Supporting Information

Rational design of potent and selective inhibitors of an epoxide hydrolase virulence factor from *Pseudomonas aeruginosa*

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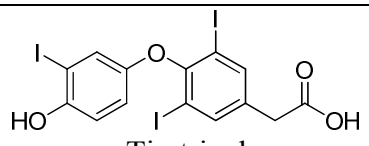
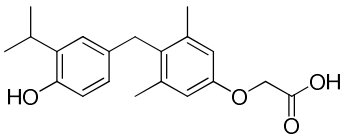
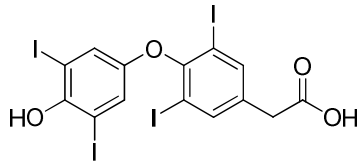
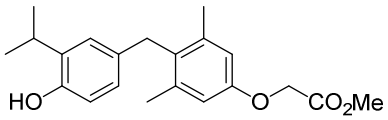
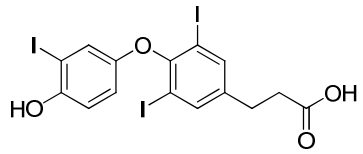
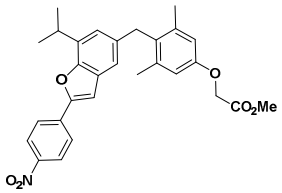
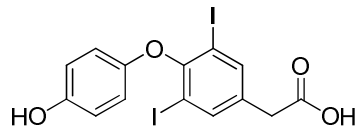
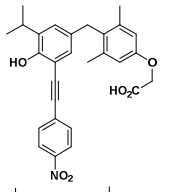
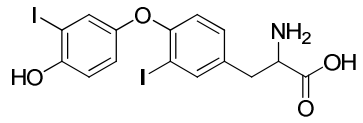
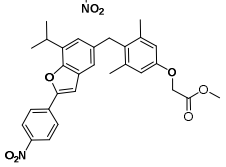
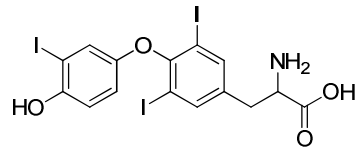
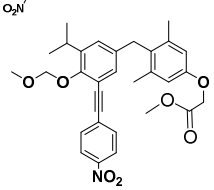
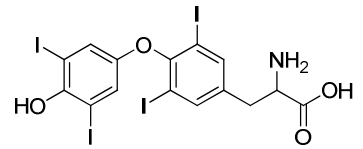
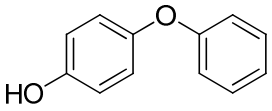
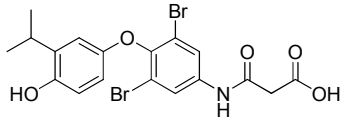
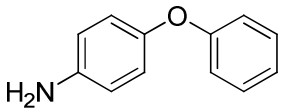
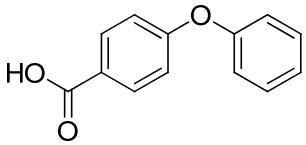
Table of contents

Table S1. Inhibition of Cif by a series of compounds similar to tiratricol

Structure	Cif IC_{50} (μM)[a]	Structure	Cif IC_{50} (μM)[a]
 Tiratricol	4.7 ± 0.6		> 100
	20 ± 2		44 ± 4
	4.4 ± 0.5		> 100[b]
	100 ± 2		> 100[b]
	80 ± 10		64 ± 4[b]
	21 ± 2		84 ± 6[b]
	> 100		> 100
 **1a** (KB2115)	2.6 ± 0.4		> 100
			> 100

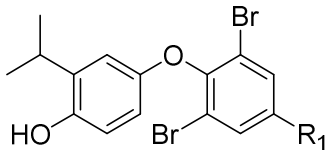
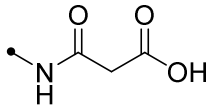
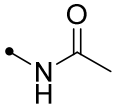
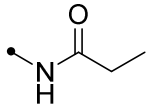
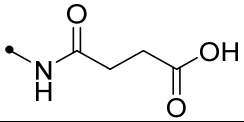
[a]Conditions: [E] = 0.6 μM; [S] = 25 μM; 37 °C for 15 min; pre-incubation 5 min at 37 °C. Results are average ± standard deviation (n = 3). [b]Synthesized elsewhere.[1]

Table S2. X-ray data collection and refinement statistics

	Cif with KB2115 (**1a**)	Cif with **8c**	Cif with **8h**
Data Collection			
Wavelength (Å)	1.0000	0.9770	0.9774
Space Group	$C222_1$	$C2$	$C2$
Unit cell dimensions:			
a,b,c (Å)	84.2, 169.5, 175.6	169.0, 83.7, 88.9	169.3, 84.1, 89.2
α,β,γ (°)	90, 90, 90	90, 100.7, 90	90, 100.6, 90
Resolution[a] (Å)	19.9-1.65 (1.75-1.65)	20.0-2.05 (2.08-2.05)	19.8-1.80 (1.90-1.80)
$R_{\text{mrgd-F}}$[b] (%)	10.2 (41.8)	9.3 (44.5)	9.5 (48.1)
I/σ_I	21.76 (7.22)	15.25 (3.53)	13.3 (3.26)
Completeness (%)	99.9 (100.0)	98.5 (97.2)	98.3 (97.5)
Redundancy	14.6 (14.2)	3.8 (3.6)	3.8 (3.8)
Refinement			
Total number of reflections	150068	75324	111909
Reflections in the test set	7519	3764	5590
R_{work}[c]/R_{free}[d] (%)	18.6/21.6	15.5/19.8	16.2/19.6
Number of atoms:			
Protein	9602	9481	9536
Solvent	1426	769	1146
Ligand	120	120	93
Ramachandran plot[e] (%)	97.8/2.1/0.0	97.9/2.1/0.0	98.1/1.9/0.0
B_{av} (Å^2)			
Protein	10.2	19.8	15.6
Solvent	25.1	28.9	28.5
Ligand	20.5	38.3	33.5
Bond length RMSD	0.007	0.008	0.007
Bond angle RMSD	1.161	1.143	1.115
PDB ID	5HKB	5HKA	5HK9

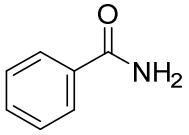
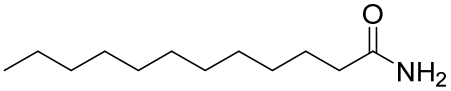
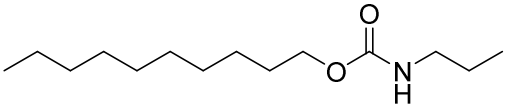
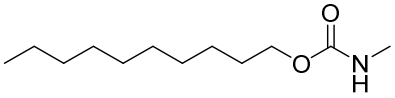
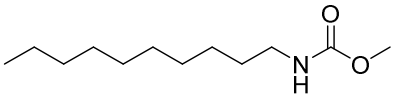
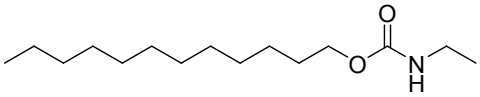
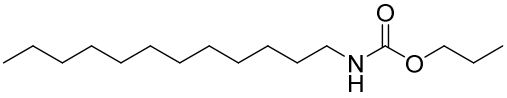
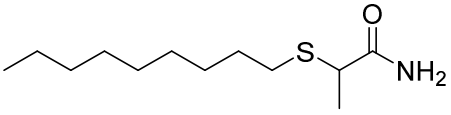
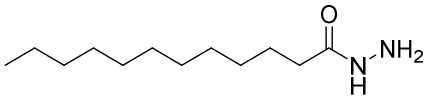
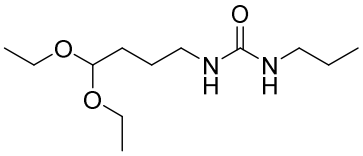
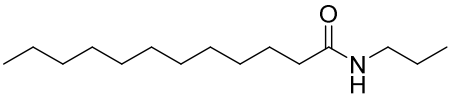
[a]Values in parentheses are for data in the highest-resolution shell.
[b]$R_{\text{mrgd-F}}$ is a robust indicator of the agreement of structure factors of symmetry-related reflections and is described in detail in Diederichs & Karplus[2].
[c]$R_{\text{work}} = \Sigma_h |F_{\text{obs}}(h) - F_{\text{calc}}(h)|/\Sigma_h F_{\text{obs}}(h)$, $h\varepsilon$ [working set]
[d]$R_{\text{free}} = \Sigma_h |F_{\text{obs}}(h) - F_{\text{calc}}(h)|/\Sigma_h F_{\text{obs}}(h)$, $h\varepsilon$ [test set]
[e]favored/allowed/outliers

Table S3. Structure-activity relationships of the R_1 substituents on thyroid hormone activity

#	 R_1	Thyroid hormone activity at 10 nM (% relative to T_3)[a]	Cif IC_{50} (μM)
T_3	-	100±8	-
1a (KB2115)		94±3	2.6
6a		68±7	9.7
1b		71±8	8.8
1c		58±2	7.5
1e		72±6	3.2

[a]Values are shown as mean ± SD (n = 3).

Table S4. Structures of inactive compounds tested on Cif inhibitory assay

Structure		Cif IC_{50} (μM)
	Terminal amide/Substructure of **8c**	>50
	Terminal amide/Potent mEH inhibitor	> 50
	Carbamate with small substituent+long alkyl chain	> 50
	Carbamate with small substituent+long alkyl chain	> 50 (40%)
	Carbamate with small substituent+long alkyl chain	> 50
	Carbamate with small substituent+long alkyl chain	> 50
	Carbamate with small substituent+long alkyl chain	> 50 (45%)
	Terminal amide/Potent mEH inhibitor	> 50
	Terminal hydrazide	> 50
	Urea with small substituent+long alkyl chain	> 50
	Amide with small substituent+long alkyl chain	> 50

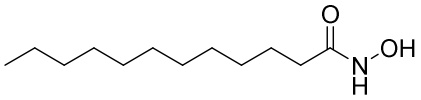
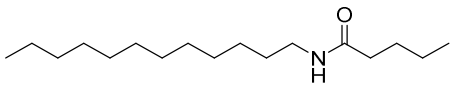
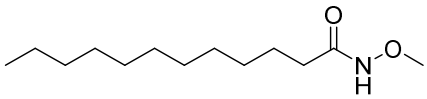
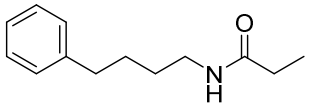
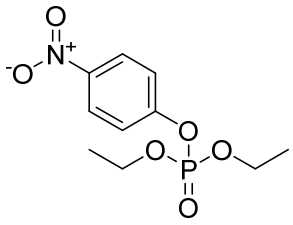
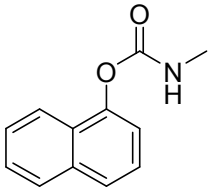
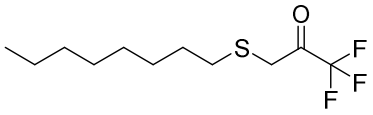
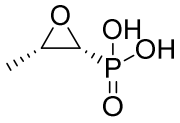
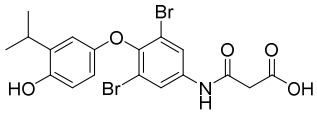
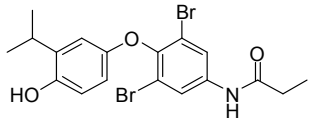
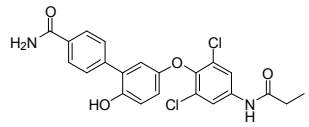
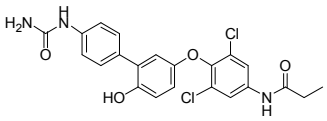
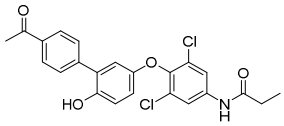
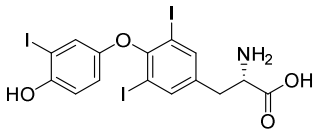
	Terminal *N*-hydroxyamide	> 50
	Amide with small substituent+long alkyl chain	> 50
	*N*-hydroxyamide with small substituent+long alkyl chain	> 50
	Amide with small substituent+long alkyl chain	> 50
	Paraoxon/Potent esterase inhibitor	> 50
	Carbamate/Potent esterase inhibitor	> 50
	Trifluoromethylketone/Potent esterase inhibitor	> 50
	Fhosfomycin/Antibiotics	> 50

Table S5. Equilibrium and kinetic parameters obtained from surface plasmon resonance experiments

	Tiratricol	**1a** (KB2115)	**8c**	**8h**	**8j**
K_D[a] (μM)	115±11	113±24	2.0±0.6	3.3±0.4	4.4±0.5
k_a (1/Ms)	-[b]	-[b]	1.3 (±0.3)×10^5	6.6 (±0.9)×10^4	4.7 (±0.9)×10^4
k_d (1/s)	-[b]	-[b]	0.17 (±0.03)	0.33 (±0.07)	0.34 (±0.07)
K_D[c] (μM)	-	-	1.4 (±0.3)	4.9 (±0.5)	7.2 (±0.1)

Results are shown as Mean ± SD (n = 3-6). [a]Data calculated based on steady state analysis. [b]Kinetic constants were outside the limit that can be measured. [c]Data calculated based on kinetic analysis.

