.2, 136.2, 150.2, 160.6. HRMS-TOF MS EI$^+$ (*m/z*): [M$^+$] calcd for C14H9NOCl2 277.0061; found 277.0050.

70: mp 179–180 °C. IR (neat, cm^{-1}) 3365, 3175, 1644, 1629, 1602, 1575, 1512, 1490, 1257, 1170, 843, 693, 614. ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.80 (s, 2H), 6.98 (AA', 2H), 7.20 (d, *J* = 8.2 Hz, 1H), 7.31 (bs, 1H), 7.47 (dd, *J* = 8.2, 2.1 Hz, 1H), 7.73 (d, *J* = 2.2 Hz, 1H), 7.90 (BB', 2H), 7.93 (bs, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 44.7, 116.5, 122.1, 125.0, 129.4, 129.6, 129.8, 131.1, 135.9, 150.6, 158.8, 167.1. HRMS-TOF MS EI$^+$ (*m/z*): [M$^+$] calcd for C14H11NO2Cl2 295.0167; found 295.0153.

*5.6.59. (3-chloro-4-(4-cyanophenoxy)benzyl)triphenylphosphonium chloride **53**.*

To **52** (0.469 g, 1.69 mmol) in acetonitrile (3 mL) was added triphenylphosphine (1.327 g, 5.07 mmol). The stirred mixture was heated to reflux under nitrogen for 5 h. The solvent was decanted and the crude solid (1.019 g) was then washed with toluene. This solid contained a polar impurity that appeared to be another phosphonium salt. The solvent was removed from the decantate, acetonitrile was added (2 mL) and reflux was continued for another 5 h giving a toluene insoluble solid (0.117 g) without the polar impurity. Purification of the crude mixture from another run (0.555 g) by Biotage chromatography (chloroform/methanol gradient, Snap ultra 25 g), gave pure product (0.316 g) and the polar impurity (0.057 g). mp 240 °C, sinters at 140 °C. IR (neat, cm^{-1}) 3313, 3051, 3009, 2987, 2868, 2775, 2225, 1605, 1588, 1485, 1437, 1249, 1208, 1109, 859, 833, 747, 720, 687. ^{1}H NMR (400 MHz, $CHCl_3$-d_1) δ 5.86 (d, *J* = 14.8 Hz, 2H), 6.86 (AA', 2H), 6.88 (dd, *J* = 8.0, 0.9 Hz, 1H), 7.10 (t, *J* = 2.4 Hz, 1H), 7.43 (dt, *J* = 8.4, 2.4 Hz, 1H), 7.59 (BB', 2H), 7.65 (m, 6H), 7.78 (m, 3H), 7.87 (m, 6H). ^{13}C NMR (100 MHz, $CHCl_3$-d_1) δ 29.2, 29.7, 43.4, 106.5, 117.3, 117.3, 118.1, 118.5, 122.62, 122.65, 126.7, 126.8, 126.8, 130.1, 130.3, 132.3, 132.4, 132.6, 133.7, 134.2, 134.35, 134.45, 135.01, 135.04, 149.99, 150.03, 160.3. Anal. Calcd for the dihydrate $C_{32}H_{28}Cl_2NO_3P$: C, 66.68; H, 4.90. Found: C, 66.77; H, 4.41.

*5.6.60. 4-(2-Chloro-4-((tetrahydro-4H-pyran-4-ylidene)methyl)phenoxy)benzonitrile **54.** 4-(2-chloro-4-methylphenoxy)benzonitrile **56.***

To **53** (0.509 g, 0.942 mmol) at -78 °C in THF (2 mL) was added cold LDA (-78 °C, 2.50 mmol, 0.79 M in THF) by syringe. The solution was stirred for 0.5 h at which point tetrahydro-4H-pyran-4-one (0.250 g, 2.50 mmol) was added by syringe in one portion. After 0.5 h at -78 °C the temperature was increased to -45 °C. After 2 h the cold bath was removed and the solution allowed to warm to rt overnight. HCl (10%, 10 mL) was added to the brown-red solution. The acid phase was extracted with EtOAc (20 mL). The EtOAc phase was washed with saturated $NaHCO_3$, then brine (20 mL) and then dried over $MgSO_4$. Removal

of solvent by rotary evaporation gave a dark colored oil (0.565 g). Biotage chromatography (hexane/ethyl acetate gradient, Snap ultra 10 g) gave the hydrolysis product **56** (0.044 g), the product (0.142 g) as an impure oil, and triphenylphospine oxide (0.195 g). The product was carried on without further purification.

56 oil. IR (neat, cm^{-1}) 3070, 2957, 2926, 2863, 2226, 1610, 1597, 1506, 1503, 1488, 1251, 1166, 1058, 900, 851, 836. ^1H NMR (400 MHz, $CHCl_3$-d_1) δ 2.37 (s, 3H), 6.92 (AA', 2H), 7.02 (d, J = 8.2 Hz, 1H), 7.12 (ddd, J = 8.2, 2.0, 0.6 Hz, 1H), 7.31 (d, J = 1.5 Hz, 1 H), 7.59 (BB', 2H). ^{13}C NMR (100 MHz, $CHCl_3$-d_1) δ 20.6, 105.8, 116.7, 118.8, 122.6, 126.5, 129.0, 131.4, 134.1, 137.0, 147.6, 161.2.

54 oil. IR (neat, cm^{-1}) 3062, 2958, 2907, 2846, 2225, 1653, 1606, 1592, 1502, 1484, 1250, 1164, 1098, 908, 890, 864, 835. ^1H NMR (400 MHz, $CHCl_3$-d_1): δ 2.41 (td, J = 5.5, 1.1 Hz, 2H), 2.53 (td, J = 5.5, 1.1 Hz, 2H), 3.69 (t, J = 5.5, 2H), 3.79 (t, J = 5.5, 2H), 6.27 (s, 1H), 6.96 (AA', 2H), 7.07 (d, J = 8.3 Hz, 1H), 7.14 (ddd, J = 8.4, 2.0, 0.4 Hz, 1H), 7.33 (d, J = 1.9 Hz, 1H), 7.61 (BB', 2H). ^{13}C NMR (100 MHz, $CHCl_3$-d_1) δ 30.5, 37.0, 68.3, 69.2, 106.0, 116.9, 118.6, 121.6, 122.4, 126.5, 128.8, 131.1, 134.1, 136.3, 139.6, 148.1, 160.9.

*5.6.61. (4-(2-Chloro-4-((tetrahydro-4H-pyran-4-ylidene)methyl)phenoxy)phenyl)methanaminium chloride **55***

To 4-(2-chloro-4-((tetrahydro-4H-pyran-4-ylidene)methyl)phenoxy)benzonitrile **54** (0.142 g, 0.436 mmol) in anhydrous THF (2 mL) under nitrogen was added 4 M $LiBH_4$ (0.34 mL, 1.36 mmol) and then 1.7 M $LiHBEt_3$ (1.2 mL, 2.00 mL). After 3 days NaOH (2 M, 5.5 mL) was added. After 1 h of stirring water (10 mL) was added, the mixture was then extracted with DCM (3 x 15 mL), and then dried over $MgSO_4$. Solvent removal gave the crude amine (0.165 g). To this amine was added EtOAc (1 mL) and then methanolic HCl (0.5M, 1 mL). Additional EtOAc (10 mL) was added and half the solvent was removed by rotary evaporation. The mixture was chilled in ice water and the resulting solid collected and dried (0.104 g, 61%). mp 189−192 °C. IR (neat, cm^{-1}) 2952, 2918, 2886, 2603, 1596, 1511, 1494, 1263, 1241, 1231, 1208, 1170, 1096, 908, 885, 866, 850, 821. ^1H NMR (400 MHz, DMSO-d_6) δ 2.33 (t, J = 5.0 Hz, 2H), 2.45 (t, J = 5.1 Hz, 2H), 3.58 (t, J = 5.5 Hz, 2H), 3.67 (t, J = 5.4 Hz, 2H), 3.99 (s, 2H), 6.32 (s, 1H), 6.98 (AA', 2H), 7.07 (d, J = 8.5 Hz, 1H), 7.24 (dd, J = 8.4, 1.9 Hz, 1H) 7.43 (d, J = 1.8 Hz, 1H), 7.48 (BB', 2H), 8.31 (bs, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 30.2, 36.6, 41.3. 67.5, 68.5, 117.0, 121.4, 121.5, 124.8, 128.9, 129.2, 130.6, 131.0, 131.9, 135.0, 139.3, 149.1, 156.9. Anal. Calcd for $C_{19}H_{21}Cl_2NO_2$: C, 62.30; H, 5.78; Cl, 19.36; N, 3.82. Found: C, 62.04; H, 6.05; Cl, 19.00; N, 3.54.

*5.6.62. 4-((2-Chloro-4-formylphenyl)thio)benzonitrile **57**.*

To **21** 4-thiobenzonitrile (1.054 g, 7.80 mmol) in DMA (7 mL) was added **1b** (1.23 g, 7.98 mmol) and K_2CO_3 (1.24 g, 8.81 mmol). The mixture was heated at 10 h at 111−115 °C under nitrogen then poured into 25 g of ice and NaOH (10%, 6 mL). The mixture was extracted with EtOAc (3 x 20 mL), dried on $MgSO_4$, filtered and then the solvent removed by rotary evaporation to give a white solid which was recrystallized from acetonitrile to give the product (1.452 g, 66%). IR (neat, cm^{-1}) 3367, 3085,

3034, 2827, 2794, 2725, 2231, 1697, 1697, 1583, 1548, 905, 895, 852, 809. ^{1}H NMR (400 MHz, $CHCl_3$-d_1) δ 7.19 (1H, d, J = 8.13); 7.53 (AA', 2H); 7.66 (dd, J = 8.11, 1.71, 1H); 7.69 (BB', 2H) 7.93 (d, J = 1.7, 1H); 9.94 (s, 1H). ^{13}C NMR (100 MHz, $CHCl_3$-d_1) δ 112.3, 118.0, 128.1, 130.7, 132.8, 134.7, 136.0, 138.6, 142.1, 198.8. Anal. Calcd for $C_{14}H_8ClNOS$: C, 61.43; H, 2.95; Cl, 12.95; N, 5.12; S, 11.71. Found: C, 61.60; H, 3.12; N, 5.05.

*5.6.63. 4-(3-Chloro-4-((4-cyanophenyl)thio)benzyl)morpholin-4-ium chloride **58.***

By method G **57** (0.451 g, 1.65 mmol) was converted to a free amine. To this oil was added 0.5 M HCl in methanol to give a white solid which was recrystallized from methanol/toluene to give **58** (274 mg, 0.719 mmol, 44%). mp 249 °C dec. IR (neat, cm^{-1}) 2521, 2497, 2461, 2437, 2386, 2229, 1590, 1119, 1081, 1033, 977, 915, 907, 868, 840, 828. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.08 (m, 2H), 3.25 (m, 2H), 3.37 (m, 5H), 3.82 (t, J = 11.3 Hz, 2H), 3.93 (d, J = 12.0 Hz, 2H), 4.36 (s, 2H), 7.40 (AA', 2H), 7.53 (d, J = 8.0 Hz, 1H), 7.65 (d, J = 7.9, 1H), 7.82 (BB', 2H), 8.00 (s, 1H), 11.64 (s, 1H). ^{13}C NMR (400 MHz DMSO-d_6) δ 50.7, 57.5, 63.1, 109.6, 118.5, 129.5, 131.5, 132.1, 132.2, 133.3, 134.4, 135.5, 140.7. Anal. Calcd for $C_{18}H_{18}Cl_2N_2OS$: C, 56.70; H, 4.76; Cl, 18.59; N, 7.35; O, 4.20; S, 8.41. Found: C, 56.73; H, 4.95; N, 7.16.

*5.6.64. 4-(4-((4-(Ammoniomethyl)phenyl)thio)-3-chlorobenzyl)morpholin-4-ium chloride **59.***

By method A **58** (233 mg, 0.611 mmol) was subjected to reduction to give the free amine. The oil was dissolved with methanol and 1 M HCl in EtOAc was added dropwise slowly with stirring to form the salt (0.241 g, 94%). Recrystallization of this compound was not successful. Biotage purification (chloroform/ethanol, Snap ultra 10 g) gave the salt (0.120 g, 46% as a semi-hydrate). mp 180 °C dec. IR 3378, 2928, 2867, 2687, 2597, 2470, 1595, 1493, 1016, 879, 825, 790. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.05 (m, 1H), 3.78 (d, J = 11.4 Hz, 2H) 3.36 (s, 20H overlaps water), 3.83 (q, J = 11.1 Hz, 2H), 3.91 (d, J = 10.7 Hz, 2H), 4.07 (q, J = 5.4 Hz, 2H), 4.29 (s, 2H), 6.91 (d, J = 8.0 Hz, 1H), 7.53 (AA', 2H), 7. 56 (d, J = 7.1 Hz, 1H), 7.62 (BB', 2H), 7.86 (s, 1H), 8.53 (s, 2H), 11.77 (s, 1H). ^{13}C NMR (100 MHz DMSO-d_6) δ 41.7. 50.6, 57.5, 63.0, 129.2, 129.5, 129.7, 130.7, 131.0, 131.5, 132.7, 133.5, 135.2, 137.2. Anal. Calcd for the semihydrate $C_{36}H_{48}Cl_6N_4O_3S_2$: C, 50.18; H, 5.62; Cl, N, 6.50. Found: C, 50.36; H, 5.09; N, 6.36.

5.6.65. (4-(4-Cyanophenoxy)phenyl)-4-oxobutanoic acid **60**.

To a mixture of 4-phenoxybenzonitrile (2.02 g, 10.34 mmol) in 1,1,2,2-tetrachloroethane (25 mL) was added succinic anhydride (1.25 g, 12.53 mmol). The reaction vessel was then placed under a purging flow of nitrogen in an oil bath heated to 50 ℃, after which anhydrous aluminum chloride (3.97 g, 29.77 mmol) was quickly added. After moderate stirring for 1.5 h, the originally pale-gold solution had turned a dark salmon hue and black-brown solid was observed at the bottom of the flask. The activity of the reaction was monitored through the production of ammonium chloride fumes generated by passing the purging gas over concentrated ammonium hydroxide. After 3 days, when no more fumes were observed, the reaction vessel was removed from the oil bath, allowed to cool to 23 ℃, and then quenched with 3M HCl (12 mL). After 1 h of stirring alumina appeared as a white solid. It was

filtered off and reserved. To the filtrate was slowly added 2N NaOH (10 mL) with the attendant formation of an aluminum hydroxide gel. The gooey solution was gravity filtered through coarse filter paper. The colloidal residual was quantitatively transferred to a large petri dish and dried over steam until dry (approximately 2 hours). The combined aluminum solids were then treated by Soxhlet extraction with chloroform for 32 h. Concentration of the chloroform solution by rotary evaporation yielded the acid as a pale white solid (1.415 g, 46%). mp 160−161 °C. IR (neat, cm^{-1}) 3066, 2923, 2229, 1713, 1676, 1590, 1496, 1404, 1234, 1165, 862, 824. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.58 (t, *J* = 6.3 Hz, 2H), 3.24 (t, *J* = 6.3 Hz, 2H), 7.21 (AA', 2H), 7.24 (AA', 2H), 7.90 (BB', 2H), 7.90 (BB', 2H), 12.15 (bs, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 28.3, 33.5, 106.8, 119.0, 119.7, 120.0, 131.1, 133.3, 135.3, 159.4, 160.1, 174.3, 197.6. Anal. Calcd for $C_{17}H_{13}NO_4$: C, 69.15; H, 4.44; N, 4.74. Found: C, 69.31; H, 4.89; N, 4.20.

5.6.66. Ethyl 4-(4-(4-cyanophenoxy)phenyl)-4-oxobutanoate **61**.

To a solution of 4-(4-(4-cyanophenoxy)phenyl)-4-oxobutanoic acid (0.322 g, 1.09 mmol) in absolute ethanol (10 mL, Midwest Grain Products Co.) was added 5 drops of acetyl chloride. The mixture was heated at reflux for 2 h, allowed to cool to rt, and then the solvent was distilled, removing approximately half of the original solution volume. The remaining solvent was removed by rotary evaporation to yield the crude ester as a colorless powder (0.34 g, 97%). The product was then recrystallized from 95% ethanol/water to give colorless needles (0.28 g, 0.86 mmol, 79%). mp 77−79 °C. IR (neat, cm^{-1}) 3098, 2982, 2223, 1730, 1685, 1586, 1494, 1239, 1214, 1162, 1107, 844. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.58 (t, *J* = 6.4 Hz, 2H), 3.24 (t, *J* = 6.4 Hz, 2H), 4.05 (q, *J* = 7.1 Hz, 2H), 7.23 (AA', 2H), 7.24 (AA', 2H), 7.91 (BB', 2H), 8.07 (BB', 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 14.6, 28.3, 33.4, 60.4, 106.9, 119.0, 120.0, 131.1, 133.2, 135.3, 159.5, 160.1, 172.8, 197.5. Anal. Calcd for $C_{19}H_{17}NO_4$: C, 70.58; H, 5.30; N, 4.33. Found: C, 70.40; H, 5.37; N, 4.18.

5.6.67. tert-Butyl (4-(4-(5-oxotetrahydrofuran-2-yl)phenoxy)benzyl)carbamate **62**.

To a stirred solution of the ester, ethyl 4-(4-(4-cyanophenoxy)phenyl)-4-oxobutanoate (0.651 g, 2.013 mmol), in dry CH_3OH (15mL), cooled to 0 ℃, were added di-*tert*-butyl dicarbonate (0.875 g, 4.01 mmol) and nickel (II) chloride hexahydrate (0.058 g, 0.244 mmol). $NaBH_4$ (0.578 g, 15.278 mmol) was then added in portions over 30 minutes. The reaction was effervescent, immediately forming a finely divided black solid; upon complete addition of the borohydride the reaction was allowed to progress for 15 h. Subsequently, the mixture was allowed to warm to 23 ℃, diethylenetriamine (216 μL) was added, and the mixture was allowed to stir for 30 min. Evaporation of the solvent gave a purple residue which was dissolved in EtOAc (50 mL) and extracted with saturated $NaHCO_3$ (2 x 50 mL). The organic layer was dried over $MgSO_4$, then the solvent removed by rotary evaporation to yield the boc-lactone as a pale white powder (0.502 g, 60%). mp 95−97 °C. IR (neat, cm^{-1}) 3398, 2978, 1771, 1682, 1600, 1501, 1233, 1137. 1012, 937, 857. ^{1}H NMR (400 MHz, $CHCl_3$-d_1) δ 1.39 (s, 9H), 2.24 (m, 1H), 2.68 (m, 3H), 4.32 (d, *J* = 6.2 Hz, 2H), 5.52 (m, 1H), 7.00 (AA', H), 7.02 (AA', 2H), 7.28 (BB', 2H), 7.28 (m, 1H), 7.32 (BB', 2H). ^{13}C NMR (100 MHz, $CHCl_3$-d_1) δ 176.9, 157.1, 155.8, 154.9, 135.7, 134.4, 128.7, 118.9, 118.2, 80.5, 77.8, 42.78, 30.2, 28.98, 28.25. This intermediate was carried on without further purification.

5.6.68. (4-(4-(5-Oxotetrahydrofuran-2-yl)phenoxy)phenyl)methanaminium chloride **63**.

To a solution of the boc-lactone **62** in EtOAc was added concentrated HCl in EtOAc The hydrochloride salt immediately precipitated as a fine white powder and was collected by vacuum filtration (0.080g, 71%). mp 242−244 °C. IR (neat, cm^{-1}) 3421, 2911, 2598, 1760, 1599, 1506, 1245, 1181, 1144, 1012, 938, 854. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.41 (bs, 3H), 7.52 (AA', 2H), 7.37 (AA', 2H), 7.07 (BB', 2H) 7.03 (BB', 2H), 5.53 (q, 1H) 4.00 (s,2H), 2.12 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.9, 156.6, 156.5, 134.9, 131.0, 129.3, 128.0, 118.8, 118.6, 80.5, 41.6, 30.3, 29.0. HRMS TOF MS EI$^+$ (*m/z*): [M]$^+$ calcd for (free amine) $C_{17}H_{17}NO_3$ 282.1202 found 282.1113. Anal. Calcd for $C_{17}H_{18}ClNO_3$: C, 63.85; H, 5.67; N, 4.38, Cl, 11.09. Found: C, 63.68; H, 5.75; N, 4.13, Cl, 10.91.

5.6.69. 4-(4-(Hydroxymethyl)phenoxy)benzonitrile **64.**

To **1a** (0.985 g, 4.42 mmol) in EtOH (13 mL) was added $NaBH_4$ (0.167 g, 2.57 mmol). After stirring at rt for 1.5 h 2 M NaOH (4 mL) was added. After stirring for an additional hour water (20 mL) was added, the phases separated, and then the water phase was extracted with DCM (2 X 20 mL), dried over $MgSO_4$ and then filtered. Rotary evaporation gave a colorless oil (1.00 g). The mixture partly dissolved into hot ether. After filtration, pentane was slowly added in portions to give a white solid (0.356, 36%). The mother liquor gave additional solid (0.111, 11%). mp 72.0−72.5 °C. IR (neat, cm^{-1}) 3414, 3278, 3068, 2945, 2890, 2224, 1634, 1596, 1494, 1240, 1197, 1164, 1004, 874, 842, 831, 809. ^{1}H NMR (400 MHz, $CHCl_3$-d_1) δ 1.73 (bs, 1H), 4.72 (s, 2H), 7.00 (AA', 2H), 7.06 (AA', 2H), 7.42 (BB', 2H), 7.60 (BB', 2H). ^{13}C NMR (100 MHz, $CHCl_3$-d_1) δ 64.7, 105.9, 117.9. 118.8, 120.5, 128.9, 134.1, 137.8, 154.3, 161.6. HRMS-TOF MS EI$^+$ (*m/z*): [M$^+$] calcd for $C_{14}H_{11}NO_2$ 225.0790; found 225.0797.

5.6.70. 4-(4-(Chloromethyl)phenoxy)benzonitrile **65.**

To **64** (0.469 g, 2.08 mmol) in DCM (20 mL) was added 12 M HCl (15 mL) and *tert*-butylammonium hydrogen sulfate (0.071 g, 0.208 mmol). After one hour of rapid stirring the mixture was diluted with DCM (15 mL) and water (30 mL). The phases were separated and the organic layer washed with saturated $NaHCO_3$ and then dried on $MgSO_4$. The solution was concentrated by rotary evaporation, ether was added and then pentane. A white solid formed (0.493 g, 97%). mp 79.5−80.1 °C. IR (neat, cm^{-1}) 3074, 2977, 2225, 1594, 1510, 1491, 1243, 1204, 1171, 1164, 874, 850, 834, 660. ^{1}H NMR (400 MHz, $CHCl_3$-d_1) δ 4.61 (s, 2H) 7.03 (AA', 2H), 7.05 (AA', 2H), 7.44 (BB', 2H), 7.62 (BB', 2H). ^{13}C NMR (100 MHz, $CHCl_3$-d_1) δ 45.5, 106.2, 118.2, 118.7, 120.4, 130.6, 134.2, 134.3, 155.0, 161.2. HRMS-TOF MS EI$^+$ (*m/z*): [M$^+$] calcd for $C_{14}H_{10}NOCl$ 243.0451; found 243.0460.