Table S6. Thyroid hormone activity and selectivity of selected compounds

	Structure	EC_{50}[a] (nM,TR activity)	Cif IC_{50} (μM, CMNGC)	Selectivity Index[b]	Relative Selectivity Index[c]
1a (KB 2115)		0.43±0.14	2.6	0.0002	1
1c		7.0±2.1	7.5	0.0009	5.3
8c		>10,000	<0.35	29	161,000
8h		>10,000	<0.35	29	161,000
8j		>10,000	<0.35	29	161,000
T_3		0.10±0.02	-	-	-

[a]Mean ± SD values are shown. [b]Selectivity Index=TR EC_{50} of the compound/Cif IC_{50} of the compound. [c]Relative selectivity = (TR EC_{50} of the compound/Cif IC_{50} of the compound)/ (TR EC_{50} of KB2115/Cif IC_{50} of KB2115). For compounds **8c**, **8h** and **8j**, Cif IC_{50} values of 0.35 μM and TR EC_{50} values of 10,000 nM were used for the calculation.

Table S7. Result of thyroid hormone activity of selected compounds

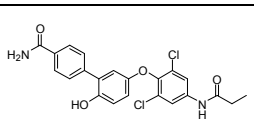
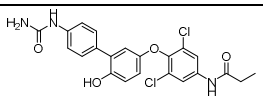
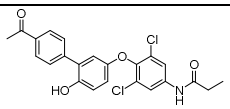
Compound	**8c**	**8h**	**8j**
Structure			
TR agonist (induction % at 3 μM)	23%	-3.5%	11%
TR agonist (induction % at 10 μM)	5.7%	2.4%	20.4%
TR antagonist (inhibition % at 10 μM)	66%	28%	33%

Table S8. Optimum mass transition conditions and key fragmentation

	Ionization mode	Transition			Cone voltage (V)	Collision voltage (V)
8c	-	443	->	216	50	27
8h	-	458	->	415	50	20
8j	-	442	->	216	50	25
AUDA	-	391	->	214	30	30

AUDA (12-(3-adamantan-1-yl-ureido) dodecanoic acid) was used as an internal standard for instrument sensitivity.

Table S9. HPLC solvent gradient for the quantification of inhibitors by LC-MS/MS

Time	Aqueous phase[a]	Organic phase[b]	Flow rate (mL/min)
0.00	95	5	0.2
3.00	95	5	0.2
5.00	2	98	0.2
10.00	2	98	0.2
10.01	95	5	0.2
12.00	95	5	0.2

[a]Milli-Q water 99.9, formic acid 0.1, volume %, [b]Methanol 99.9, formic acid 0.1, volume %.

Table S10. HPLC solvent gradient for the purity determination

Time	Aqueous phase[a]	Organic phase[b]	Flow rate (mL/min)
0.00	90	10	0.3
15.00	0	100	0.6
25.00	0	100	0.6
25.01	90	10	0.3
35.00	90	10	0.3

[a]Milli-Q water 99.9, formic acid 0.1, volume %, [b]Acetonitrile 99.9, formic acid 0.1, volume %.

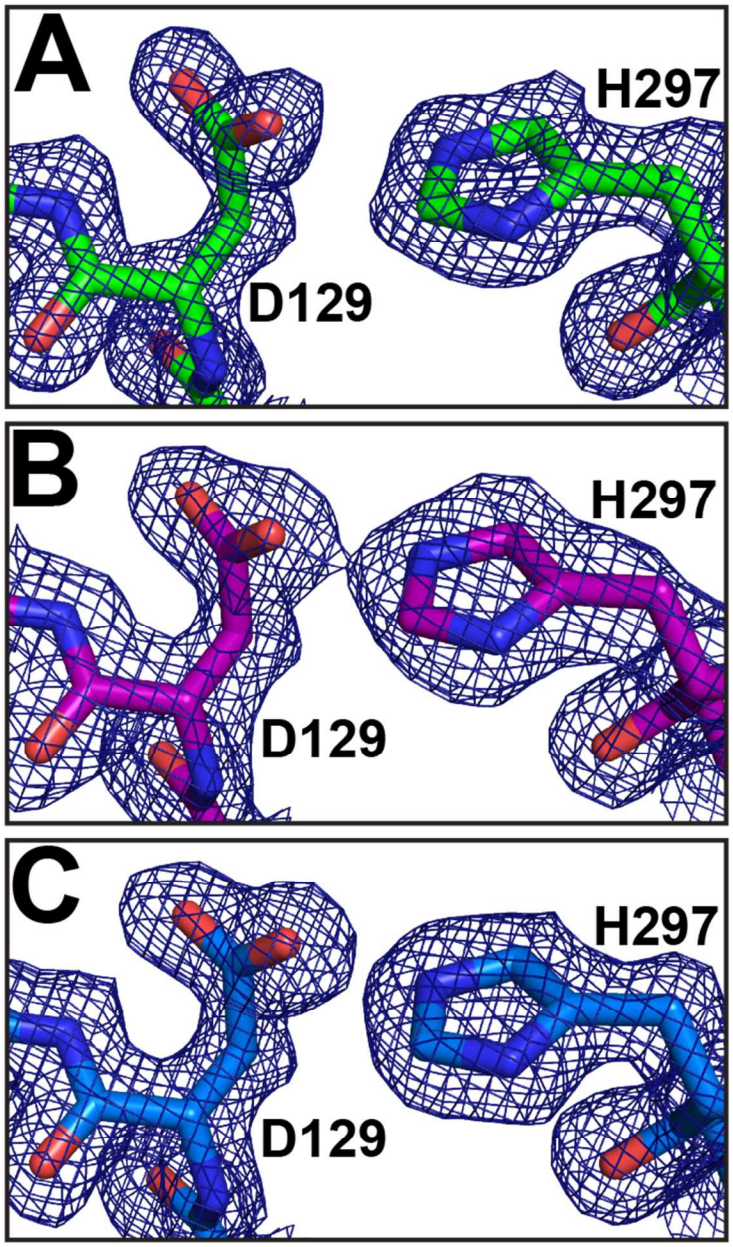


Figure S1. 2mFo-DFc simulated annealing omit maps of D129/H297 in Chain B. Each panel contains stick representations of the residues Asp 129 and His 297 from the final models of Cif with **1a** (A, carbons in green), Cif with **8c** (B, carbons in purple), and Cif with **8h** (C, carbons in blue). The residues have been overlaid with the 2mFo-Fc map (blue mesh) from a simulated annealing omit map heated to 3000K, with residues Asp 129 and His 297 removed. The maps are contoured to 1σ. All panels display the same view of the two active site residues from the final model. Non-carbon atoms are colored by element (O, red; N, dark blue).

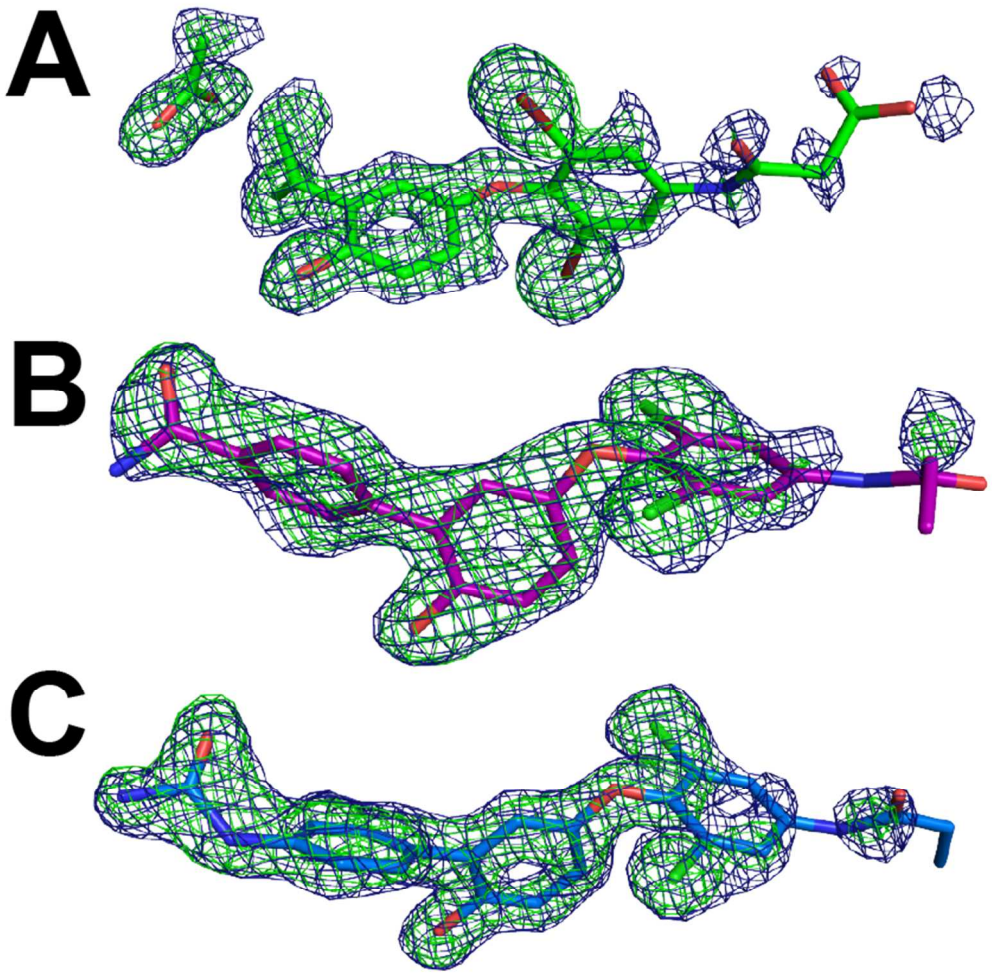


Figure S2. Fo-Fc and 2Fo-Fc maps of bound **1a**, **8c**, and **8h**, from Chain B. Each panel contains stick representations of the inhibitors from the final models of Cif with **1a** and acetate (A, carbons in green), Cif with **8c** (B, carbons in purple), and Cif with **8h** (C, carbons in blue). The models have been overlaid with the 2mFo-Fc map (blue mesh) and mFo-Fc map (green mesh) from the map generated before the inhibitors were placed into the model. 2mFo-Fc contoured to 1σ, and mFo-Fc contoured to 3σ. Non-carbon atoms are colored by element (O, red; N, dark blue; Br, maroon; Cl, green).

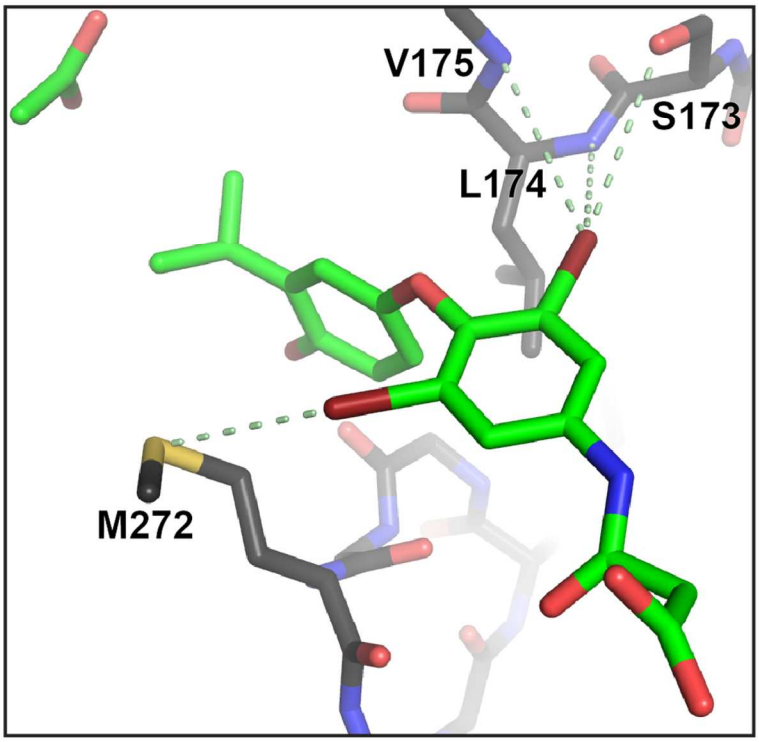


Figure S3. Potential halogen bonds between Cif Chain B and **1a**. Stick representations of **1a** (carbons in green) and Cif (carbons in dark grey) depict the halogen bonds (dashed lines in pale green) forming among the bromines on the small molecule and residues S173, L174, V175, and M272 of the protein. Non-carbon atoms are colored by element (O, red; N, dark blue; S, yellow; Br, maroon).

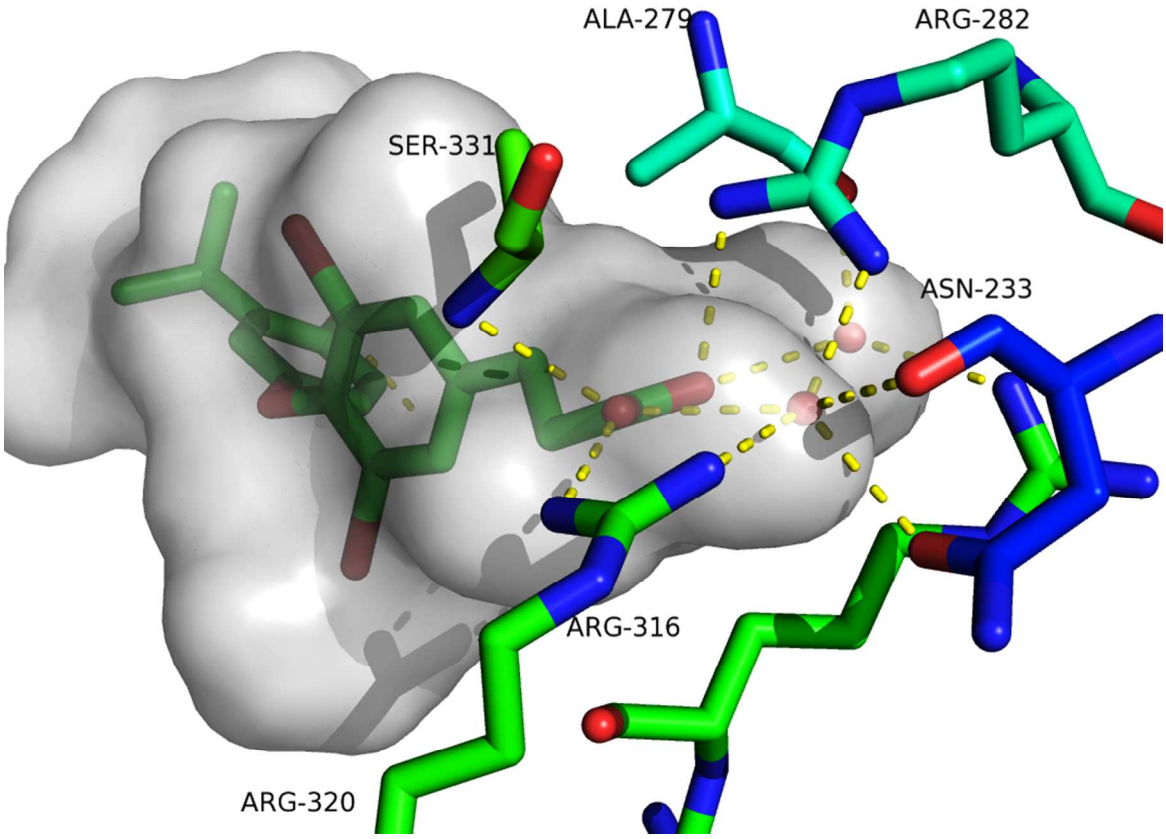


Figure S4. X-ray structure of KB compound bound to TRβ. Human thyroid hormone receptor β ligand binding domain in complex with KB131084 (PDB: 2J4A).

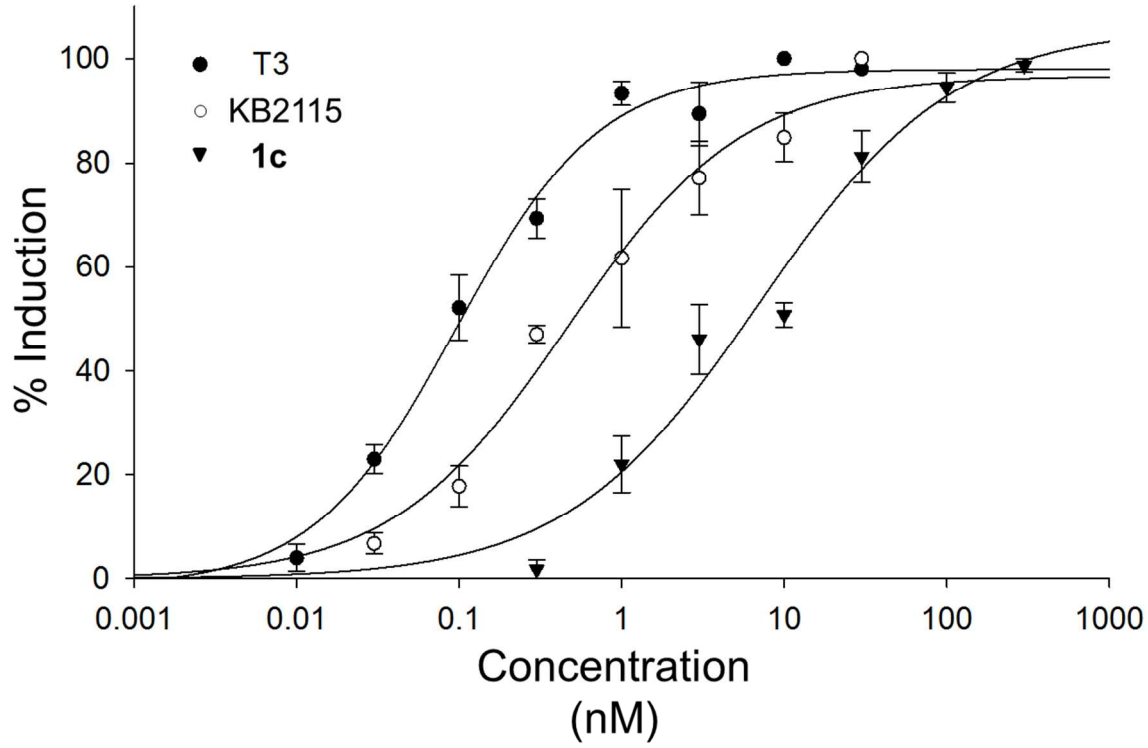


Figure S5. Thyroid hormone assay concentration-response curve. Percentages of maximal luciferase induction for each test compound were calculated by taking luciferase response in solvent control (DMSO) as 0% and the maximum luciferase induction by each compound as 100%. Every assay was repeated at least three separate times, and mean ± se values are shown.

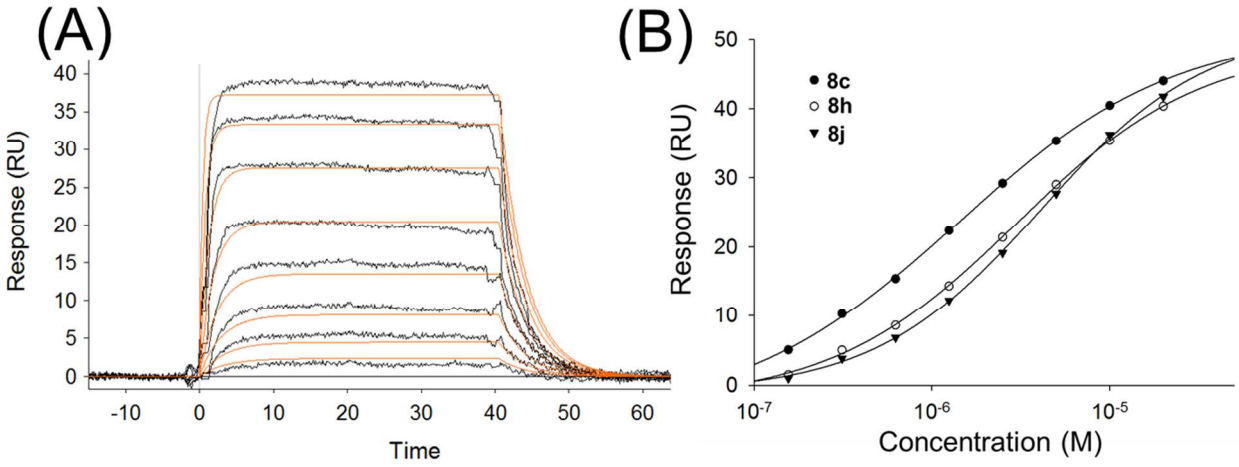


Figure S6. Cif:inhibitor binding interaction analysis by SPR. (A) Representative sensorgram for compound **8h**. Compound **8h** was injected in a two-fold concentration series at 156 nM-20 µM. Fitted curves (orange lines) are superimposed over experimental curves. The figure was generated using Scrubber2 software (BioLogic Software). (B) Binding isotherms for affinity determination. Responses at equilibrium were plotted against compound concentration and fit to a simple binding isotherm. Compound **8c**, **8h** or **8j** was injected in a two-fold concentration series at 156 nM-20 µM. RU: Resonance units.

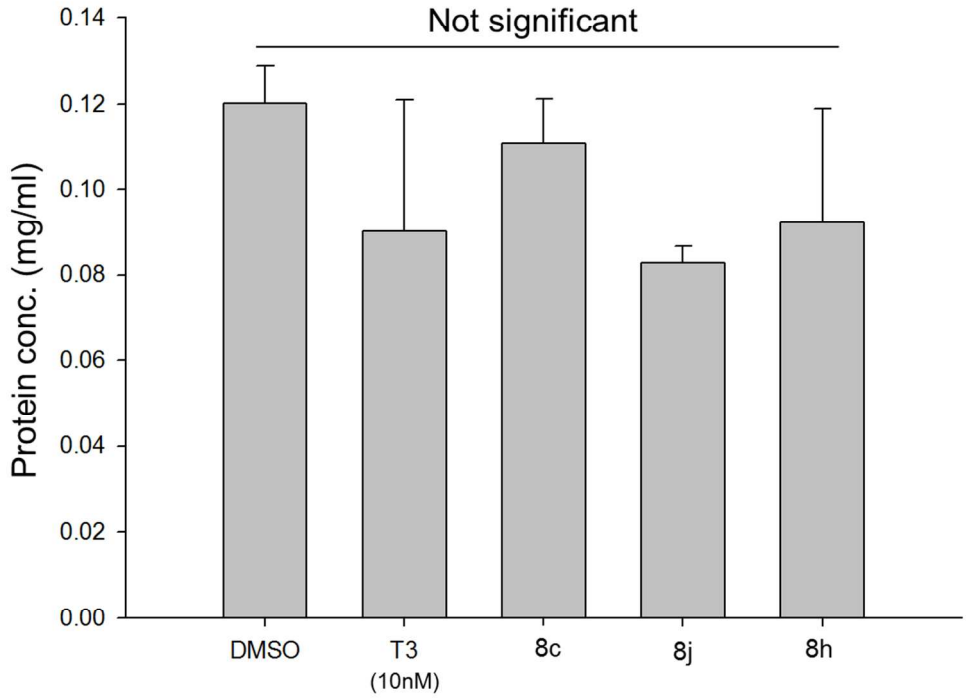


Figure S7. Effects of the tested compounds on protein concentration of GH3.TRE-Luc cells. Cell viability in each well was determined by measuring total protein concentration using the bicinchoninic acid (BCA) assay following the manufacture's protocol. Treatment with T_3 (10 nM) or inhibitor (10 μM) did not change the protein concentration significantly compared to control (DMSO treatment). Data were analyzed using SigmaPlot 11.0 for Windows (Systat Software Inc., San Jose, CA). Kruskal-Wallis One Way ANOVA on Ranks was performed with p values<0.05 considered significant.

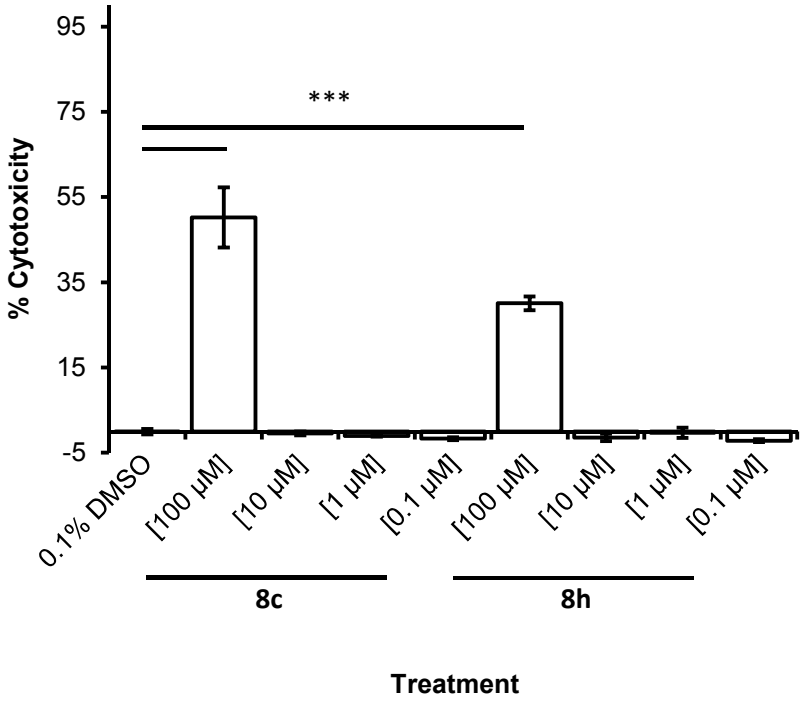


Figure S8. Cytotoxicity of **8c** and **8h** on CFBE cells. Percent cytoxicity was quantified using CFBE cells and the Cytotox 96 non-radioactive cytotoxicity assay (Promega). A_{490} values were corrected by subtraction of the corresponding value for negative control treatment (medium) and normalized to yield 100% toxicity for the positive control treatment (0.1% Triton-X100). n = 3, error bars = se. ***, P< 0.001 by ANOVA followed by Tukey's HSD post-hoc test.