5.6.71. 1-(4-(4-Cyanophenoxy)benzyl)-1H-imidazol-3-ium chloride **66**.

To **65** (0.217 g, 0.890 mmol) in toluene (1 mL) was added imidazole (0.605 g, 8.90 mmol). The mixture was heated at 90 °C for 1 h and then EtOAc (35 mL) was added. The mixture was washed with water (3 x 25 mL), dried over $MgSO_4$, and the solvent removed by rotary evaporation to give the free amine. The amine was treated with HCl in methanol (0.5 M, 3 mL) followed by anhydrous ether (15 mL) which gave the salt (0.220 g, 79%). mp 142−170 °C sealed tube. IR (neat, cm^{-1}) 3328, 3133, 3108, 3042, 2945, 2711, 2623, 2226, 1611, 1598, 1550, 1499, 1240, 1168, 869, 846, 813, 756. ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.46 (s, 2H),

7.10 (AA', 2H), 7.19 (AA', 2H), 7.54 (BB', 2H), 7.70 (m, 1H), 7.82 (m, 1H), 7.85 (BB', 2H), 9.32 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 51.0, 105.4, 118.3, 118.7, 120.4, 122.0, 130.7, 131.8, 134.7, 135.4, 154.8, 160.7. Anal. Calcd for the semihydrate $C_{34}H_{29}Cl_2N_6O_3$: C, 63.75; H, 4.56; Cl, 11.07; N, 13.12. Found: C, 63.79; H, 4.21; Cl, 11.00; N, 12.89.

5.6.72. 4-(4-((1H-imidazol-1-yl)methyl)-2-chlorophenoxy)benzonitrile and 1-(3-chloro-4-(4-cyanophenoxy)benzyl)-1H-imidazol-3-ium chloride ***67.***

To **52** (0.430 g, 1.55 mmol) in toluene was added imidazole (1.05 g, 15.5 mmol). The mixture was heated at 83 °C for 5 h. After cooling the supernatant a solid formed containing largely imidazole. The supernatant was taken up into EtOAc (30 mL), washed with water (4 x 20 mL), and then dried over $MgSO_4$ to give the free amine (0.191 g, 40 %). The water layers were back extracted with DCM (2 x 20 mL), dried, and the solvent removed to give additional amine (0.247 g, 52 %). IR (neat, cm-1) 3105, 2226, 1608, 1595, 1502, 1488, 1250, 1167, 1060, 906, 854, 835, 753. ^{1}H NMR (400 MHz, $CHCl_3$-d_1) δ 5.14 (s, 2H), 6.95 (AA', 2H), 6.95 (overlapping, 1H), 7.09 (m, 2H), 7.15 (bs, 1H), 7.30 (d, J = 1.1 Hz, 1H), 7.59 (bs, 1H), 7. 62 (BB', 2H). ^{13}C NMR (50 MHz, $CHCl_3$-d_1) δ 49.6, 106.5, 117.2, 118.6, 119.2, 123.0, 127.0, 127.6, 129.8, 130.4, 134.23, 135.1, 137.4, 150.2, 160.5. HRMS TOF MS EI$^+$ Calcd for (*m/z*): [M+] calcd for $C_{17}H_{12}N_3OCl$ 309.0669. Found 309.0661. To the free amine (0.435 g, 1.40 mmol) was added HCl in EtOAc (1 M, 3 mL). The solvent was removed by rotary evaporation to give a hygroscopic glass **67** (0.512 g) which contained traces of acetic acid. IR (neat, cm^{-1}) 3099, 3025, 2928, 2794, 2706, 2571, 2460, 2226, 1715, 1607, 1595, 1573, 1544, 1488, 1248, 1166, 1061, 901, 823, 752, 689. ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.48 (s, 2H), 7.06 (AA', 2H), 7.37 (d, J = 8.5 Hz, 1H), 7.53 (dd, J = 8.4, 2.0 Hz, 1H), 7.71 (t, J = 1.5 HZ, 1H), 7.85 (m, 4H), 9.33 (s, 1H). ^{13}C NMR (50 MHz, DMSO-d_6) δ 50.3, 105.6, 117.3, 118.6, 120.4, 122.0, 123.3, 125.8, 129.5, 131.2, 134.0, 134.8, 135.6, 149.8, 160.2. This compound was carried on without further purification.

5.6.73. 1-(4-(4-(Ammoniomethyl)phenoxy)benzyl)-1H-imidazol-3-ium chloride **68.**

By Method A **66** (0.190 g, 0.609 mmol) gave the free amine (0.224 g). The crude amine was dissolved in methanol (10 mL) and then treated with methanolic HCl (0.5 M, 3 mL). The solid collected (o.432 g) was found to be impure. The material was cycled between the free base with NaOH and the salt with methanolic HCl twice more giving ultimately the pure salt as a glass (0.042 g, 20%). IR (neat, cm^{-1}) 3397, 2928, 2859, 2718, 2603, 1602, 1574, 1540, 1502, 1453, 1238, 1172, 875, 834, 816, 751. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.99 (q, J = 5.5 Hz, 2H), 5.46 (s, 2H), 7.03 (AA', 2H), 7.05 (AA', 2H), 7.49 (BB', 2H), 7.53 (BB', 2H), 7.70 (t, J = 1.6 Hz, 1H), 7.80 (t, J = 1.6 Hz, 1H), 8.33 (s, 3H), 9.3 (t, J = 1.3 Hz, 1H) . ^{13}C NMR (100 MHz, DMSO-d_6) δ 41.5, 51.0, 118.8, 118.9, 120.3, 121.9, 129.5, 130.2, 130.4, 131.0, 135.3, 156.3, 156.8. Anal. Calcd for the semihydrate $C_{34}H_{40}Cl_4N_6O_3$: C, 56.52; H, 5.58; Cl, 19.63; N, 11.63. Found: C, 56.82; H, 5.69; Cl, 19.81; N, 11.74.

5.6.74. 1-(4-(4-(Ammoniomethyl)phenoxy)-3-chlorobenzyl)-1H-imidazol-3-ium chloride ***69***.

By Method A 67 (0.250 g, 0.722 mmol) was converted into the free amine (0.241 g). To 0.163 g (0.519 mmol) of this amine in EtOAc (2 mL) was added methanolic HCl (0.5M, 2.8 mL). The precipitate was collected and then dried (0.141 g, 70%

from the amine). mp 273 °C dec. IR (neat, cm^{-1}) 3123, 3028, 2919, 2819, 2604, 1613, 11600, 1566, 1514, 1490, 1259, 1211, 1174. 910, 855, 832, 818, 812, 757, 682. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.99 (q, J = 5.6 Hz, 2H), 5.46 (s, 2H), 6.99 (AA', 2H), 7.14 (d, J = 8.4 Hz, 1H), 7.48 (dd, J = 8.4, 2.1 Hz, 1H) 7.53 (BB', 2H), 7.71 (t, J = 1.6 Hz, 1H), 7.81 (d, J = 2.1 Hz, 1H), 7.85 (t, J = 1.6 Hz, 1H), 8.48 (s, 3H), 9.34 (t, J = 1.3 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 41.5, 50.3, 117.3, 120.4, 121.6, 121.9, 125.0, 129.2, 129.3, 131.0, 131.1, 132.7, 135.5, 151.4, 156.3. Anal. Calcd for the semihydrate $C_{34}H_{38}Cl_6N_6O3$: C, 51.60; H, 4.84; Cl, 26.88; N, 10.62. Found: C, 51.38; H, 4.98; Cl, 26.00; N, 10.51.

5.6.75. 4-(4-((1H-imidazol-1-yl)methyl)-2-chlorophenoxy)benzamide **71.**

The chloro-amide **70** (0.020 g, 0.0675 mmol) was converted to the imidazole derivative as described for **67** to give the imidazole-amide (0.013 g, 49%). IR (neat, cm^{-1}) 3343, 3182, 3116, 2925, 1664, 1610, 1597, 1579, 1504, 1490, 1250, 1169, 906, 855, 739. ^{1}H NMR (400 MHz, $CHCl_3$-d_1) δ 5.22 (s, 2H), 6.93 (s, 1H), 6.94(AA', 2H), 7.2 (d, J = 8.1 Hz, 1H), 7.25 (s, 1H), 7.29 (dd, J = 8.2, 2.2 Hz, 2H), 7.55 (d, J = 2.1 Hz, 1H), 7.79 (s, 1 H), 7.88 (BB', 2H), 7.91 (bs, 1H). ^{13}C NMR (100 MHz, $CHCl_3$-d_1) δ 48.3, 116.2, 119.6, 122.4, 125.2, 128.2, 128.9, 129.2, 129.7, 129.9, 136.2, 137.4, 150.0, 158.9, 167.1. HRMS-TOF MS EI$^+$ (m/z) [M$^+$] calcd for $C_{17}H_{14}N_3OCl$ 327.0775; Found 327.0784. Due to the small amount of this byproduct and its poor activity the compound was not further characterized.

*5.6.76. 4-(2-Chloro-4-(morpholinomethyl)phenoxy)benzaldehyde **72**.*

To **36** (0.506 g, 1.39 mmol) in methylene chloride (5 ml) at -45 ℃ under nitrogen was added DIBAL-H (1 M in hexane, 3.98 ml, 3.98 mmol) dropwise. After 1 h of stirring the cold mixture was poured into rapidly stirring rt 1 M HCl and then stirred for 15 min. The mixture was extracted with DCM (3 x 10 mL), washed with 2.5 M NaOH and then dried with $MgSO_4$. Removal of solvent by rotary evaporation gave an orange oil (0.45 g, 88.9%). ^{1}H NMR (400 MHz, $CHCl_3$–d_1) δ 2.48 (t, J = 4.4 Hz, 4H), 3.5 (s, 2H), 3.74 (t, J = 4.4 Hz, 4H), 6.98 (AA', 2H), 7.09 (BB', 1H), 7.50 (BB', 1H), 7.85 (AA', 2H), 9.93 (s, 1H). ^{13}C NMR (400 MHz, $CHCl_3$–d_1) δ 190.7, 162.5, 149.4, 136.8, 131.9, 131.4, 131.3, 128.8, 126.9, 122.46, 116.7, 66.9, 62.2, 53.6. HRMS-TOF MS ES$^+$ (m/z): [M+] calcd for $C_{18}H_{18}ClNO_3$ 331.10; found 331.0. The material was carried on without further purification.

*5.6.77. 4-(3-Chloro-4-(4-((dimethylammonio)methyl)phenoxy)benzyl)morpholin-4-ium chloride **73**.*

By Method F **72** (0.325 g, 0.980 mmol) was converted to the crude amine (0.368 g). Flash chromatography with EtOAc then 10% methanol/EtOAC, followed by 100% methanol gave the amine (0.158 g). The amine in DCM (3 mL) was treated with methanolic HCl (0.5M, 2.5 mL). The mixture was reduced by rotary evaporation to a few mL and then EtOAc was added in portions to give the salt (0.177 g, 42%). mp 257 °C dec. IR (neat, cm^{-1}) 2974, 2902, 2872, 2552, 2504, 2472, 1614, 1604, 1511, 1493, 1285, 1260, 1123, 937, 928, 867, 804, 846. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.66 (d, J = 3.6 Hz, 6H) 3.09 (m, 2H), 3.24 (d, J = 11.7 Hz, 2H), 3.84 (t, J = 11.1 Hz, 2H), 3.93 (m, 2H), 4.25 (d, J = 4.1 Hz, 2H), 4.34 (s, 2H), 7.06 (AA', 2H) 7.20 (d, J = 8.5 Hz, 1H), 7.61 (BB', 2H), 7.65 (d, J = 8.8 Hz, 1H), 7.99 (bs, 1H), 10.98 (bs, 1H), 11.78 (bs, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ

41.3, 50.6, 57.5, 58.5, 63.0, 117.6, 121.4, 124.8, 127.0, 132.2, 133.2, 133.8, 151.9, 157.0. Anal. Calcd for $C_{20}H_{27}Cl_3N_2O_2$: C, 55.38; H, 6.27; Cl, 24.52; N, 6.46. Found: C, 55.03; H, 6.50; Cl, 24.75; N, 6.30.