Methods

Measurement of mEH inhibition by fluorescent assay

Human microsomal epoxide hydrolase (mEH) was produced in a polyhedron positive baculovirus expression system and was partially purified as described previously.[3] No esterase or glutathione transferase activities, which can interfere with EH assays, were detected in the purified enzyme. IC_{50} values were determined as described previously[4] using cyano (6-methoxy-naphthalen-2-yl) methyl glycidyl carbonate (CMNGC) as a fluorescent substrate. Recombinant human mEH (1.6 μg/mL) was incubated with compound for 5 min in 100 mM Tris/HCl buffer (pH 8.5) containing 0.1 mg/mL of BSA at 30 °C prior to substrate introduction ([S] = 25 μM). Activity was measured by determining the appearance of the 6-methoxy-2-naphthaldehyde with an excitation wavelength of 330 nm and an emission wavelength of 465 nm for 10 min. 2-(Nonylthio) propanamide was used as positive control giving an IC_{50} of 6.0 μM.

Measurement of sEH inhibition by radioactivity-based assay (*t*-DPPO assay)

Recombinant human sEH was produced in insect High Five cells using recombinant baculovirus expression vectors, and purified by affinity chromatography as reported previously.[5] The enzymes appeared as single bands of ca. 62 kDa by Coomassie Brilliant Blue staining following SDS-PAGE separation.

IC_{50} values were determined as described previously[6] with slight modifications, using racemic [^{3}H] *trans*-diphenylpropene oxide (*t*-DPPO). Purified recombinant human sEH was diluted in 100 mM sodium phosphate buffer (pH 7.4) containing 0.1 mg/mL BSA, and was incubated in triplicate with inhibitors for 5 min at 30 ºC prior to the introduction of the radiolabeled substrate (*t*-DPPO: 50 μM; ~10,000 cpm/assay). The mixture was incubated at 30 ºC for 10 min and the reaction was quenched by the addition of 60 μL of methanol. The remaining substrate was extracted by vigorous mixing with 200 μL of isooctane. The radioactivity of the aqueous phase was measured using a liquid scintillation counter (Perkin Elmer Tri-Carb 2810TR, Shelton, CT). Epoxide hydrolase activity was determined as a percentage of the radioactivity corresponding to the diol in the aqueous phase relative to the control. A potent soluble epoxide hydrolase inhibitor 12-(3-adamantan-1-yl-ureido) dodecanoic acid (AUDA) was used as positive control giving an IC_{50} of 16 ± 4 nM.

Measurement of solubility in sodium phosphate buffer

An excess of the test compound (~0.5 mg) was added to a vial containing sodium phosphate buffer, 0.1 M pH 7.4 (0.25 mL) without co-solvent, and a suspension of the mixture was equilibrated during 1 h of sonication and 24 h of shaking at room temperature, followed by centrifugation. The aqueous supernatant was analyzed by LC–MS/MS.

Measurement of *in vitro* stability

The *in vitro* human liver microsomal stability assay was performed as described previously with slight modifications.[7] Human liver microsomal protein (0.2 mg/mL) was incubated with a solution of test compound (1 μM) in Tris-HCl buffer (pH 7.4) containing 5 mM $MgCl_2$ and 1 mM NADPH. The incubation mixture was shaken at 37 ºC for 60 min. Samples were taken out

every 10 min. The absolute quantity of parent compounds remaining at each time point was analyzed by LC-MS/MS described below and was converted to a percentage.

Quantification of the inhibitors by mass spectrometry

Inhibitors were quantified using a Waters Quattro Premier triple quadrupole tandem mass spectrometer (Micromass, Manchester, UK) interfaced to an electrospray ionization (ESI) source. The ESI was performed following HPLC in the negative mode at 2.51 kV capillary voltage. The source and the desolvation temperatures were set at 120 and 350 ºC, respectively. Cone gas (N_2) and desolvation gas (N_2) were maintained at flow rates of 10 and 700 L/h, respectively. Optimized conditions for mass spectrometry are shown in Table S8. Dwell time was set to 0.1 s. A regression curve for each compound was obtained from at least five different concentrations of standard stock solutions ($r^2 > 0.99$). 12-(3-Adamantan-1-yl-ureido) dodecanoic acid (AUDA) was used as an internal standard for instrument sensitivity and was added just before the analysis. The final concentration of AUDA was adjusted to 50 nM. The MS was coupled with a Waters Acquity UPLC (Waters, and Milford, MA, USA). The Phenomenex Kinetex C18 RP UPLC column (150 mm × 2.1 mm, particle size 1.7 μm) was used to separate these compounds. The HPLC solvent gradient is shown in Table S9.

Plasma protein binding assay

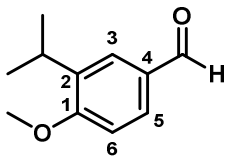
Mouse plasma protein binding assay was performed with inhibitor concentration at 1 μM as described previously[8]. Balb C mouse plasma was purchased from Innovative Research, Inc. (catalog #:IMSBC-N). A rapid equilibrium dialysis device method was used (#89809, Thermo Scientific, IL).

Purity assessment of the inhibitors by HPLC-UV

Purity determination of synthetic compounds was performed on an Agilent 1200 Series HPLC with a G1322A degasser, a G1311A Quatpump, and a G1315D Agilent detector. The Varian Pursuit5 C18 RP HPLC column (150 mm × 2.1 mm, particle size 5 μm) was used. The UV absorption between 190 nm and 400 nm was monitored, and the purity was determined by the peak area at 254 nm. Gradients are described in Table S10. In addition, all final products showed a single spot on TLC (silica gel matrix, fluorescent indicator, Sigma-Aldrich, 99569) under UV light (254 mm), >95% purity on ^{1}H NMR, and gave sharp melting point for crystalline compounds when measured.

Detailed synthetic methods

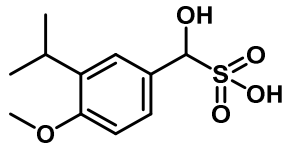
3-Isopropyl-4-methoxybenzaldehyde.



The title compound was synthesized as described previously.[9] To a DMF solution of 2-isopropylanisole (8.59 g, 57.3 mmol) was added dropwise phosphoryl chloride (26.9 g, 176 mmol, 3.1 equiv) at 90 °C, and stirred overnight at 90 °C. The reaction mixture was cooled to rt,

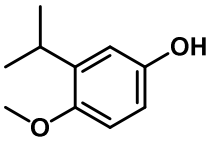
then ice-cold water was slowly added. The reaction mixture was extracted with ethyl acetate. The organic layer was combined and washed with saturated $NaHCO_3$ aqueous solution and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford 8.50 g (47.8 mmol, 83%) of title compound as a mixture with starting material (~2:1) as a brown oil. The compound was taken to the next step without further purification. ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.88 (s, 1H, *CHO*), 7.77 (d, 1H, *J* = 2.1 Hz, H-3), 7.71 (dd, 1H, *J* = 8.4, 2.1 Hz, H-5), 6.95 (d, *J* = 8.4 Hz, 1H, H-6), 3.92 (s, 3H, O*CH*$_3$), 3.36 – 3.27 (m, 1H, isopropyl C*H*), 1.24 (d, *J* = 6.9 Hz, 6H, isopropyl (C*H*$_3$)$_2$).

Hydroxy (3-isopropyl-4-methoxyphenyl) methanesulfonic acid.



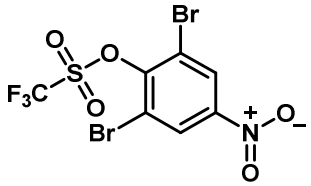
The title compound was synthesized as described previously.[9] To a THF: hexane (60 mL:48 mL) solution of 3-isopropyl-4-methoxybenzaldehyde (8.5g, 47.8 mmol) was added sodium bisulfite (13.1 g, 125 mmol, 2.6 equiv) in 48 mL water at rt and stirred overnight. The resulting precipitate was filtered and the residue was washed with THF:hexane (3:1), then dried to give pure title compound as a white powder (8.3 g, 31.9 mmol, 67%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.26 (d, *J* = 2.1 Hz, 1H), 7.22 (dd, *J* = 8.5, 2.3 Hz, 1H), 6.80 (d, *J* = 8.4 Hz, 1H), 5.61 (d, *J* = 5.1 Hz, 1H), 4.86 (d, *J* = 5.1 Hz, 1H), 3.76 (s, 3H), 3.19 (septet, *J* = 7.0 Hz, 1H), 1.14 (d, *J* = 6.9 Hz, 6H).

3-Isopropyl-4-methoxyphenol (**2a**).



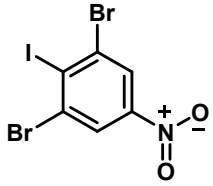
The title compound was synthesized as described previously.[9] To a MeOH solution of hydroxy (3-isopropyl-4-methoxyphenyl) methanesulfonic acid (8.2 g, 31.5 mmol) was added p-toluene sulfonic acid monohydrate (7.20 g, 37.8 mmol, 1.2 equiv) at rt, then cooled to 0 °C. To this was added dropwise 16 mL of H_2O_2 30% aqueous solution and stirred overnight at rt. To this was added 65 mL of sodium dithionite (18.6 g) in water at 0 °C, and stirred 0.5 h. The mixture was filtered, and the residue was washed with ethyl acetate. Hexane was added to the filtrate until the organic layer was separated, and the aqueous layer was extracted with ethyl acetate/hexane. The organic layer was combined and washed with saturated $NaHCO_3$ aqueous solution and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford 4.10 g (24.7 mmol, 78%) of pure title compound as a yellowish oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.73 – 6.71 (m, 2H), 6.61 (dd, *J* = 8.8, 3.5 Hz, 1H), 4.44 (s, 1H), 3.78 (s, 3H), 3.28 (m, 1H), 1.18 (d, *J* = 6.9 Hz, 1H).

2, 6-Dibromo-4-nitrophenyl trifluoromethanesulfonate.



The title compound was synthesized as described previously.[9] To an ice-cold DCM solution of 2, 6-dibromo-4-nitrophenol (8 g, 26.9 mmol) was added pyridine (4.36 mL), and to this mixture was added dropwise 5.44 mL of triflic anhydride (32.4 mmol, 1.2 equiv) in 4 mL DCM. The reaction mixture was slowly warmed to rt, and stirred 0.5 h at rt. Aqueous 1 M HCl solution was added dropwise and the DCM layer was separated. The aqueous layer was extracted with DCM. The DCM layer was combined and washed with saturated $NaHCO_3$ aqueous solution and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford 10.6 g (24.7 mmol, 92%) of title compound as a white powder. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.53 (s, 2H).

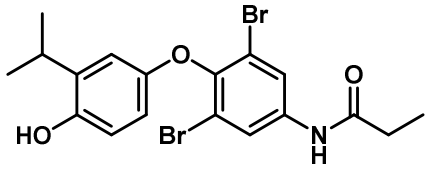
1, 3-Dibromo-2-iodo-5-nitrobenzene (**3a**).



The title compound was synthesized as described previously.[9] To a DMF solution of 2, 6-dibromo-4-nitrophenyl trifluoromethanesulfonate (10.6 g, 24.7 mmol) was added sodium iodide (16 g, 107 mmol, 4.3 equiv) at rt, then heated to 100 °C, cooled to rt, and stirred overnight at rt. Water was added and stirred for 0.5 h, then the mixture was filtered. The residue was washed with water, then dried to give a title compound (8.31 g, 20.4 mmol, 83%) as a brown powder. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.38 (s, 2H).

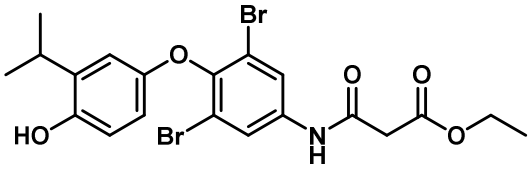
1,3-Dibromo-2-(3-isopropyl-4-methoxyphenoxy)-5-nitrobenzene (**4a**).
See main text.
4-(2, 6-Dibromo-4-nitrophenoxy)-2-isopropylphenol (**5a**).
See main text.
4-(4-Amino-2, 6-dibromophenoxy)-2-isopropylphenol (**6a**).
See main text.
N-(3, 5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy) phenyl) acetamide (**1b**).
See main text.

N-(3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenyl)propionamide (**1c**).



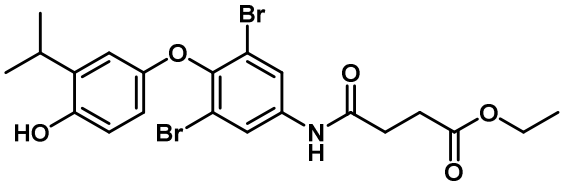
The title compound was synthesized from **6a** and propionyl chloride following the general procedure D to give the desired product as an off-white powder (46 mg, 51%); mp 199-200 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.84 (s, 2H), 7.08 (s, 1H), 6.78 (d, *J* = 3.0 Hz, 1H), 6.63 (d, *J* = 8.7 Hz, 1H), 6.39 (dd, *J* = 8.7, 3.0 Hz, 1H), 4.45 (s, 1H), 3.17 (septet, *J* = 6.9 Hz, 1H), 2.41 (q, *J* = 7.6 Hz, 2H), 1.26 (t, *J* = 7.5 Hz, 3H). 1.23 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 172.5, 149.5, 149.3, 143.7, 138.2, 135.6, 122.7, 117.8, 115.3, 112.8, 111.5, 29.6, 26.5, 22.3, 9.4. ESI-TOF-MS (+) calcd for $C_{18}H_{20}Br_2NO_3(M+H)^+$ 455.97. Found 455.97. Purity (HPLC-UV): 99% (^{t}R=11.3 min).

Ethyl 3-((3, 5-dibromo-4-(4-hydroxy-3-isopropylphenoxy) phenyl) amino)-3-oxopropanoate (**1d**).



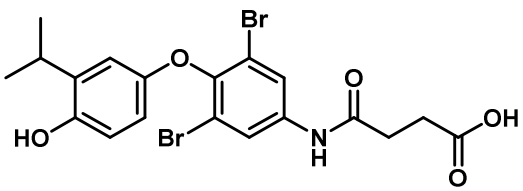
The title compound was synthesized from **6a** and ethyl malonyl chloride following the general procedure D to give the desired product (150 mg, 73%) as a yellowish amorphous solid; mp 47-60 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.51 (s, 1H), 9.03 (s, 1H), 7.95 (s, 2H), 6.67 – 6.65 (m, 2H), 6.27 (dd, *J* = 8.7, 3.1 Hz, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.49 (s, 2H), 3.15 (septet, *J* = 6.9 Hz, 1H), 1.21 (t, *J* = 7.1 Hz, 3H), 1.11 (d, *J* = 6.9 Hz, 6H). ESI-TOF-MS (+) calcd for $C_{20}H_{22}Br_2NO_5$ $(M+H)^+$ 513.98. Found 513.98. Purity (HPLC-UV): >99% (^{t}R=11.5 min).

Ethyl 4-((3, 5-dibromo-4-(4-hydroxy-3-isopropylphenoxy) phenyl) amino)-4-oxobutanoate (**1f**).



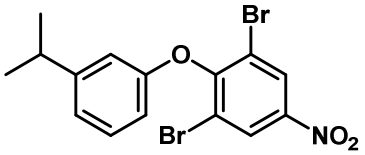
The title compound was synthesized from **6a** and ethyl 4-chloro-4-oxobutyrate following the general procedure D to give the desired product (111 mg, 53%) as white needles; mp 146-150 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.83 (s, 2H), 7.81 (s, 1H), 6.78 (d, *J* = 3.0 Hz, 1H), 6.63 (d, *J* = 8.7 Hz, 1H), 6.38 (dd, *J* = 8.6, 3.1 Hz, 1H), 4.50 (s, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.17 (septet, *J* = 6.9 Hz, 1H), 2.76 (t, *J* = 6.5 Hz, 2H), 2.67 – 2.65 (m, 2H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.23 (d, *J* = 6.9 Hz, 6H). ESI-TOF-MS (-) calcd for $C_{21}H_{24}Br_2NO_5$ $(M+H)^+$ 527.99, found 527.97. Purity (HPLC-UV): 95% (^{t}R=11.78 min).

4-((3, 5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy) phenyl) amino)-4-oxobutanoic acid (**1e**).



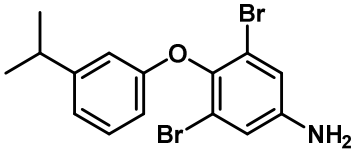
Compound **1f** (60 mg, 114 μmol) was dissolved in 20 mL of 1 M $NaOH_{aq}$, then stirred 5h at 40 °C. After cooling to rt, to this reaction mixture was slowly added 1 M HCl_{aq}, and extracted with ethyl acetate 4 times. The organic layer was combined and washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The title compound was recrystallized from acetone/hexane to give the title compound (8 mg, 14%) as a white powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.18 (s, 1H), 10.28 (s, 1H), 9.02 (s, 1H), 7.97 (s, 2H), 6.66 – 6.64 (m, 2H), 6.26 (dd, J = 8.7, 3.1 Hz, 1H), 3.15 (septet, J = 7.0 Hz, 1H), 2.55 (m, 4H), 1.11 (d, J = 6.9 Hz, 6H). ESI-TOF-MS (+) calcd for $C_{19}H_{20}Br_2NO_5$ $(M+H)^+$ 499.96 found 499.94. Purity (HPLC-UV): 96% (^{t}R=10.2 min).

1,3-Dibromo-2-(3-isopropylphenoxy)-5-nitrobenzene.



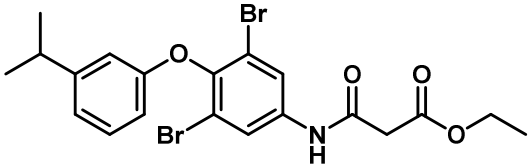
The title compound was synthesized from 3-isopropylphenol and **3a** following the general procedure A to give the desired product (536 mg, 96%) as a yellow solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.51 (s, 2H), 7.22 (t, J = 7.9 Hz, 1H), 6.98 (d, J = 8.5 Hz, 1H), 6.74 (d, J = 2.0 Hz, 1H), 6.54 (dd, J = 8.2, 2.6 Hz, 1H), 2.88 (septet, J = 6.7 Hz, 1H), 1.24 (d, J = 6.9 Hz, 6H).

3, 5-Dibromo-4-(3-isopropylphenoxy) aniline.



The title compound was synthesized from 1,3-dibromo-2-(3-isopropylphenoxy)-5-nitrobenzene following the general procedure C to give the desired product (204 mg, 80%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.19 (t, J = 7.9 Hz, 1H), 6.90 (m, 3H), 6.68 (t, J = 2.1 Hz, 1H), 6.46 (dd, J = 8.2, 2.6 Hz, 1H), 5.59 (s, 2H), 2.89 – 2.79 (m, 1H), 1.16 (d, J = 6.9 Hz, 6H).

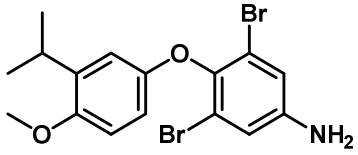
Ethyl 3-((3,5-dibromo-4-(3-isopropylphenoxy)phenyl)amino)-3-oxopropanoate (**1g**).



The title compound was synthesized from 3, 5-dibromo-4-(3-isopropylphenoxy) aniline and ethyl malonyl chloride following the general procedure D to give the desired product (56 mg, 54%) as a white amorphous solid; mp 87-89 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.51 (s, 1H), 7.89 (s, 2H), 7.19 (t, J = 7.9 Hz, 1H), 6.92 (d, J = 7.6 Hz, 1H), 6.73 (t, J = 2.0 Hz, 1H), 6.55 (dd, J = 8.2, 2.6 Hz, 1H), 4.28 (q, J = 7.1 Hz, 2H), 3.49 (s, 2H), 2.86 (septet, J = 6.9 Hz, 1H), 1.35 (t,

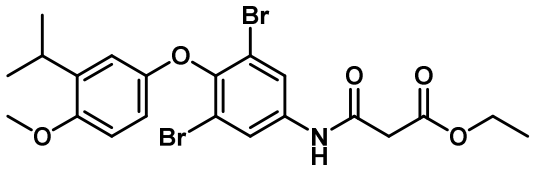
J = 7.1 Hz, 3H), 1.23 (d, *J* = 6.9 Hz, 6H). ESI-TOF-MS (+) calcd for $C_{20}H_{22}Br_2NO_4$ $(M+H)^+$ 497.98, found 497.96. Purity (HPLC-UV): 99% (^{t}R=13.2 min).

3, 5-Dibromo-4-(3-isopropyl-4-methoxyphenoxy) aniline.



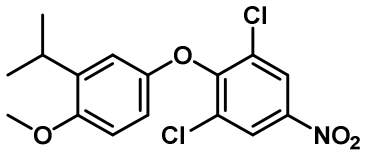
The title compound was synthesized from compound **4a** following the general procedure C to give the desired product (292 mg, 89%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 6.88 (s, 2H), 6.82 (d, *J* = 8.8 Hz, 1H), 6.71 (d, *J* = 3.1 Hz, 1H), 6.36 (dd, *J* = 8.9, 3.1 Hz, 1H), 5.56 (s, 2H), 3.73 (s, 3H), 3.19 (septet, *J* = 6.9 Hz, 1H), 1.11 (d, *J* = 6.9 Hz, 7H).

Ethyl 3-((3, 5-dibromo-4-(3-isopropyl-4-methoxyphenoxy) phenyl) amino)-3-oxopropanoate (**1h**).



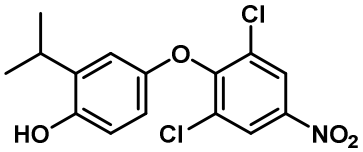
The title compound was synthesized from 3, 5-dibromo-4-(3-isopropyl-4-methoxyphenoxy) aniline following the general procedure D to give the desired product (44 mg, 40%) as pink crystals; mp 145-149 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.49 (s, 1H), 7.88 (s, 2H), 6.82 (d, *J* = 3.1 Hz, 1H), 6.70 (d, *J* = 8.9 Hz, 1H), 6.44 (dd, *J* = 8.8, 3.1 Hz, 1H), 4.28 (q, *J* = 7.2 Hz, 2H), 3.78 (s, 3H), 3.49 (s, 2H), 3.28 (septet, *J* = 6.9 Hz, 1H), 1.34 (t, *J* = 7.2 Hz, 3H), 1.10 – 1.09 (m, 6H).ESI-TOF-MS (+) calcd for $C_{21}H_{24}Br_2NO_5$ $(M+H)^+$ 527.99 found 527.99. Purity (HPLC-UV): >99% (^{t}R=13.2 min).

1, 3-Dichloro-2-(3-isopropyl-4-methoxyphenoxy)-5-nitrobenzene (**4i**).



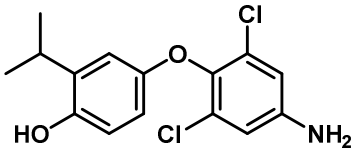
The title compound was synthesized from **2a** and 1,3-dichloro-2-fluoro-5-nitrobenzene following the general procedure A to give the desired product (510 mg, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 2H), 6.84 (d, *J* = 3.1 Hz, 1H), 6.72 (d, *J* = 8.9 Hz, 1H), 6.46 (dd, *J* = 8.8, 3.1 Hz, 1H), 3.80 (s, 3H), 3.30 (m, 1H), 1.19 (d, *J* = 6.9 Hz, 6H).

4-(2, 6-Dichloro-4-nitrophenoxy)-2-isopropylphenol (**5i**).



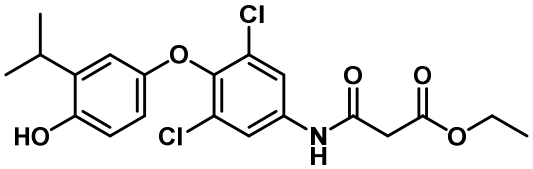
The title compound was synthesized from **4i** following the general procedure B to give the desired product (467 mg, 95%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.30 (s, 2H), 6.81 (d, *J* = 3.1 Hz, 1H), 6.66 (d, *J* = 8.7 Hz, 1H), 6.41 (dd, *J* = 8.7, 3.1 Hz, 1H), 4.64 (s, 1H), 3.19 (septet, *J* = 6.9 Hz, 1H), 1.24 (d, *J*=6.9 Hz, 6H).

4-(4-Amino-2, 6-dichlorophenoxy)-2-isopropylphenol (**6i**).



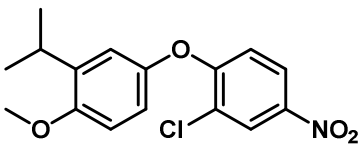
The title compound was synthesized from **5i** following the general procedure C to give the desired product (156 mg, 60%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.95 (s, 1H), 6.68 (s, 2H), 6.67 – 6.61 (m, 2H), 6.27 (d, *J* = 8.7 Hz, 1H), 5.57 (s, 2H), 3.16 – 3.12 (m, 1H), 1.10 (d, *J* = 6.9 Hz, 6H).

Ethyl 3-((3, 5-dichloro-4-(4-hydroxy-3-isopropylphenoxy) phenyl) amino)-3-oxopropanoate (**1i**).



The title compound was synthesized from **6i** following the general procedure D to give the desired product as a yellowish amorphous solid (63 mg, 58%); 125-131°C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.51 (s, 1H), 7.67 (s, 2H), 6.80 (d, *J* = 3.1 Hz, 1H), 6.63 (d, *J* = 8.7 Hz, 1H), 6.40 (dd, *J* = 8.6, 3.1 Hz, 1H), 4.73 (s, 1H), 4.28 (q, *J* = 7.1 Hz, 2H), 3.49 (s, 2H), 3.17 (septet, *J* = 6.9 Hz, 1H), 1.34 (t, *J* = 7.1 Hz, 3H), 1.22 (d, *J* = 6.9 Hz, 6H). ESI-TOF-MS (-) calcd for $C_{20}H_{20}Cl_2NO_5$ $(M-H)^-$ 424.08 found 424.09. Purity (HPLC-UV): 98% (^{t}R=11.2 min).

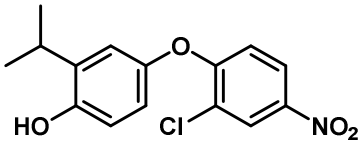
2-Chloro-1-(3-isopropyl-4-methoxyphenoxy)-4-nitrobenzene (**4j**).