*5.6.78. 4-(3-Chloro-4-(4-imidazolophenoxy)benzyl)morpholin-4-ium chloride **74**.*

To **36** (0.342 g, 0.936 mmol) in DMA (1 mL, 0.196 mmol) was added ethylene diamine (1.0 mL, 15.0 mmol) and sodium hydrosulfide hydrate (11 mg). The mixture was stirred in an oil bath at 120 °C for 2 h. The mixture was poured into water, extracted with EtOAc (3 x 20 mL) and then dried over $MgSO_4$. Solvent removal by rotary evaporation gave the free amine (0.408 g). The salt was precipitated from EtOAc with methanolic HCl (0.5 M, 5.6 mL), concentrated by rotary evaporation at 55 °C, vacuum filtered, and oven dried, giving the product (0.363g, 0.823 mmol, 88% yield). mp 298−299 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.10 (m, 2H) , 3.29 (m, 2H) , 3.83 (t, J = 11.4 Hz, 2H) , 3.98 (s, 4H) , 4.37 (s, 2H), 7.19 (AA‘, 2H), 7.41 (d, J = 8.4 Hz, 1H), 7.72 (d, J = 8.6 Hz, 1H), 8.03 (s, 1H), 8.10 (BB‘, 2H), 10.75 (s, 2H), 11.76 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 44.2, 50.6, 57.5, 63.1, 116.9, 123.0, 125.6, 128.6, 131.3, 132.5, 134.0, 150.4, 164.0. Anal. Calcd for the dihydrate $C_{20}H_{28}Cl_3N_3O_{bb}$: C, 49.96; H, 5.87; Cl, 22.12; N, 8.74. Found: C, 49.60; H, 5.40; Cl 22.30; N 8.57.

*5.6.79. 3-Chloro-4-(4-formylphenoxy)benzaldehyde **75**.*

To 3-chloro-4-fluorobenzaldehyde (6.433 g, 0.0406 mol) was added 4-hydroxybenzaldehyde (5.13 g, 0.0420 mol) and K_2CO_3. The mixture was heated in DMA for 15 h at 115 °C and then poured onto ice (30 g) and NaOH (10%, 3.5 mL). The gummy solid was taken up into DCM (75 mL) and then extracted with water (3 x 75 mL). The DCM phase was dried over $MgSO_4$ and the solvent was removed by rotary evaporation giving viscous oil (13.1 g). The oil was distilled by Kugelrohr (57 ^{0}C at 0.2 torr) to remove volatile materials. The residue (10.2 g) was then distilled (177−211 °C at 0.05 torr) to give a colorless viscous oil (8.95 g, 86%) which gradually became a camphor-like solid. mp 50−52 °C. IR (neat, cm^{-1}) 3067, 2839, 2730, 1694, 1605, 1583, 1502, 1485, 1246, 1210, 1189, 1156, 1054, 923, 906, 806, 820. ^{1}H NMR (400 MHz, $CHCl_3$-d_1) δ 7.13 (AA', 2H), 7.18 (d, J = 8.4 Hz, 1H), 7.81 (dd, J = 8.4, 2.0 Hz, 1H), 7.93 (BB', 2H), 8.04 (d, J = 2.0 Hz, 1H), 9.96 (s, 1H), 9.98 (s, 1H). ^{13}C NMR (50 MHz, $CHCl_3$-d_1) δ 116.6, 118.3, 121.0, 127.2, 129.7, 132.2, 132.6, 133.7, 156.1, 160.7, 189.4, 190.5. HRMS TOF MS ES$^+$ (m/z): [M+] calcd for $C_{14}H_9ClO_3$ 260.0240; found 260.0239. The compound was carried on without further purification.

*5.6.80. 4-(3-Chloro-4-(4-(morpholin-4-iummethyl)phenoxy)benzyl)morpholin-4-ium chloride **76**.*

By Method F **75** (0.386 g, 1.48 mmol) was converted to the free amine (0.563g). The amine was dissolved in methanol (2 mL) and then treated with methanolic HCl (0.5M, 6.5 mL) and ether to precipitate the salt (0.511 g, 72%). The salt was digested in refluxing acetonitrile to give the analytical sample. mp 290 °C dec. IR (neat, cm^{-1}) 3383, 2983, 2361, 1603, 1505, 1256, 1173, 950, 877, 858, 826. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.07 (m, 4H), 3.22 (m, 4H), 3.83 (m, 4H), 3.92 (m, 4H), 4.32 (m, 4H), 7.06 (AA’, 2H), 7.20 (d, J = 8.4 Hz, 1H), 7.64 (m, 3H), 7.96 (s, 1H), 11.49 (bs, 1H), 11.57 (bs, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ

50.5, 50.6, 57.5, 58.2, 63.0, 117.7, 121.3, 124.5, 124.8, 127.0, 132.2, 133.6, 133.8, 152.0, 157.1. Anal. Calcd for $C_{22}H_{29}Cl_3N_2O_3$: C, 55.53; H, 6.14; Cl, 22.35, N, 5.89. Found: C, 55.27; H, 5.74; Cl, 23.07; N, 5.65.

*5.6.81. 4-(4-(1H-imidazol-1-yl)phenoxy)-3-chlorobenzaldehyde **77**.*

To **1b** (0.634 g, 4 mmol) in DMA (4 mL) was added 4-(1H-imidazol-1-yl)phenol (0.646 g, 4 mmol) and anhydrous K_2CO_3 (0.608 g, 4.4 mmol). The mixture was then heated at 115 °C for 22 h under nitrogen. EtOAc (30 mL) was added and the mixture was extracted with water (4 x 30 mL), and then dried over $MgSO_4$ to give an oil (0.780 g, 65%). ^{1}H NMR (400 MHz, $CHCl_3$-d_1) δ 7.05 (d, J = 8.4 Hz, 1H), 7.18 (AA', 2H), 7.23 (s, 1H), 7.27 (s, 1H) 7.44 (BB', 2H), 7.75 (dd, J = 8.4, 2.0 Hz, 1H)), 7.80 (s, 1H), 8.03 (d, J = 2.0 Hz, 1H), 9.93 (s, 1H). ^{13}C NMR (100 MHz, $CHCl_3$-d_1) δ 118.4, 118.8, 120.7, 123.5, 126.0, 129.7, 130.6, 132.2, 132.8, 134.2, 135.7, 154.4, 157.6, 189.5. The product was carried on without further purification.

*5.6.82. 4-(4-(4-(1H-imidazol-3-ium-1-yl)phenoxy)-3-chlorobenzyl)morpholin-4-ium chloride **78**.*

By Method F **77** (0.707 g, 2.37 mmol) with added HOAc (2.4 mL) was converted to the amine, an oil (0.915 g), containing 22% of the alcohol [4-(4-(1H-imidazol-1-yl)phenoxy)-3-chlorophenyl)methanol]. Biotage separation using 0.48 g of this material (EtOAc/methanol gradient, Snap ultra 25 g) gave a product-containing fraction (0.213 g) with 3.5% of the alcohol. Treatment with methanolic HCl (0.5 M, 3.4 mL) followed by rotary evaporation gave a highly hygroscopic glass (0.274 g). The solid was taken up into a minimum amount of methanol and a solid was then precipitated by slow addition of EtOAc over several hours. The solid was then digested in reluxing acetonitrile. mp 264−266 °C (sealed tube) dec. IR (neat, cm^{-1}) 3382, 3091, 3032, 2932, 2599, 1639, 1600, 1570, 1544, 1508, 1250, 1122, 957, 864, 833. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.12 (bs, 3H), 3.25 (bs, 4H?, overlaps water), 3.91 (bs, 4H), 4.36 (s, 2H), 7.24 (AA', 2H), 2.28 (d, J = 8.4 Hz, 1H), 7.70 (dd, J = 8.4, 2.0, 1H), 7.82 (BB', 2H), 7.89 (m, 1H), 9.66 (s, 1H), 11. 88 (bs, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 50.6, 57.5, 63.0, 118.4, 121.1, 121.8, 124.3, 125.0, 127.6, 130.6, 132.4, 134.0, 134.6, 151.6, 156.9. Anal. Calcd for the dihydrate: C, 50.17; H, 5.47; Cl, 22.21; N, 8.78. Anal. Calcd for the monohydrate: C, 52.13; H, 5.25; Cl, 23.08; N, 9.12; O, 10.42. Found: C, 51.31; H, 5.33.

*5.6.83. (4-(4-(1H-imidazol-1-yl)phenoxy)-3-chlorophenyl)methanol **79**.*

This compound was isolated as a byproduct (0.090 g) in the preparation of **78**. Recrystallization from EtOAc gave the solid free amine (0.54 g). mp 92−93 °C. IR (neat, cm^{-1}) 3214, 3119, 2917, 2853, 1514, 1488, 1243, 1057, 965, 904, 830, 735. ^{1}H NMR (400 MHz, DMSO-d_6) δ (bs, 1H), 4.71 (s, 2H), 7.03 (AA', 2H), 7.06 (d, J = 8.3 Hz, 1H), 7.19 (s, 1H), 7.23 (s, 1H), 7.29 (dd, J = 8.4, 2.1 Hz, 1H), 7.33 (BB', 2H), 7.53 (d, J = 2.0, Hz, 1H), 7.78 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 63.9, 118.3, 118.6, 121.6, 123.3, 126.4, 126.6, 129.4, 130.2, 132.6, 135.8, 138.9, 150.8, 156.6. Anal. Calcd for the semihydrate $C_{32}H_{28}Cl_2N_4O_5$: C, 62.04; H, 4.56. Found: C, 61.62; H, 4.22.

5.6.84. 3-(4-(4-Cyanophenoxy)phenyl)propanamide **80**.

To **7** (0.534 g, 1 mmol) in acetonitrile (8 mL) was added N-hydroxysuccinimide (0.230 g, 2 mmol). The mixture was sonicated to dissolve most of the solids and then 3-(((ethylimino)methylene)amino)-N,N-dimethylpropan-1-aminium chloride (0.767 g, 2 mmol) was added followed by another 5 seconds of sonication. After stirring for 5 h water (10 mL) was added and the mixture was then extracted with CH_2Cl_2 (3 x 20 mL). The solution was dried over Na_2SO_4, filtered, and then the solvent removed by rotary evaporation to give the active ester (1.031 g). Concentrated aqueous ammonia (29%, 6 mL) was added and the mixture was then stirred overnight. Water (40 mL) was added and the solid then collected by vacuum filtration. The solid was washed with water (10 mL) in three portions. The solid was dried to give the amide (0.414, 78%). mp 146.0–148.5 °C. IR (neat, cm^{-1}) 3385, 3352, 3189, 3064, 2928, 2229, 1651, 1631, 1598, 1496, 1241, 1204, 1172, 873, 848, 830. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.38 (t, J = 7.7 Hz, 2H), 2.83 (t, J = 7.7 Hz, 2H), 6.77 (s, 1H), 7.06 (AA', 4H), 7.29 (s, 1H), 7.31 (BB', 2H), 7.82 (BB', 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 30.1, 36.6, 104.8, 117.6, 118.7, 120.2, 130.1, 134.5, 138.5, 152.3, 161.4, 173.3. HRMS-TOF MS EI$^+$ (*m/z*): [M$^+$] calcd for $C_{16}H_{14}N_2O_2$ 266.105; found 266.1052. Anal. Calcd for $C_{16}H_{14}N_2O$: C, 72.17; H 5.30, N, 10.52. Found: C, 72.07; H, 5.52; N, 10.69.