The title compound was synthesized from **2a** and 3-chloro-4-fluoronitrobenzene following the general procedure A to give the desired product (893 mg, 84%) as a yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, *J* = 2.7 Hz, 1H), 8.02 (dd, *J* = 9.2, 2.7 Hz, 1H), 6.97 (d, *J* = 2.7 Hz, 1H),

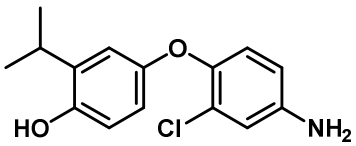
6.89 – 6.85 (m, 2H), 6.78 (d, *J* = 9.2 Hz, 1H), 3.86 (d, *J* = 3.1 Hz, 3H), 3.41 – 3.24 (m, 1H), 1.20 (d, *J* = 6.9 Hz, 6H).

4-(2-Chloro-4-nitrophenoxy)-2-isopropylphenol (**5j**).



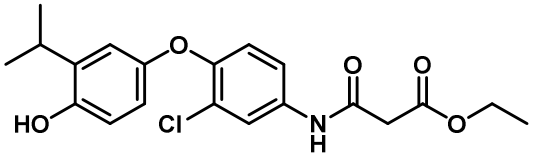
The title compound was synthesized from **4j** following the general procedure B to give the desired product (1.0 g, quant.) as a brown powder. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.37 (d, *J* = 2.7 Hz, 1H), 8.02 (dd, *J* = 9.2, 2.7 Hz, 1H), 6.96 (t, *J* = 1.6 Hz, 1H), 6.84 – 6.75 (m, 3H), 4.85 (s, 1H), 3.23 (septet, *J* = 6.8 Hz, 1H), 1.25 (d, *J* = 6.9 Hz, 6H).

4-(4-Amino-2-chlorophenoxy)-2-isopropylphenol (**6j**).



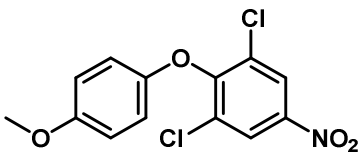
The title compound was synthesized from **5j** following the general procedure C to give the desired product as a reddish solid (616 mg, 68%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.01 (s, 1H), 6.76 (d, *J* = 8.7 Hz, 1H), 6.69 (s, 1H), 6.69 – 6.66 (m, 2H), 6.51 (dt, *J* = 8.3, 1.9 Hz, 1H), 6.41 (dd, *J* = 8.7, 3.0 Hz, 1H), 5.32 (s, 2H), 3.15 (septet, *J* = 6.9 Hz, 1H), 1.11 (d, *J* = 6.8 Hz, 6H).

Ethyl 3-((3-chloro-4-(4-hydroxy-3-isopropylphenoxy) phenyl) amino)-3-oxopropanoate (**1j**).



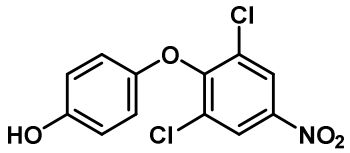
The title compound was synthesized from **6j** following the general procedure D to give the desired product as white crystals (82 mg, 36%); mp 132.2-133.3 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.31 (s, 1H), 9.23 (s, 1H), 7.88 (d, *J* = 2.5 Hz, 1H), 7.34 (dd, *J* = 9.0, 2.6 Hz, 1H), 6.88 (d, *J* = 8.9 Hz, 1H), 6.79 (d, *J* = 3.0 Hz, 1H), 6.76 (d, *J* = 8.6 Hz, 1H), 6.59 (dd, *J* = 8.6, 3.0 Hz, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.44 (s, 2H), 3.18 (septet, *J* = 6.9 Hz, 1H), 1.20 (t, *J* = 7.1 Hz, 3H), 1.13 (d, *J* = 6.9 Hz, 6H). ESI-TOF-MS (-) calcd for $C_{20}H_{21}ClNO_5$ $(M-H)^-$ 390.12, found 390.10. Purity (HPLC-UV): 99% (^{t}R=10.8 min).

1,3-Dichloro-2-(4-methoxyphenoxy)-5-nitrobenzene (**4k**).



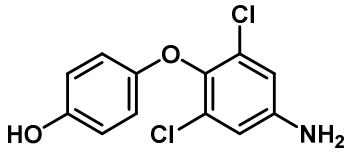
The title compound was synthesized from 1,3-dichloro-2-fluoro-5-nitrobenzene and 4-methoxyphenol following the general procedure A to give the desired product as a white powder (15.2 g, 97 %). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.30 (s, 2H), 6.84 (dd, *J*=6.6, 1.2 Hz, 2H), 6.77 (dd, *J* = 6.6, 1.2 Hz, 1H), 3.78 (s, 3H).

4-(2,6-Dichloro-4-nitrophenoxy)phenol (**5k**).



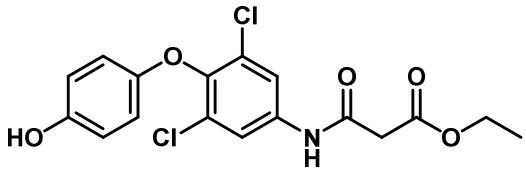
The title compound was synthesized from **4k** following the general procedure B to give the desired product (7.5 g, 63%) as a yellowish powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.28 (s, 1H), 8.50 (s, 2H), 6.72 (s, 4H).

4-(4-Amino-2, 6-dichlorophenoxy) phenol (**6k**).



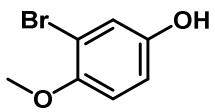
The title compound was synthesized from **5k** following the general procedure C to give the desired product (6.4 g, quant) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.05 (s, 1H), 6.69 (s, 2H), 6.67 (d, *J* = 13.8 Hz, 2H), 6.58 (d, *J* = 9.1 Hz, 2H), 5.73 (s, 2H).

Ethyl 3-((3, 5-dichloro-4-(4-hydroxyphenoxy) phenyl) amino)-3-oxopropanoate (**1k**).



The title compound was synthesized from **6k** following the general procedure D to give the desired product (3.89 g, 76%) as a white powder; mp 150.8-151.6 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.51 (s, 1H), 7.67 (s, 2H), 6.83 – 6.62 (m, 4H), 4.58 (s, 1H), 4.28 (q, *J* = 7.1 Hz, 2H), 3.49 (s, 2H), 1.34 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (151 MHz, DMSO- d_6) δ 167.1, 164.5, 152.6, 149.3, 142.3, 136.8, 128.7, 119.3, 115.9, 115.3, 60.6, 43.6, 13.9. ESI-TOF-MS (-) calcd for $C_{17}H_{14}Cl_2NO_5$ $(M-H)^-$ 382.03 found 383.05. Purity (HPLC-UV): 95% (^{t}R=9.7 min).

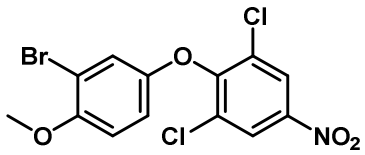
3-Bromo-4-methoxyphenol (**2l**).



The title compound was synthesized as described previously with slight modifications.[10] To a DCM solution of 3-bromo-4-methoxybenzaldehyde (2 g, 9.3 mmol) was added *m*-CPBA (3.2 g,

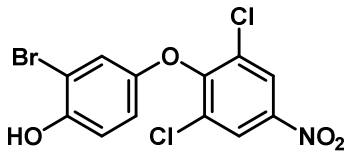
18.5 mmol, 2 equiv) at rt, then heated to 40 °C, and stirred overnight. After cooling to rt, aqueous sodium thiosulfate solution was added followed by saturated $NaHCO_{3aq}$, then the DCM layer was separated, and the aqueous layer was extracted with DCM. The DCM layer was combined and washed with a solution of saturated $Na_2S_2O_3$, saturated $NaHCO_3$ aqueous solution, and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. To this was added 50 mL ethanol followed by sodium ethoxide (21% in ethanol, 3.47 mL) at rt, then the solution was refluxed for 14 h then cooled and concentrated. Purification by flash column chromatography gave the desired compound as a white powder (630 mg, 33%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.08 (d, *J* = 2.8 Hz, 1H), 6.81 – 6.68 (m, 2H), 4.81 (s, 1H), 3.84 (s, 3H).

2-(3-Bromo-4-methoxyphenoxy)-1, 3-dichloro-5-nitrobenzene (**4l**).



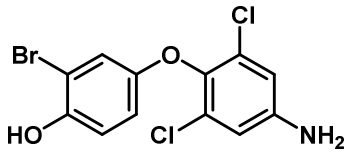
The title compound was synthesized from **2l** and 1,3-dichloro-2-fluoro-5-nitrobenzene following the general procedure A to give the desired product (2.06 g, quant). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.31 (s, 2H), 7.08 (d, *J* = 3.0 Hz, 1H), 6.84 (d, *J* = 9.0 Hz, 1H), 6.76 (dd, *J* = 9.0, 3.0 Hz, 1H), 3.87 (s, 3H).

2-Bromo-4-(2,6-dichloro-4-nitrophenoxy)phenol (**5l**).



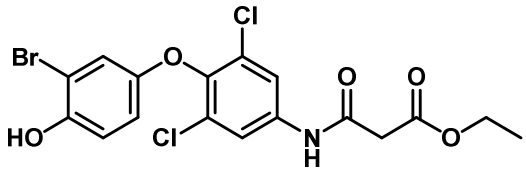
The title compound was synthesized from **4l** following the general procedure B to give the desired product as a yellowish solid (2.0 g, quant). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.31 (s, 2H), 6.99 (s, 1H), 6.96 (d, *J*=3.0 Hz, 1H), 6.75 (dd, *J* = 9.0, 2.0 Hz, 1H), 5.34 (s, 1H).

4-(4-Amino-2,6-dichlorophenoxy)-2-bromophenol (**6l**).



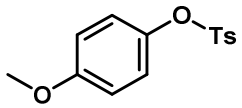
The title compound was synthesized from **5l** following the general procedure C to give the desired product (195 mg, 85%) as a yellowish solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.90 (s, 1H), 6.88 (d, *J* = 8.9 Hz, 1H), 6.84 (d, *J* = 3.0 Hz, 1H), 6.69 (s, 2H), 6.66 (dd, *J* = 8.9, 3.1 Hz, 1H), 5.65 (s, 2H).

Ethyl 3-((4-(3-bromo-4-hydroxyphenoxy)-3, 5-dichlorophenyl) amino)-3-oxopropanoate (**1l**).



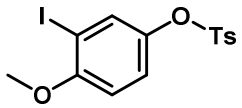
The title compound was synthesized from **6l** following the general procedure D to give the desired product as an off-white powder (42 mg, 40%); mp 140-142 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.55 (s, 1H), 7.69 (s, 2H), 6.95 – 6.93 (m, 2H), 6.75 (dd, *J* = 9.0, 3.0 Hz, 1H), 5.25 (s, 1H), 4.28 (q, *J* = 7.1 Hz, 2H), 3.49 (s, 2H), 1.34 (t, *J* = 7.2 Hz, 3H). ESI-TOF-MS (-) calcd for $C_{17}H_{13}BrCl_2NO_5$ $(M-H)^-$ 459.94 found 459.94. Purity (HPLC-UV): >99% (^{t}R=10.6 min).

4-Methoxyphenyl 4-methylbenzenesulfonate.



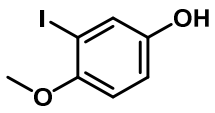
The title compound was synthesized as described previously with slight modifications.[11] To a THF solution of 4-methoxyphenol (4.97 g, 40 mmol) was added *p*-toluenesulfonyl chloride (7.63 g, 40 mmol, 1 equiv) and pyridine (3.22 mL, 40 mmol, 1 equiv) at rt, and stirred overnight. To this was added water and MTBE and the organic layer was separated, and the aqueous layer was extracted with MTBE. The organic layer was combined and washed with $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a title compound (6.04 g, 21.7 mmol, 54%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.3 Hz, 2H), 7.30 (d, *J* = 7.9 Hz, 2H), 6.88 (d, *J* = 9.2 Hz, 2H), 6.77 (d, *J* = 9.2 Hz, 2H), 3.77 (s, 3H), 2.45 (s, 3H).

3-Iodo-4-methoxyphenyl 4-methylbenzenesulfonate.



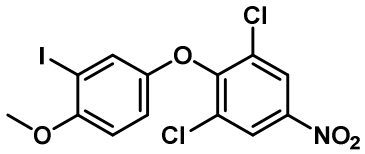
The title compound was synthesized as described previously with slight modifications.[11] To a tetrachloromethane (5 mL) solution of compound (4.37 g, 15.7 mmol) was added water (6 mL), iodine (3.17 g, 25.0 mmol), iodic acid (1.10 g, 6.3 mmol), sulfuric acid (1 mL), and acetic acid (12 mL) at rt, and the solution was refluxed overnight. After cooling to rt, to this was added MTBE and water, and the organic layer was separated, and the aqueous layer was extracted with MTBE. The organic layer was combined and washed with aqueous sodium thiosulfate solution 4 times, 1 M NaOH aqueous solution twice, water and brine, then dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a title compound (5.59 g, 13.8 mmol, 88%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.3 Hz, 2H), 7.36 – 7.34 (m, 3H), 6.95 (dd, *J* = 8.9, 2.8 Hz, 1H), 6.68 (d, *J* = 9.0 Hz, 1H), 3.83 (s, 3H), 2.46 (s, 3H).

3-Iodo-4-methoxyphenol (**2m**).



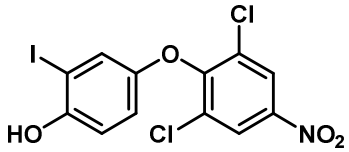
The title compound was synthesized as described previously with slight modifications.[11] To a *t*-BuOH solution of 3-iodo-4-methoxyphenyl 4-methylbenzenesulfonate (5.59 g, 13.8 mmol) was added 20% NaOH aqueous solution (20 mL) at rt, then refluxed overnight. After cooling to rt, MTBE and aqueous 1 M HCl solution was added and the organic layer was separated. The aqueous layer was extracted with MTBE. The organic layer was combined and washed with water and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a title compound (2.85 g, 11.4 mmol, 82%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.30 (d, J = 2.9 Hz, 1H), 6.81 (dd, J = 8.8, 2.9 Hz, 1H), 6.72 (d, J=8.8 Hz, 1H), 4.49 (s, 1H), 3.82 (s, 3H).

1, 3-Dichloro-2-(3-iodo-4-methoxyphenoxy)-5-nitrobenzene (**4m**).



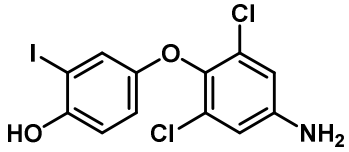
The title compound was synthesized from **2m** and 1,3-dichloro-2-fluoro-5-nitrobenzene following the general procedure A to give the desired product (10.3 g, 64%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 (s, 2H), 7.27 (m, 1H), 6.82 – 6.72 (m, 2H), 3.85 (s, 3H).

4-(2, 6-Dichloro-4-nitrophenoxy)-2-iodophenol (**5m**).



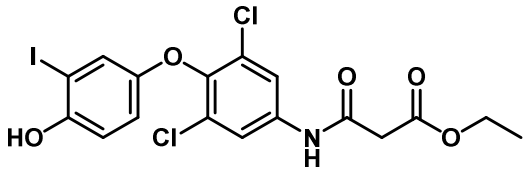
The title compound was synthesized from **4m** following the general procedure B to give the desired product (3.9 g, 80%) as a brownish solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.31 (s, 2H), 7.12 (d, J=3.0 Hz, 1H), 6.93 (d, J = 8.9 Hz, 1H), 6.78 (dd, J = 8.9, 3.0 Hz, 1H), 5.16 (s, 1H).

4-(4-Amino-2, 6-dichlorophenoxy)-2-iodophenol (**6m**).



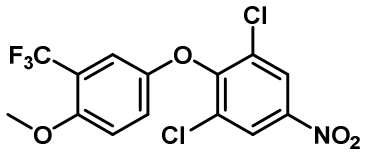
The title compound was synthesized from **5m** following the general procedure C to give the desired product (4 g, quant) as a dark brown solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.97 (s, 1H), 7.01 (d, J = 3.0 Hz, 1H), 6.80 (d, J = 8.9 Hz, 1H), 6.69 (s, 2H), 6.67 (dd, J = 8.9, 3.2 Hz, 1H), 5.64 (s, 2H).

Ethyl 3-((3,5-dichloro-4-(4-hydroxy-3-iodophenoxy)phenyl)amino)-3-oxopropanoate (**1m**).



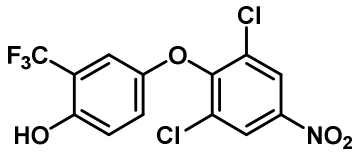
The title compound was synthesized from **6m** following the general procedure D to give the desired product (303 mg, 49%) as an off-white amorphous powder; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.55 (s, 1H), 7.69 (s, 2H), 7.10 (d, *J* = 2.9 Hz, 1H), 6.91 (d, *J* = 8.9 Hz, 1H), 6.77 (dd, *J* = 8.9, 2.9 Hz, 1H), 5.03 (s, 1H), 4.28 (q, *J* = 7.1 Hz, 2H), 3.49 (s, 2H), 1.34 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 167.0, 164.6, 152.3, 149.5, 141.8, 137.1, 128.5, 124.2, 119.4, 115.6, 115.1, 84.3, 60.6, 43.6, 13.9. ESI-TOF-MS (-) calcd for $C_{17}H_{13}Cl_2INO_5$ $(M-H)^-$ 507.93 found 507.91. Purity (HPLC-UV): 96% (^{t}R=10.8 min).

1,3-Dichloro-2-(4-methoxy-3-(trifluoromethyl)phenoxy)-5-nitrobenzene (**4n**).



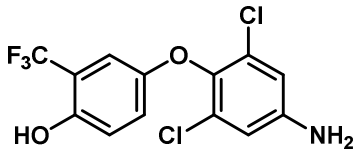
The title compound was synthesized from 4-methoxy-3-(trifluoromethyl)phenol and 1,3-dichloro-2-fluoro-5-nitrobenzene following the general procedure A to give the desired product (828 mg, 83%) as a white powder. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.32 (s, 2H), 7.11 (d, *J* = 3.0 Hz, 1H), 6.96 – 6.93 (m, 2H), 3.89 (s, 3H).

4-(2,6-Dichloro-4-nitrophenoxy)-2-(trifluoromethyl)phenol (**5n**).



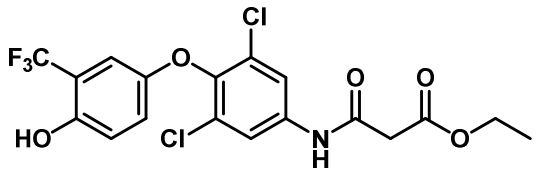
The title compound was synthesized from **4n** following the general procedure B with a modification that boron tribromide solution was added dropwise at -78 °C, to give the desired product (300 mg, 89%) as an off-white solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.32 (s, 2H), 7.02 (d, *J* = 3.2 Hz, 1H), 6.95 – 6.84 (m, 2H), 5.74 (bs, 1H).

4-(4-Amino-2,6-dichlorophenoxy)-2-(trifluoromethyl)phenol (**6n**).



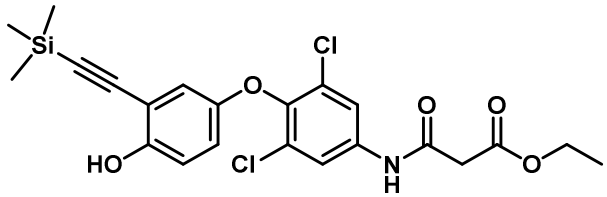
The title compound was synthesized from **5n** following the general procedure C to give the desired product (250 mg, 91%) as a black solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.26 (s, 1H), 6.99 – 6.95 (m, 1H), 6.95 – 6.88 (m, 1H), 6.85 (d, J = 3.0 Hz, 1H), 6.70 (s, 2H), 5.67 (s, 2H).

Ethyl 3-((3, 5-dichloro-4-(4-hydroxy-3-(trifluoromethyl) phenoxy) phenyl) amino)-3-oxopropanoate (**1n**).



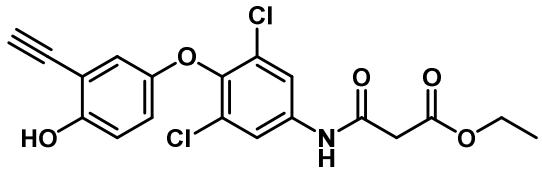
The title compound was synthesized from **6n** following the general procedure D to give the desired product (45 mg, 29%); mp 131-133 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.59 (s, 1H), 10.35 (s, 1H), 7.80 (s, 2H), 6.98 (d, J = 9.5 Hz, 1H), 6.94 (m, 2H), 4.13 (q, J = 7.0 Hz, 2H), 3.49 (s, 2H), 1.21 (t, J = 7.1 Hz, 3H). ESI-TOF-MS (-) calcd for $C_{18}H_{13}Cl_2F_3NO_5$ $(M-H)^-$ 450.02 found 450.01. Purity (HPLC-UV): 97% (^{t}R=10.9 min).

Ethyl 3-((3,5-dichloro-4-(4-hydroxy-3-((trimethylsilyl)ethynyl)phenoxy)phenyl)amino)-3-oxopropanoate.



To a toluene:TEA (50 mL: 25 mL) solution of compound **1m** (1 g, 1.96 mmol) was added TMS acetylene (5 mL, 35 mmol, 18 equiv), $PdCl_2(PPh_3)_2$ (84 mg, 120 µmol, 6.1 mol%), and CuI (32 mg, 169 µmol, 8.6 mol%) and stirred overnight at rt. The target compound was purified by column chromatography to give a crude product (500 mg, 1.04 mmol, 53%), which was used for the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.53 (s, 1H), 7.68 (s, 2H), 6.90 – 6.81 (m, 2H), 6.70 (s, 1H), 5.63 (s, 1H), 4.28 (q, J = 7.1 Hz, 3H), 3.49 (s, 2H), 1.34 (t, J = 7.1 Hz, 3H), 0.26 (s, 9H).

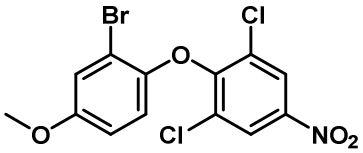
Ethyl 3-((3, 5-dichloro-4-(3-ethynyl-4-hydroxyphenoxy) phenyl) amino)-3-oxopropanoate (**1p**).



To an ice-cold EtOH solution of ethyl 3-((3,5-dichloro-4-(4-hydroxy-3-((trimethylsilyl)ethynyl)phenoxy)phenyl)amino)-3-oxopropanoate (450 mg, 0.938 mmol) was added potassium fluoride (272 mg, 4.69 mmol, 5 equiv), warmed to rt, and stirred 5 h. The target compound was purified by column chromatography to give the desired compound as an off-white powder (200 mg, 52%); mp 135.5-135.9 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.53 (s, 1H),

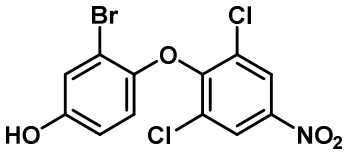
7.68 (s, 2H), 6.88 (d, J = 9.0 Hz, 1H), 6.84 (dd, J = 9.1, 3.0 Hz, 1H), 6.77 (d, J = 3.0 Hz, 1H), 5.55 (s, 1H), 4.28 (q, J = 7.1 Hz, 2H), 3.49 (s, 2H), 3.44 (s, 1H), 1.34 (t, J = 7.2, 3H). ESI-TOF-MS (-) calcd for $C_{19}H_{14}Cl_2NO_5$ $(M-H)^-$ 406.03 found 406.02. Purity (HPLC-UV): 96% (^{t}R=10.1 min).

2-(2-Bromo-4-methoxyphenoxy)-1,3-dichloro-5-nitrobenzene (**4q**).



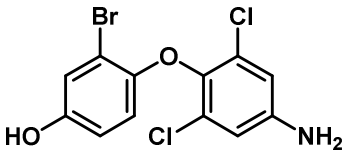
The title compound was synthesized from 2-bromo-4-methoxyphenol and 1,3-dichloro-2-fluoro-5-nitrobenzene following the general procedure A to give the desired product as a yellowish powder (800 mg, 76%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.30 (s, 2H), 7.21 (d, J = 2.9 Hz, 1H), 6.71 (dd, J = 9.0, 2.9 Hz, 1H), 6.37 (d, J = 9.0 Hz, 1H), 3.78 (s, 3H).

3-Bromo-4-(2,6-dichloro-4-nitrophenoxy)phenol (**5q**).



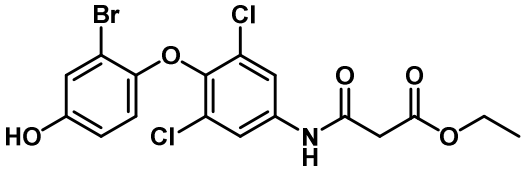
The title compound was synthesized from **4q** following the general procedure B to give the desired product as a brown oil (761 mg, 99%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.30 (s, 2H), 7.18 (d, J = 2.9 Hz, 1H), 6.66 (dd, J = 8.9, 2.9 Hz, 1H), 6.33 (d, J = 8.9 Hz, 1H), 4.95 (s, 1H).

4-(4-Amino-2,6-dichlorophenoxy)-3-bromophenol (**6q**).



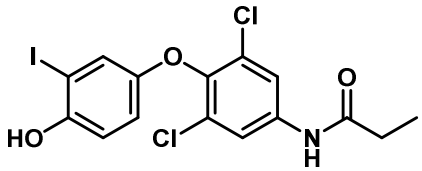
The title compound was synthesized from **5q** following the general procedure C to give the desired product as a yellowish solid (738 mg, quant). ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.49 (s, 1H), 7.02 (d, J = 2.8 Hz, 1H), 6.69 (s, 2H), 6.64 (dd, J = 8.9, 2.8 Hz, 1H), 6.30 (d, J = 8.9 Hz, 1H), 5.65 (s, 2H).

Ethyl 3-((4-(2-bromo-4-hydroxyphenoxy)-3, 5-dichlorophenyl) amino)-3-oxopropanoate (**1q**).