5.6.85. 3,3'-((((Azanediylbis(methylene))bis(4,1-phenylene))bis(oxy))bis(4,1-phenylene))dipropanamide **81**.

Amidonitrile **80** (0.150 g, 0.563 mmol) was dissolved in 95% ethanol (14 mL) and concentrated aqueous ammonia was added (2 mL). Hydrogenation (60 psi) for 21 h gave a mixture of **80** and **81**. The mixture was applied to silica gel and eluted with EtOAc, which gave recovered **80** (0.078 g). Subsequent elution with methanol gave **81** (0.031 g, 11%). This solid was digested in refluxing DCM to give **81** (0.017 g, 6%). mp 183–184 °C. IR (neat, cm^{-1}) 3387, 3195, 3036, 2925, 1650, 1629, 1604, 1504, 1416, 1244, 1200, 1167, 1102, 1013, 875, 840, 823. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.35 (t, J = 7.7 Hz, 2H), 2.78 (t, J = 7.7 Hz, 2H), 3.66 (s, 2H), 6.75 (s, 2H), 6.90 (AA', 2H), 6.92 (AA', 2H), 7.21 (BB', 2H), 7.29 (s, 1H), 7.34 (BB', 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 30.1, 36.7, 51.5, 117.7, 118.1. 118.4, x129.4, 129.6, 130.1, 134.6, 135.8, 136.4, 155.0, 155.5, 173.4. HRMS-TOF MS EI$^+$ (*m/z*): [M$^+$] calcd for $C_{32}H_{33}N_3O_4$ 523.2471; found 523.2495.

5.6.86. Ethyl 3-(4-(4-((3-(4-(4-(aminomethyl)phenoxy)phenyl)propanamido)methyl)phenoxy)phenyl)propanoate **82**.

A neat sample of **3a** (0.396 g, 1.323 mmol) upon standing for six months at rt formed **82** as a slightly grey solid isolated from EtOAc/hexane (0.066 g, 9%) and then recrystallized from ethanol. mp 143–158 °C. IR (neat, cm^{-1}) 3297, 3038, 2928, 1732, 1641, 1605, 1553, 1504, 1256, 1227, 1166, 1103, 1013, 876, 832, 815. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.15 (t, J = 7.1 Hz, 3H), 2.44 (t, J = 7.6 Hz, 2H), 2.59 (t, J = 7.6 Hz, 2H), 2.83 (t, J = 7.4 Hz, 4H), 3.68 (s, 2H), 4.04 (q, J = 7.2 Hz, 2H), 4.23 (d, J = 6.0 Hz, 2H), 6.89 (AA', 8H), 7.14 (BB', 2H), 7.21 (BB, 4H), 7.30 (BB', 2H), 8.32 (t, J = 5.7 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 14.1, 29.5, 30.3, 35.2, 37.0, 41.4, 45.0, 59.8, 118.1, 118.2, 118.3, 118.4, 128.5, 128.8, 129.8, 134.5, 135.5, 136.0, 139.2, 155.1, 155.2, 155.5, 171.2, 172.2. HRMS-TOF MS ES$^+$ (*m/z*): [M + H]$^+$ calcd for $C_{34}H_{37}N_2O_8$ 553.2702; found 553.2709.

5.6.87. Bis-(4-(4-(2-carboxyethyl)phenoxy)benzyl)ammonium chloride **83**.

To bis-ester amine **9a** (0.164 g, 0.282 mmol) in 95% ethanol (3 mL) was added 2N NaOH (0.71 mL, 1.41 mmol). After 2 h water (3 mL) was added to dissolve solids and the solution was stirred another 1.5 h at which point 12 M HCl was added dropwise. The flask was cooled to 0 °C and then vacuum filtered to give **83** (0.125 g, 79%). mp 251.5–254 °C dec with gas evolution. IR (neat, cm^{-1}) 3337, 2227, 1731, 1655, 1597, 1498, 1243, 1202, 1168, 875, 837. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.53 (t, J = 7.7 Hz, 4H), 2.82 (t, J = 7.6 Hz, 4H) 4.08 (s, 4H), 6.94 (AA', 4H), 7.01 (AA' 4H), 7.26 (BB', 4H) 7.51 (BB', 4H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 29.6, 35.3, 49.4, 118.1, 119.0, 129.9, 131.9, 136.5, 154.3, 157.5, 173.7. HRMS-TOF MS EI$^+$ in sodium acetate (*m/z*): $[M + Na]^+$ calcd for $C_{32}H_{31}NO_6{}^{23}Na$ 548.2049; found 548.2072.

*5.6.88. 4,4'-((((((Methylammonio)bis(methylene))bis(4,1-phenylene))bis(oxy))bis(3-chloro-4,1-phenylene))bis(methylene))bis(morpholin-4-ium) chloride **84**. Attempted preparation of 1-(4-(2-chloro-4-(morpholinomethyl)phenoxy)phenyl)-N-methylmethanamine via the imine. 1-(4-(2-chloro-4-(morpholinomethyl)phenoxy)phenyl)-N-methylmethanimine.*

To **72** (0.45 g, 1.35 mmol) in DCE (5 mL) was added with rapid stirring methylammonium chloride (10 mmol, 0.7 g) and 2.5 M NaOH (10 mmol, 4 mL). The reaction was allowed to stir under nitrogen overnight. The mixture was then extracted with DCE (3 x 5 mL), dried with $MgSO_4$ and the solvent removed with rotary evaporation. A brown oil formed (0.485g, 94.7%). IR (neat, cm^{-1}) 3034, 2952, 2853, 1650, 1607, 1596, 1584, 1505, 1467, 1246, 1115. ^{1}H NMR (400 MHz, $CHCl_3$–d_1) δ 2.46 (t, 4.4 Hz,5H), 3.47 (d, J = 6.4 Hz, 2H), 3.49 (d, J = 1.6, 3H), 3.73 (t, J = 4.8 Hz, 8H), 6.95 (AA', 2H), 7.01 (d, J = 8.4 Hz, 1H), 7.21 (BB', 1H), 7.47 (BB', 1H), 7.67 (AA', 2H), 8.24 (d, J = 1.6 Hz, 1H). ^{13C} NMR (400 MHz, $CHCl_3$–d_1) δ 161.4, 159.1, 150.5, 135.6, 131.2, 129.5, 128.6, 121.4, 117.8, 117.2, 66.9, 62.2, 53.5, 48.1, 43.5. HRMS-TOF MS ES$^+$ (*m/z*): $[M^+]$ calcd for $C_{19}H_{21}ClN_2O_2$ 344.13; found 344.1. This material was carried on without further purification.

To 1-(4-(2-chloro-4-(morpholinomethyl)phenoxy)phenyl)-N-methylmethan imine (0.485 g, 1.41 mmol) in DCE (4 mL) was added sodium triacetoxyborohydride (0.3 g, 1.4 mmol). The reaction was stirred overnight under nitrogen. The mixture was quenched with $NaHCO_3$, extracted with EtOAc (3 x 10 mL), and then dried over $MgSO_4$. Removal of solvent by rotary evaporation gave an oil (0.171g, 38%) which was shown to be a tertiary amine. IR (neat, cm^{-1}) 3028, 2952, 2857, 2805, 1609, 1600, 1506, 1489, 1248, 1116, 1010, 866, 843, 828. ^{1}H NMR (400 MHz, $CHCl_3$-d_1) δ ~1.25 (t, J = 7 Hz, 9H), 2.45 (s, 4H), 3.45 (s, 2H), 3.48 (d, J = 2 Hz, 2H), 3.72 (t, J = 4.4 Hz, 4 H), 6.90 (d, J = 2.4 Hz, 1H), 6.21 (AA', 2H), 7.15 (BB', 1H), 7.30 (AA', 2H), 7.44 (BB', 1H). ^{13}C NMR (400 MHz, $CHCl_3$-d_1) δ 155.9, 151.6, 134.6, 131.1, 131.0, 130.2, 128.4, 125.5, 120.3, 117.7, 66.9, 62.3, 61.1, 53.5, 43.4, 42.1, 29.7. Mass spectroscopy indicated only starting material. HRMS-TOF MS ES$^+$ (*m/z*): $[M^+]$ calcd for $C_{19}H_{21}ClN_2O_2$ 344.13; found 344.1. To this material (0.45g, 92.3%) in DCM (3 mL) was added 0.5M HCl (6 mL). The precipitate was collected and washed with methanol and EtOAc. The solid was recrystallized in hot methanol giving the tertiary ammonium salt **84** (0.171g, 38%). mp 270 °C dec. ^{1}H NMR (400 MHz, $CHCl_3$-d_1) δ 3.10 (s, 4H), 3.26 (s, 4H), 3.76 (s, 4H), 3.93 (s, 4H), 4.20 (d, J = 12.8 Hz, 2H), 4.389 (t, J = 13.2 Hz, 4H), 7.06 (AA', 4H), 7.20 (BB', 2H), 7.60 (AA', 6H), 7.89 (BB', 2H), 10.60 (s, 0.4H), 11.01 (s, 0.6H). ^{13}C NMR (400, $CHCl_3$-d_1) δ 157.8, 152.8, 134.3, 134.1, 132.8, 127.4, 125.8, 125.7, 122.2, 118.6, 79.5, 64.0, 59.1, 58.8, 51.7. Anal. Calcd for

$C_{37}H_{44}Cl_5N_3O_4$: C, 57.56; H, 5.74; N, 5.44. Found: C, 57.62; H, 5.72; N, 5.41. The secondary monomethylammonium salt was not detected. Direct reductive amination of aldehyde **72** also gave only **84**.

*5.6.89. 4-(4-(4-Cyanophenoxy)-3-fluorobenzyl)morpholin-4-ium chloride **85**.*

By Method F **1d** (0.386 g, 1.6 mmol) gave the crude free amine 0.467 g. The amine was treated with methanolic HCl (0.5 M, 3.5 mL). EtOAc was added to precipitate the salt (0.402 g, 72%). mp 247−248 °C dec. IR (neat, cm^{-1}) 3099, 3034, 2995, 2980, 2956, 2929, 2532, 2469, 2421, 2225, 1601, 1582, 1508, 1501, 1297, 1284, 1273, 1229, 1178, 1123, 967, 909. 881, 866, 843, 800, 749. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.08 (m, 2H), 3.28 (d, J = 12.8 Hz, 2H), 3.83 (t, J = 11.7 Hz, 2H), 3.95 (d, J = 11.4 Hz, 2H), 4.36 (s, 2H), 7.17 (AA', 2H), 7.43 (t, J = 8.4 Hz, 1H), 7.53 (d, J = 8.1 Hz, 1H), 7.83 (d, J = 11.9 Hz, 1H), 7.86 (BB', 2H), 11.57 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 48.6, 50.6, 57.7, 63.1, 105.8, 117.2, 118.6, 120.4, 120.6, 123.4, 128.3, 129.1, 134.8, 141.9, 152.0, 152.4, 160.3. Anal. Calcd for the semihydrate $C_{36}H_{38}Cl_2F_2N_4O_5$: 60.42, H, 5.35, N, 7.83. Found 60.74; H, 5.47, N 7.53.

*5.6.90. 4-(4-(4-(Ammoniomethyl)phenoxy)-3-fluorobenzyl)morpholin-4-ium chloride **86**.*

By Method A **85** (0.332 g, 0.952 mmol) was converted to the free amine (0.325 g). Methanolic HCl (0.5 M, 6 mL) was added to the amine followed by EtOAc (5 mL). Solvent was removed by rotary evaporation until some solid formed at which point additional EtOAc (12 mL) was added to complete the precipitation of the salt (0.265 g, 41%). mp 261 °C dec. IR (neat, cm^{-1}) 2912, 2690, 2587, 2544, 2476, 1601, 1510, 1294, 1275, 1233, 1173, 1124. 1083, 967, 889, 870, 831. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.08 (bs, 2H), 3.24 (d, J = 10.1 Hz, 2H), 3.85 (t, J = 10.9 Hz, 2H), 3.92 (s, 2H), 3.99 (q, J = 5.2 Hz, 2H), 4.34 (s, 2H), 7.05 (AA' 2H), 7.24 (t, J = 8.5 Hz, 1H), 7.49 (d, J = 8.7 Hz, 1H), 7.52 (BB', 2H), 7.81 (d, J = 11.6 Hz, 1H), 8.45 (bs, 3H), 11.80 (bs, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 41.5, 50.6, 57.7, 63.1, 117.0, 120.3, 120.5, 122.1, 127.0, 128.9, 129.3, 131.1, 143.4, 143.5 151.8, 154.3, 156.7. Anal. Calcd for $C_{18}H_{23}Cl_2FN_2O_2$: C, 55.64; H, 5.96; H, 7.20. Found: 55.76; H, 6.19; N, 6.94.

*5.6.91. 4-(3-Bromo-4-(4-cyanophenoxy)benzyl)morpholin-4-ium chloride **87**.*

By Method F **1e** (9.453 g, 1.5 mmol) was converted to the crude amine (0.531 g). Methanolic HCl (0.5 M, 3.5 mL) was added to the amine. Addition of EtOAc (11 mL) gave the salt (0.494 g, 80%). mp 234 °C dec IR (neat, cm^{-1}) 3099, 3075, 2999, 2936, 2873, 2536, 2520, 2499, 2463, 2440, 2229, 1608, 1593, 1504, 1480, 1245, 1215, 1167, 1121, 1082, 1063, 1047, 975, 962, 919, 877, 853, 864, 833. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.09 (bs, 2H), 3.27 (d, J = 11.0 Hz, 2H), 3.82 (t, J = 11.4 Hz, 2H), 3.95 (d, J = 11.9 Hz, 2H), 7.10 (AA', 2H), 7.37 (d, J = 8.2 Hz, 1H), 7.73 (dd, J = 8.3, 1.7 Hz, 1H), 7.86 (BB', 2H) 8.12 (d, J = 1.3 Hz, 1H), 11.5 (bs, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 50.7, 57.5, 63.1, 105.7, 115.2, 117.5, 118.6, 122.8, 128.61, 133.1, 134.8, 137.0, 151.7, 160.1. Anal. Calcd for $C_{18}H_{18}BrClN_2O_3$: C, 52.77; H, 4.43; N, 6.84. Found: C 52.82; H, 4.63; N 6.60.

*5.6.92. 4-(4-(4-(Ammoniomethyl)phenoxy)-3-bromobenzyl)morpholin-4-ium chloride **88**.*

By Method A **87** (0.300, 0.732 mmol) was converted to the crude amine (0.299 g). The oil was dissolved in DCM (8 mL) and methanolic HC (0.5M, 3.5 mL) was then added. Rotary evaporation gave an oil that solidified on standing. The compound was

dissolved in methanol (1 mL) and EtOAc was added in small portions over several hours. A white solid (0.275 g) slowly formed. The solid was recrystallized from methanol/ACN (0.204 g, 62%). mp 246 °C dec. IR (neat, cm^{-1}) 3115, 3079, 3023, 2951, 2914, 2708, 2608, 2439, 2398, 1617, 1587, 1512, 1487, 1260, 1111, 1082, 965, 871, 847, 826. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.08 (bs, 2H), 3.24 (d, J = 11.6 Hz, 2H), 3.82 (t, J = 11.3 Hz, 2H), 3.94 (d, J = 12.1 Hz, 2H), 4.00 (q, J = 5.2 Hz, 2H), 4.33 (s, 2H), 7.02 (AA', 2H), 7.10 (d, J = 8.3 Hz, 1H), 7.52 (BB', 2H), 7.67 (d, J = 7.4 Hz, 1H), 8.10 (s, 1H) 8.42 (bs, 3H), 11.62 (bs, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 41.6, 50.6, 57.5, 63.1, 114.4, 117.6, 118.5, 121.0, 127.2, 129.4, 131.1, 132.8, 136.8, 153.3, 156.4. Anal. Calcd for $C_{18}H_{23}BrCl_2N_2O_2$: C, 48.02; H, 5.15; N, 6.22. Found: C, 47.93; H, 5.36; N, 6.42.

5.6.93. 4-(3-Chloro-4-(4-cyano-2-fluorophenoxy)benzyl)morpholin-4-ium chloride **89**.

By Method G **1g** (275 mg, 1 mmol) was converted to the salt (0.737, 96%). mp 209–210 °C. IR (neat, cm^{-1}) 3060, 2938, 2581, 2464, 2237, 1602, 1589, 1497, 1465, 1300, 1274, 1118, 862, 844, 791, 627, 612. ^{1}H NMR (400MHz, DMSO-d_6) δ 3.06 (s, 2H), 3.56 (d, J = 2.4 Hz, 2H), 3.84 (s, 2H), 4.34 (s, 2H), 4.34 (s, 2H), 7.11 (d, J = 8.0 Hz, 1H), 7.14 (s, 1H), 7.35 (d, J = 8.4 Hz, 1H), 7.69 (d, J = 8.4 Hz, 1H), 8.10 (s, 1H), 7.72 (d, J = 8.4 Hz, 1H), 8.10 (d, J = 10.8 Hz, 1H), 11.75 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 51.2, 57.8, 63.5, 106.6, 116.6, 118.9, 118.9, 135.3, 153.8, 156.3, 160.4. Anal. Calcd for semihydrate $C_{36}H_{36}Cl_4F_2N_4O_5$: C, 55.12; H, 4.63; N, 7.14. Found: C, 55.47; H, 4.65; N, 6.69.

5.6.94. 4-(4-(4-(Ammoniomethyl)-2-fluorophenoxy)-3-chlorobenzyl)morpholin-4-ium chloride **90**.

By Method A **89** (383.2 mg, 1 mmol) was converted to the salt (0.327 g, 48.9%). mp 231 °C dec. IR (neat, cm^{-1}) 3363, 2961, 2895, 257, 2467, 1599, 1512, 1495, 1439, 1285, 1268, 1242, 1123, 1081, 1063, 970, 867, 835. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.08 (s, 2H), 3.22 (d, J = 1.6 Hz, 2H), 3.21 (d, J = 1.6 Hz, 2H), 3.92 (s, 2H), 4.05 (s, 2H), 4.33 (s, 2H), 7.03 (d, J = 8.4 Hz, 1H), 7.16 (t, J = 8.4 Hz, 1H), 7.37 (d, J = 8.4 Hz, 1H), 7.64 (d, J = 1.6 Hz, 1H), 7.67 (d, J = 1.6 Hz, 1H), 7.98 (s, 1H), 8.56 (s, 3H), 11.73 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 41.6, 51.0, 57.9, 63.6, 79.6, 118.4, 118.6, 119.3, 121.1, 123.8, 126.7, 127.1, 131.4, 132.4, 132.6, 134.3, 143.0, 151.4, 152.7, 153.9. HRMS TOF MS ES$^+$ ESI in Na Acetate (m/z): [M$^+$] calcd for $C_{18}H_{21}ClFN_2O_3$ 351.1276; found 351.1280. Anal. Calcd for the monohydrate $C_{18}H_{24}Cl_3FN_2O_2$: C, 48.94; H, 5.48. Found: C, 48.77; H, 4.98.

5.6.95. 4-(4-(4-Cyanophenxy)-3,5-difluorobenzyl)morpholin-4-ium **91**.

By Method F using DCM **1f** (1.000 g, 3.858 mmol) was converted to the free amine (1.228 g). Analysis by GC/MS after 1 h showed 2.6% of residual **1f** and 4.3% of the corresponding alcohol. No further reaction occurred after another 3 h. The product was recrystallized from EtOAc/hexanes (0.852 g, 65%). mp 125–126 °C. IR (neat, cm^{-1}) 2960, 2855, 2810, 2227, 1601, 1512, 1502, 1236, 1117, 1039, 867, 839. ^{1}H NMR (400 MHz, $CHCl_3$-d_1) δ 2.48 (bs, 4H), 3.49 (bs, 2H), 3.75 (bs, 4H), 7.00 (AA', 2H), 7.08 (d, J = 8.5 Hz, 2H), 7.62 (BB', 2H). ^{13}C NMR (100 MHz, $CHCl_3$-d_1) δ 53.5, 62.1, 66.9, 106.6, 112.5, 112.7, 116.0, 118.6. 134.5, 137.9, 154.23, 154.32, 156.78, 156.83, 160.7. To the free amine (0.300 g, 0.909 mmol) was added methanolic HCl (0.5 M 3 mL) producing the hygroscopic salt **91** (0.323 g, 97%). mp 223–224 °C. IR (neat, cm^{-1}) 2999, 2866, 2523, 2461, 2444, 2411, 221, 1601, 1518, 1501, 1418, 1262, 1245, 1167, 1042, 965, 876, 860. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.09 (d, J = 8.4 Hz, 2H), 3.35

(d, *J* = 10.6 Hz, 2H), 3.85 (t, *J* = 5.6 Hz, 2H), 3.96 (d, *J* = 5.8 Hz, 2H), 7.25 (d, *J* = 8.8, 2H), 7.72 (d, *J* = 8.4, 2H), 7.88 (dt, *J* = 2.8, 4.8, 9.4, 2H), 11.78 (s, 1H). ^{13}C NMR (100 MHz, DMSO-*d*$_6$) *δ* 51.2, 57.8, 63.5, 106.6, 116.6, 116.9, 118.9, 135.3, 153.8, 156.3, 160.4. Anal. Calcd for $C_{18}H_{17}ClF_2N_2O_2$: C, 58.94; H, 4.67; N, 7.64; Cl, 9.66. Analysis for the semihydrate $C_{36}H_{36}Cl_2F_4N_4O_5$: C, 57.53; H, 4.83; N, 7.45. Found: C, 58.12; H, 4.69; N, 7.54.

5.6.96. 4-(4-(4-(Ammoniomethyl)phenoxy)-3,5-difluorobenzyl)morpholin-4-ium chloride **92.**

By Method A **91** (366.7 mg, 1 mmol) was converted to the dihydrochloride salt (0.191 g, 51.1%). mp 276 °C. IR (neat, cm^{-1}) 3374, 2982, 2870, 2645, 2566, 2469, 2358, 1601, 1512, 1478, 1456, 1428, 1120, 1080, 996, 867, 836, 798, 763, 663. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) *δ* 3.09 (s, 2H), 3.38 (s, 3H), 3.87 (s, 3H), 3.97 (d, *J* = 3.6 Hz, 3H), 4.37 (s, 2H), 7.05 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 8.8 Hz, 2H), 7.70 (s, 2H), 8.43 (s, 3H), 12.00 (s, 1H). ^{13}C NMR (100 MHz, DMSO-*d*$_6$) *δ* 41.5, 50.7, 57.4, 63.1, 79.2, 114.9, 116.4, 117.0, 129.0, 131.0, 153.6, 153.7, 156.14, 156.19, 157.0. Anal. Calcd for $C_{18}H_{17}Cl_2FN_2O_2$: C, 53.08; H, 5.44; N, 6.88. Found: C, 53.27; H, 5.56; N, 6.76.

5.6.97. Ethyl 3-(4-(4-cyanophenoxy)-3,5-difluorophenyl)propenoate **93.**

To a 100 mL treated flame dried round bottom 3-neck flask under nitrogen was added NaH (0.455 g, 18.965 mmol, as a mineral oil dispersion). The mineral oil was removed with hexanes and then anhydrous THF (15 mL) was added and the mixture was cooled in an ice bath. Triethyl phosphonoacetate (1.88 mL, 9.483 mmol) was added dropwise via a dry Newman funnel over 7 min followed with THF (2 x 2 mL) washes. Once gas evolution ceased the reactant 4-(4-cyanophenoxy)-3,5-difluorobenzaldehyde (2.458 g, 9.4827 mmol) was added in one portion with THF (3 mL) washes. The ice bath was then replaced by an oil bath at 45 °C. After 15 min of heating GC/MS showed the product and no starting aldehyde. The reaction mixture was heated for 80 min at 50–60 °C. The reaction mixture was left at room temperature for 2 days then poured onto ice (21 g), using ethyl acetate (25 mL) and water (40 mL) to transfer the contents. The mixture was allowed to evaporate in the hood for 1 day, giving a ring of tan colored solid and white flakes in the liquid. Filtration, washing with water (2 x 2 mL) and oven drying at 55 °C for 2.75 h gave 2.757 g solid. NMR showed the presence of product and the carboxylate salt in a 1:1 ratio. The product was dissolved in EtOAc (5 mL) and then hexane was added slowly in portions over two days (30 mL). A first crop of gummy solid was obtained (0.100 g) which appeared to contain the sodium carboxylate. Subsequent crops gave the product as a white solid. (1.163 g, 37%). mp 98.0–99.8°C. IR (cm^{-1}) 3062, 2981, 2934, 2902, 2226, 1710, 1641, 1602, 1513, 1502, 1438, 1417, 1350, 1305, 1273, 1244, 1205, 1176, 1137, 1111, 1034, 994, 858, 839, 815, 602; ^{1}H NMR (400 MHz, $CHCl_3$-*d*$_1$) δ 1.27 (t, 3H); 4.21 (q, 4H); 6.82 (d, 1H); 7.21 (d, 2H); 7.66 (d, 1H); 7.845 (d, 2H); 7.82 (d, 2H); ^{13}C NMR (100 MHz, $CHCl_3$-*d*$_1$) δ 14.1, 60.4, 79.1, 106.0, 111.8, 113.1, 116.0, 118.4, 121.2, 128.7, 130.0, 133.5, 134.8, 141.5, 153.8, 156.2, 160.0, 165.8. Anal. Calcd for: $C_{18}H_{13}F_2NO_3$: C, 65.65; H, 3.98; N, 4.25. Found: C, 65.42; H, 4.06; N, 4.25.

5.6.98. Ethyl 3-(4-(4-cyanophenoxy)-3, 5-diflourophenyl) propanoate **94.**

To a 10 mL round bottom flask under Argon was added 1,2-bis(diphenylphosphino)benzene (23 mg, 51.5 mmol), $Cu(CO_2CH_3)_2{\cdot}H_2O$ (76 mg, 0.380), freshly distilled toluene (1.5-2 mL), and then warm degassed tert-butyl alcohol (0.500 mL, 5.23 mmol) by syringe. The mixture turned blue. After stirring for 20 min, polymethylhydrosiloxane (0.350 mL, 5.23 mmol) was added, causing the color to change from blue to green. This mixture was then transferred by syringe to another flask containing solid **93** (0.776 g, 2.29 mmol) causing the color to change to black. Everything dissolved within 20 min. The reaction mixture was stirred at rt for 2 days after which additional PMHS (50 µL) was added. Both the catalyst mixture and the compound were kept under Argon pressure the entire time. The reaction progress was followed via GC/MS, which showed 96% reduced product after one day. After four days the mixture was diluted with ethyl acetate (5 mL), washed with KOH (1 N, 10 mL), HCl (1 N, 10 mL), and an excess of sat'd. aqueous NaCl, then the aqueous layers were combined and back washed with ethyl acetate (5 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, concentrated via rotary evaporation, giving a light yellow oil (1.123 g). The oil was purified by Kugelrohr distillation, giving a colorless oil at 184–185 °C and 0.04 mm Hg, which was further purified by Biotage chromatography (hexane/ethyl acetate, Snap ultra 25) to give white crystals (0.446 g, 59 %). mp 52–53 °C. IR (cm^{-1}) 3094, 3067, 2981, 2938, 2908, 2870, 2227, 1728, 1632, 1600, 1514, 1501, 1446, 1416, 1374, 1355, 1288, 1236, 1186, 1165, 1109, 1035, 858, 837, 798, 750; ^{1}H NMR (400 MHz, $CHCl_3$–d_1) δ 1.158 (t, 3H); 2.689 (t, 2H); 2.900 (t, 2H); 4.067 (q; 2H); 7.123 (d, 2H); 7.279 (d, 2H); 7.854 (d, 2H); ^{13}C NMR (100 MHz, $CHCl_3$–d_1) δ 14.2, 30.3, 35.0, 60.8, 106.5, 112.6, 116.0, 118.6, 128.2, 134.1, 139.9, 154.2, 160.7, 172.1. Anal. Calcd for $C_{18}H_{15}F_2NO_3$: C, 65.25; H, 4.56; F, 11.47; N, 4.23. Found: C, 65.27; H, 4.77; N, 4.40.

5.6.99. 4-(2,6-Difluoro-4-(3-hydroxypropyl)phenoxy)phenyl methyl ammonium chloride **95.**

To a 25 mL round bottom oven dried flask under Argon were added via syringe **94** (0.474 g, 1.43 mmol), and anhydrous THF (2.0 mL). In a glove box $LiBH_4$ (76 mg, 3.49 mmol) was added to a 5 mL oven dried flask. The flask was septum capped and then in a hood anhydrous THF (2 mL) was added. The $LiBH_4$ solution was then transferred to the solution of the ester-nitrile followed by $LiHB(C_2H_5)_3$ (1.7 M, 1.92 mL, 3.267 mmol), after which the color changed to light yellow. After stirring for 3 days under Argon the reaction mixture was worked up by adding 10% NaOH (5.5 mL), which produced gas evolution. After 20 min H_2O (10 mL) was added and the solution was then extracted with DCM (3 x 20 mL), dried over $MgSO_4$, vacuum filtered, and concentrated via rotary evaporation, giving a yellow oil (0.484 g). The salt was prepared by dissolving the oil in ethyl acetate (10 mL) then adding methanolic HCl (0.5 M, 3.0 mL). EtOAc was added and the solvent was partly removed by rotary evaporation. More EtOAc was added and the rotary evaporation was repeated but no solid was isolated. Complete removal of solvent gave a yellow glass (0.347 g). Biotage reverse phase chromatography of 0.250 g of this glass (water/methanol, Snap Ultra C18 12 g, methanol application to samplet) gave a complicated chromatogram. The first two fractions, after solvent removal, were treated with methanol (1.5 mL) and ethyl acetate (6 mL). Partial removal of the solvent by rotary evaporation gave white, needle-like crystals (0.094 g, 0.284 mmol, 20 % yield). mp 224–225 °C. IR (cm^{-1}) 3299, 2886, 2728, 2633, 1632, 1599, 1507, 1447, 1385, 1365, 1341, 1230, 1170, 1135, 1047,

1023, 985, 971, 914, 862, 846, 833, 799, 606 ; ^{1}H (400 MHz, DMSO-d_6) δ 1.742 (q, 2H), 1.985 (s, 1H), 2.663 (t, 2H), 3.345 (s, 1H), 3.421 (t, 2H), 3.962 (s, 2H), 4.569 (s, 1H), 6.967 (d, 2H), 7.177 (d, 2H), 7.481 (d, 2H). ^{13}C (400 MHz, DMSO-d_6) δ 31.5, 33.8, 41.9, 60.1, 113.1, 115.1, 129.1, 131.4, 142.2, 154.1, 156.6, 157.7. Anal. Calcd for: $C_{16}H_{18}ClF_2NO_2$: C, 58.28; H, 5.50; Cl, 10.75; N, 4.25. Found: C, 58.51; H, 5.72; N 3.99.

5.6.100. 4-(4-(4-(2-Ammoniopropan-2-yl)phenoxy)-3,5-difluorobenzyl)morpholin-4-ium chloride **96.**

The free amine of **91** (0.767 g, 2.322 mmol) was converted to the crude free base (0.723 g, 86%) by Ciganek's method.[57] The base was treated with methanolic HCl (0.5 M, 10 mL). EtOAc was added (15 mL) and the volume of solvent was reduced by rotary evaporation. Additional EtOAc was added in portions to complete the crystallization. Filtration gave a tan solid (0.661 g) which was recrystallized from CH_3OH/EtOAc to give the salt (0.622 g, 62%). mp 283.5–284.0 °C dec. IR (neat, cm^{-1}) 2981, 2948, 2775, 2715, 2638, 2622, 2574, 2549, 2488, 1598, 1511, 1441, 1354, 1339, 1262, 1213, 1178, 1167, 1146, 1126, 1066, 1041, 877, 869, 861, 839. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.62(s, 6H), 3.09 (m, 2H), 3.31 (m, 2H), 3.86 (m, 2H), 3.95 (m, 2H), 4.37 (s, 2H), 7.07 (AA', 2H), 7.58 (BB', 2H) 7.71 (AA', 2H) 8.67 (s, 3H), 11.94 (bs, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 27.5, 48.6, 50.7, 55.0, 57.4, 63.1, 114.8, 116.6, 127.1, 137.7, 153.6, 153.7, 156.1, 156.2, 156.4. Anal. Calcd for $C_{20}H_{28}Cl_2F_2N_2O_2$: C, 55.18; H, 6.02; N, 6.44. Found: C, 55.38; H, 6.17; N, 6.34.

5.6.101. 3,5-Difluoro-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)benzaldehyde **97.**

To 4-(1,5-dimethyl-2,4-dioxa-3-borabicyclo[3.1.0]hexan-3-yl)phenol (2.0 g, 9.09 mmol, Oakwood) was added 3,4,5-trifluorobenzaldehyde (1.455 g, 9.09 mmol, Oakwood), anhydrous K_2CO_3 (1.256 g, 0.09 mmol), and DMF (7 mL). The mixture was stirred under nitrogen at 80 °C overnight. The reaction was not complete by GC/MS. After additional heating at 93 °C for 6 h the mixture was poured onto ice (5 g). EtOAc and water were added and the pH adjusted to 7 with 1M HCl. The phases were separated and the water layer was extracted twice with EtOAc. The combined organic layers were washed with water and then brine. The organic phase was dried over $MgSO_4$ and reduced in volume by rotary evaporation. Slow addition of hexanes gave a white solid (2.58 g). Kugelrohr distillation (up to 195 °C/0.04 mm) gave the product (2.28 g, 70%). An analytical sample was obtained by recrystallization from EtOAc/hexanes. mp 95.0–95.5 °C. IR (neat, cm^{-1}) 3065, 2978, 2931, 2851, 2810, 2741, 2710, 1705, 1597, 1505, 1389, 1360, 1338, 1240, 1167, 1143, 1089, 1042, 857, 688. ^{1}H NMR (400 MHz, $CHCl_3$-d_1) δ 1.34 (s, 12H), 6.94 (AA', 2H), 7.56 (AA', fluorine coupled, 2H), 7.79 (BB', 2H), 9.93 (t, J= 1.74 Hz, 1H). ^{13}C NMR (100 MHz, $CHCl_3$-d_1) δ 24.8, 83.8, 113.4, 113.5, 113.6, 113.7, 114.8, 129.8, 132.9, 133.0, 136.7, 155.1, 122.12, 157.6, 157.7, 159.4, 188.6. HRMS-TOF MS EI$^+$ (*m/z*): [M$^+$ + 1] calcd for $C_{19}H_{19}BF_2O_4$ 360.1344; found 360.1346.

5.6.102. 4-(3,5-Difluoro-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)benzyl)morpholin-4-ium chloride **98.**

To **97** (0.582 g, 1.616 mmol) in DCM (6 mL) was added morpholine (146 μL, 1.664 mmol). After brief stirring $NaHB(OAc)_3$ (0.480 g, 2.262 mmol) was added. The mixture was stirred under nitrogen for 2 h at which point saturated $NaHCO_3$ (12 mL) was added. After 30 min of stirring the layers were separated and the water phase then extracted with DCM (2 x 15 mL). The organic

phase was dried over $MgSO_4$, filtered, and then the solvent was removed by rotary evaporation to give an oil (0.679 g) which showed 93% conversion to product by GC/MS. The oil was treated with methanolic HCl (0.5 M, 4 mL). EtOAc was added and the solvents partly removed by rotary evaporation. Addition of EtOAc and evaporation was done twice more at which point more crystallization occurred. Filtration gave the salt (0.547 g, 72%). mp 245–247 °C dec. IR (neat, cm^{-1}) 2972, 2932, 2873, 2542, 2474, 1600, 1519, 1508, 1406, 1357, 1345, 1240, 1200, 1166, 1125, 1103, 1042, 1013, 905, 867, 855, 826, 651. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.28(s, 12H), 3.10 (bs, 2H), 3.82 (bs, 2H), 3.93 (bs, 2H), 4.35 (s, 2H), 7.01 (AA', 2H), 7.64 (AA', 2H), 7.67 (BB', 2H), 11.36 (bs, 0.5H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 24.7, 50.9, 57.7, 63.2, 83.7, 114.5, 116.3, 116.5, 136.6, 153.6, 153.7, 156.1, 156.2, 159.4. Anal. Calcd for $C_{23}H_{29}BClF_2NO_4$: C, 59.06; H, 6.25; N, 2.99. Found: C, 58.91; H, 6.21; N, 2.78.

5.6.103. 4-(4-(4-Boronophenoxy)-3,5-difluorobenzyl)morpholin-4-ium chloride **99.**

To the boronate **98** (0.192 g, 0.410 mmol) in THF (0.8 mL) was added a solution of $NaIO_4$ (97 mg, 0.453 mmol) in HCl (1 M, 1.5 mL) in three portions. After 11 mins the reaction was poured into EtOAc and $NaHCO_3$ (aq) was added to give a pH of 5. The layers were separated. Additional $NaHCO_3$ (aq) was added until the solution turned slightly turbid and the pH was about 6. The water layer was again extracted with EtOAc. Finally the pH was increased to 9 and the water layer was immediately again extracted with EtOAc. The organic layer was dried over $MgSO_4$ and the solvent was removed by rotary evaporation without application of heat to give the product (0.171 g) containing some unconverted boronate and an unidentified side product. Longer reaction times gave more side product. To this solid was added methanol (1 mL) and then HCl in CH_3OH (0.5 M, 1 mL). EtOAc (15 mL) was added and the solvent was removed by rotary evaporation until solid appeared. Filtration gave the product (0.121 g, 77% from the morpholine boronate salt) contaminated with 2.4 % of starting material. The product was recrystallized from CH_3OH/EtOAc. mp 254–255 °C dec. IR (neat, cm^{-1}) 3487, 3245, 3047, 2913, 2872, 2536, 2463, 1595, 1578, 1519, 1374, 1342, 1124, 1115, 1066, 870, 860, 847, 730. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.09(m, 2H), 3.83 (m, 2H), 3.96 (m, 2H), 4.36 (s, 2H), 6.95 (AA', 2H), 7.65 (AA', 2H), 7.78 (BB', 2H), 8.01 (bs, 2H), 11.58 (bs, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 50.8, 57.5, 63.1, 113.8, 116.2, 127.9, 128.9, 136.1, 153.68, 153.73, 156.16, 156.21, 158.5. HRMS TOF MS ES$^+$ (*m/z*): [M^+ + 1] calcd for $C_{17}H_{19}{}^{11}BF_2NO_4$ 350.1375; found 350.1371. Anal. Calcd for $C_{17}H_{19}BClF_2NO_4$: C, 52.95; H, 4.97; N, 3.63. Found: C, 52.27; H, 5.50; N, 4.25.

5.6.104. Methyl 4-(2,6-difluoro-4-formylphenoxy)benzoate **100.**

To 3,4,5-trifluorobenzaldehyde (1.601 g, 10.00 mmol) was added methyl 4-hydroxybenzoate (1.522 g, 10.00 mmol), K_2CO_3 (1.382 g, 10.00 mmol), and DMF (7.5 mL). The mixture was heated at 93 °C under nitrogen 3.5 h at which point it was allowed to cool and then was poured into water (50 mL) containing ice (15 g). The solid was collected by filtration and washed with water. The solid (2.525 g) was recrystallized from DCM/hexanes to give the product (2.346 g, 80%). mp 88.5–89.5 °C. IR (neat, cm^{-1}) 3065, 3002, 2954, 2845, 2806, 1708, 1599, 1502, 1448, 1435, 1416, 1387, 1279, 1238, 1196, 1111, 1040, 865, 765, 738, 711, 691. ^{1}H NMR (400 MHz, $CHCl_3$-d_1) δ 3.91 (s, 3H), 7.00 (AA', 2H), 7.59 (AA', 2H), 8.04 (', 2H), 9.94 (t, J = 1.8 Hz, 1H). ^{13}C NMR (100

MHz, $CHCl_3$-d_1) δ 52.1, 113.5, 113.6, 113.66, 113.72, 115.2, 125.7, 131.8, 133.38, 133.44, 133.51, 133.5, 135.9, 136.0, 136.2, 154.9, 155.0, 157.48, 157.52, 160.3, 166.2, 188.5. Anal. Calcd for $C_{15}H_{10}F_2O_4$: C, 61.65; H, 3.45. Found: C, 61.43; H, 3.60.

5.6.105. 4-(3,5-Difluoro-4-(4-(methoxycarbonyl)phenoxy)benzyl)morpholin-4-ium chloride **101.**

To aldehyde **100** (1.00 g, 3.42 mmol) was added morpholine (314 μL, 3.59 mmol) and DCM (7 mL). After stirring briefly $NaHB(OAc)_3$ was added with additional DCM (7.5 mL). After 1 h GC/MS showed 3.5% of starting material and 2.7% of the alcohol from aldehyde reduction. The workup of Method F gave a yellow oil (1.189 g). The oil was taken up into ethyl acetate (5 mL) and treated with HCl in methanol (0.5 M, 7 mL). After removal of methanol by rotary evaporation the product crystalized (0.929, 68%). mp 230–230.5 °C. IR (neat, cm^{-1}) 3018, 2955, 2864, 2533, 2459, 1722, 1600, 1518, 1502, 1434, 1354, 1345, 1264, 1236, 1200, 1159, 1082, 1008, 964, 908, 880, 869, 762. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.09 (m, 2H), 3.33 (m, 2H), 3.83 (s, 3H), 3.84 (m, 2H), 3.96 (m, 2H) 4.38 (bs, 2H), 7.15 (AA', 2H), 7.71 (AA', 2H), 7.98 (BB', 2H), 11.70 (bs, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 50.7, 52.1, 57.4, 63.1, 115.1, 116.4, 116.6, 124.8, 128.6, 131.6, 153.4, 153.5, 155.9, 156.0, 160.3, 165.4. Anal. Calcd for $C_{19}H_{20}ClF_2NO_4$: C, 57.08; H, 5.04; N, 3.50. Found: C, 56.84; H, 5.12; N, 3.67.

5.6.106. 4-(2,6-Difluoro-4-(morpholinomethyl)phenoxy)phenyl)methanol **102.**

To ester **101** (0.298 g, 0.745 mmol) in anhydrous THF (2 mL) was added $LiAlH_4$ (0.425 g, 11.2 mmol). After 1.5 h at reflux the reaction was allowed to cool at which point water (0.44 mL), NaOH (15%, 0.44 mL), and additional water (1.3 mL) were slowly added sequentially. The mixture was allowed to stir until almost all black residue was gone at which point EtOAc was added. The solvent was decanted, the residue washed with EtOAc, and the combined organic phases then dried over $MgSO_4$. Rotary evaporation gave an oil (0.232 g) which recrystallized from DCM/hexane to give the product 0.256 g, 100%). mp 103–105 °C. IR (neat, cm^{-1}) 3410, 2960, 2931, 2861, 2811, 1602, 1505, 1440, 1234, 1115, 1038, 866. ^{1}H NMR (400 MHz, $CHCl_3$-d_1) δ 1.74 (bs, 1H), 2.47 (m, 4H), 3.48 (s, 2H), 3.74 (m, 4H), 4.64 (s, 2H), 6.93 (AA', 2H), 7.03 (AA', 2H), 7.30 (BB', 2H). ^{13}C NMR (100 MHz, $CHCl_3$-d_1) δ 53.5, 62.2, 64.8, 66.9, 112.4, 112.6, 115.3, 128.55, 128.63, 135.4, 154.69, 154.74, 157.18, 127.23, 157.3. Anal. Calcd for $C_{18}H_{19}F_2NO_3$: C, 64.47; H, 5.71; N, 4.18. Found: C, 64.02; H, 5.90; N, 4.07.

6. Abreviations Used: 1,2 BDP - 1,2-bis(diphenylphosphino)benzene, DCE - dichloroethane, DIBALH – diisobutylaluminum hydride, DMA - dimethylacetamide, EDCI - 3-(((ethylimino)methylene)amino)-N,N-dimethylpropan-1-aminium chloride, EtOAc – ethyl acetate, MsOH – methanesulfonic acid, PMHS – polymethylhydrosiloxane, HEPES - (4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid), RPMI - Roswell Park Memorial Institute (culture medium), FBS- Fetal bovine serum.

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K.H, A.M., D.A.L., V.M., T.W., C.V-E., and B.B. generated and analyzed data.

J.P.H wrote the paper with a significant contribution from G.D. and D.A.L.

8. Notes

The authors declare no competing financial interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version.

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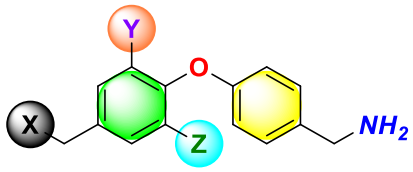
Graphical Abstract



X = $HOCH_2CH_2$, Y, Z = H T.b. rhod. IC_{50} = 0.96 μM, Cytotoxicity L6 IC_{50} = 170, Cytotoxicity Human Cell Lines IC_{50} = > 400, SI > 420

X = $HOCH_2CH_2$, Y = Cl, Z = H T.b. rhod. IC_{50} = 0.47 μM, Cytotoxicity L6 IC_{50} = 49, Cytotoxicity Human Cell Lines IC_{50} = > 200, SI > 410

X = morpholino, **Y = Cl, Z = H** T.b. rhod. IC_{50} = 0.53 μM, Cytotoxicity L6 IC_{50} = 81 Cytotoxicity Human Cell Lines IC_{50} > 300, SI > 570

X = morpholino, **Y, Z = F** T.b. rhod. IC_{50} = 0.16 μM, Cytotoxicity L6 IC_{50} = 120 Cytotoxicity Human Cell Lines IC_{50} > 200, SI > 1200

Highlights

- Compounds active against Human African Trypanosomiasis at low micromolar levels
- Low toxicity against human cell lines
- Selectivity index against human cell lines at or better than 1200
- Active against *Trypanosoma brucei rhodesiense* but no other protozoans