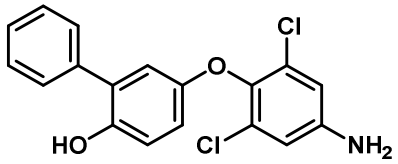
The title compound was synthesized from **6q** following the general procedure D to give the desired product as a white powder (49 mg, 46%); mp 147.5-148.3 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.56 (s, 1H), 9.57 (s, 1H), 7.78 (s, 2H), 7.04 (d, J = 2.8 Hz, 1H), 6.62 (dd, J = 8.9, 2.9 Hz, 1H), 6.33 (d, J = 8.9 Hz, 1H), 4.11 (q, J = 7.1 Hz, 2H), 3.47 (s, 2H), 1.19 (t, J = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 167.2, 164.8, 153.3, 145.7, 142.1, 137.3, 128.4, 128.4, 119.7, 119.4, 115.3, 114.8, 110.2, 60.8, 43.7, 14.0. ESI-TOF-MS (-) calcd for $C_{17}H_{13}BrCl_2NO_5$ $(M-H)^-$ 459.94, found 459.94. Purity (HPLC-UV): 99% (^{t}R=10.5 min).

N-(3, 5-Dichloro-4-(4-hydroxy-3-iodophenoxy) phenyl) propionamide (**7**).



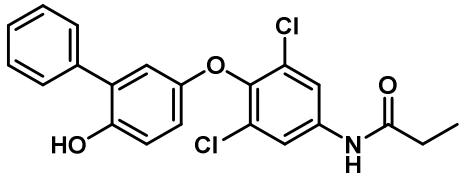
The title compound was synthesized from **6m** and propionyl chloride following the general procedure D to give the desired product (2.58 g, 75%) as an off-white solid. IR (neat) 3313, 3086 (broad), 1661, 1590, 1529, 1467 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.24 (s, 1H), 10.05 (s, 1H), 7.82 (s, 2H), 7.07 (d, J = 3.0 Hz, 1H), 6.81 (d, J = 8.9 Hz, 1H), 6.70 (dd, J = 8.9, 3.0 Hz, 1H), 2.35 (q, J = 7.5 Hz, 2H), 1.09 (t, J = 7.5 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 172.6, 152.3, 149.6, 141.2, 137.9, 128.4, 124.1, 119.2, 115.7, 115.2, 84.4, 29.6, 9.4.

5-(4-Amino-2,6-dichlorophenoxy)-[1,1'-biphenyl]-2-ol.



The title compound was synthesized from compound **6m** following the general procedure E from 4-(4-amino-2,6-dichlorophenoxy)-2-iodophenol to give the desired product as a yellowish powder (131 mg, 50%). ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.49 – 7.47 (m, 2H), 7.37 – 7.35 (m, 2H), 7.30 – 7.23 (m, 1H), 6.80 (d, J = 8.8 Hz, 1H), 6.74 (s, 2H), 6.65 (d, J = 3.1 Hz, 1H), 6.59 (dd, J = 8.8, 3.0 Hz, 1H).

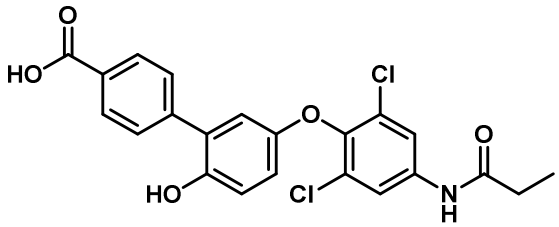
N-(3, 5-dichloro-4-((6-hydroxy-[1,1'-biphenyl]-3-yl)oxy)phenyl)propionamide (**8a**).



The title compound was synthesized from 5-(4-amino-2,6-dichlorophenoxy)-[1,1'-biphenyl]-2-ol and propionyl chloride following the general procedure D from 5-(4-amino-2, 6-dichlorophenoxy)-[1,1'-biphenyl]-2-ol to give the desired product as a white crystals (48 mg,

58%); mp 164.4-165.6 °C; IR (neat) 3296, 3171 (broad), 1662, 1590, 1532, 1466 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ 10.21 (s, 1H), 9.35 (s, 1H), 7.82 (s, 2H), 7.48 – 7.47 (m, 2H), 7.38 (dd, J = 8.3, 7.0 Hz, 2H), 7.30 – 7.28 (m, 1H), 6.88 (d, J = 8.8 Hz, 1H), 6.67 – 6.63 (m, 2H), 2.34 (q, J = 7.5 Hz, 2H), 1.09 (t, J = 7.5 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 172.6, 149.6, 149.6, 141.5, 137.9, 137.7, 128.9, 128.6, 128.4, 128.0, 126.8, 119.1, 116.9, 115.9, 114.4, 29.6, 9.4. ESI-TOF-MS (-) calcd for $C_{21}H_{16}Cl_2NO_3$ $(M-H)^-$ 400.06, found 400.04. Purity (HPLC-UV): 99% (^{t}R=11.3 min).

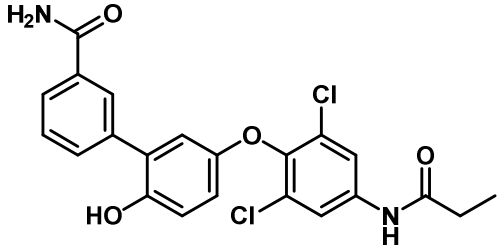
5'-(2, 6-Dichloro-4-propionamidophenoxy)-2'-hydroxy-[1, 1'-biphenyl]-4-carboxylic acid (**8b**).



The title compound was synthesized from **7** and 4-carboxyphenylboronic acid following the general procedure E to give the desired product (12 mg, 15%) as a yellowish powder; mp 228-230 °C; ^1H NMR (600 MHz, Acetone-d_6) δ 11.20 (s, 1H), 9.37 (s, 1H), 8.40 (s, 1H), 8.06 (d, J = 8.6 Hz, 2H), 7.88 (s, 2H), 7.72 – 7.70 (m, 2H), 6.99 (d, J = 8.8 Hz, 1H), 6.87 (d, J = 3.1 Hz, 1H), 6.75 (dd, J = 8.8, 3.1 Hz, 1H), 2.41 (q, J = 7.5 Hz, 2H), 1.15 (t, J = 7.5 Hz, 3H). 444.06 (444.05) Purity (HPLC-UV): 96% (^{t}R=9.86 min) ESI-TOF-MS (-) calcd for $C_{22}H_{16}Cl_2NO_5$ $(M-H)^-$ 444.05. Found 444.05.

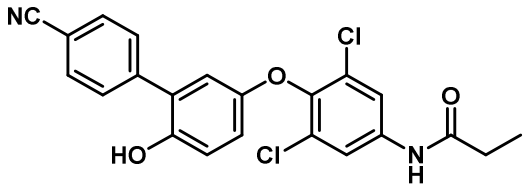
5'-(2,6-Dichloro-4-propionamidophenoxy)-2'-hydroxy-[1,1'-biphenyl]-4-carboxamide (**8c**). See main text.

5'-(2,6-Dichloro-4-propionamidophenoxy)-2'-hydroxy-[1,1'-biphenyl]-3-carboxamide (**8d**).



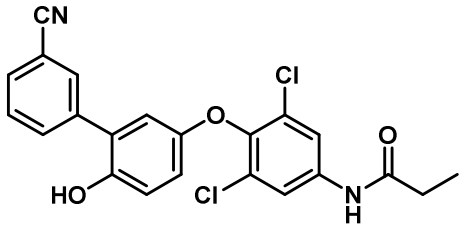
The title compound was synthesized from 7 and 3-aminocarbonylphenylboronic acid following the general procedure E to give the desired product as an off-white powder (23 mg, 29%); mp 136.3-140.5°C; ^1H NMR (600 MHz, Acetone-d_6) δ 9.36 (s, 1H), 8.25 (s, 1H), 8.11 (s, 1H), 7.88 (m, 3H), 7.72 (d, J = 7.8 Hz, 1H), 7.50 – 7.47 (m, 2H), 6.96 (m, 1H), 6.88 (s, 1H), 6.68 (dd, J = 8.8, 3.1 Hz, 1H), 6.61 (s, 1H), 2.40 (q, J = 7.5 Hz, 2H), 1.15 (t, J = 7.5 Hz, 3H). δ ESI-TOF-MS (-) calcd for $C_{22}H_{17}Cl_2N_2O_4$ $(M-H)^-$ 443.06 found 443.07. Purity (HPLC-UV): 98% (^{t}R=9.0 min).

N-(3,5-dichloro-4-((4'-cyano-6-hydroxy-[1,1'-biphenyl]-3-yl)oxy)phenyl)propionamide (**8e**).



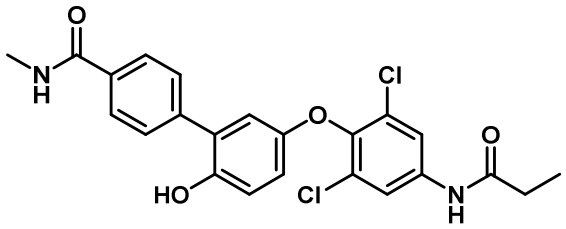
The title compound was synthesized from 7 and 4-cyanophenylboronic acid following the general procedure E to give the desired product as an off-white powder (30 mg, 40%); mp 231.6-232.0 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.22 (s, 1H), 9.67 (s, 1H), 7.85 – 7.83 (m, 4H), 7.71 – 7.70 (m, 2H), 6.92 (d, J = 8.9 Hz, 1H), 6.78 (d, J = 3.2 Hz, 1H), 6.70 (dd, J = 8.9, 3.1 Hz, 1H), 2.34 (q, J = 7.5 Hz, 2H), 1.09 (t, J = 7.5 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 173.0, 150.3, 150.1, 143.1, 141.8, 138.2, 132.4, 130.3, 129.0, 126.9, 119.6, 119.4, 117.7, 116.3, 116.2, 109.8, 30.0, 9.9. ESI-TOF-MS (-) calcd for $C_{22}H_{15}Cl_2N_2O_3$ $(M-H)^-$ 425.05 found 425.04. Purity (HPLC-UV): 97% (^{t}R=11.1 min).

N-(3,5-dichloro-4-((3'-cyano-6-hydroxy-[1,1'-biphenyl]-3-yl)oxy)phenyl)propionamide (**8f**).



The title compound was synthesized from 7 and 3-cyanophenylboronic acid following the general procedure E to give the desired product as an off-white powder (37 mg, 87%); mp 211.6-212.8 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.22 (s, 1H), 9.62 (s, 1H), 7.95 (s, 1H), 7.82 (s, 3H), 7.76 – 7.75 (m, 1H), 7.60 (t, J = 7.8 Hz, 1H), 6.91 (d, J = 8.9 Hz, 1H), 6.84 (d, J = 3.1 Hz, 1H), 6.65 (dd, J = 8.8, 3.1 Hz, 1H), 2.35 (q, J = 7.5 Hz, 2H), 1.09 (t, J = 7.5 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 172.6, 149.7, 149.7, 141.4, 138.8, 137.7, 133.8, 132.5, 130.6, 129.4, 128.6, 126.2, 119.1, 118.9, 117.1, 116.1, 115.2, 111.2, 29.6, 9.4. ESI-TOF-MS (-) calcd for $C_{22}H_{15}Cl_2N_2O_3$ $(M-H)^-$ 425.05 found 425.05. Purity (HPLC-UV): 98% (^{t}R=11.1 min).

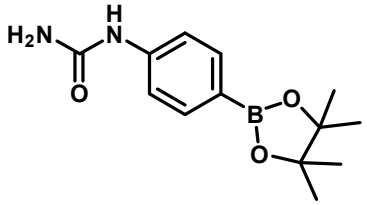
5'-(2,6-Dichloro-4-propionamidophenoxy)-2'-hydroxy-N-methyl-[1,1'-biphenyl]-4-carboxamide (**8g**).



The title compound was synthesized from 7 and 4-(*N*-methylaminocarbonyl)phenylboronic acid following the general procedure E to give the desired product as an off-white powder (25 mg, 31%); mp 161.3-165.2°C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.22 (s, 1H), 9.47 (s, 1H), 8.42 (q, J = 4.5 Hz, 1H), 7.83 (d, J = 8.6 Hz, 4H), 7.57 (d, J=8.4 Hz, 2H), 6.89 (d, J = 8.9 Hz, 1H), 6.76

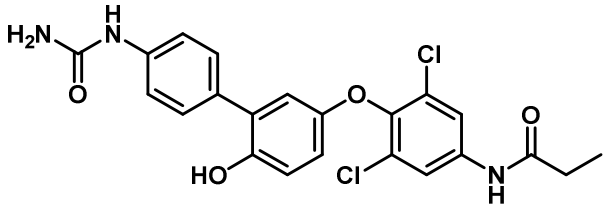
(d, J = 3.2 Hz, 1H), 6.63 (dd, J = 8.9, 3.2 Hz, 1H), 2.79 (d, J = 4.5 Hz, 3H), 2.34 (q, J = 7.5 Hz, 2H), 1.09 (t, J = 7.5 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 172.6, 166.4, 149.7, 149.6, 141.5, 140.4, 137.7, 132.9, 128.8, 128.6, 127.6, 126.8, 119.1, 117.0, 116.0, 114.8, 29.6, 26.3, 9.4. ESI-TOF-MS (-) calcd for $C_{23}H_{19}Cl_2N_2O_4$ $(M-H)^-$ 457.08. Found 457.08. Purity (HPLC-UV): 97% (^{t}R=9.40 min).

1-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)urea.



The title compound was synthesized as described previously with slight modifications.[12] To an ice-cold DCM solution of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (150 mg, 685 μmol) was added in one-portion chlorosulfonyl isocyanate (84 μL, 754 μmol, 1.1 equiv) and stirred 1 h. Water was added and stirred 2 h. To this reaction mixture was added DCM and water, the DCM layer was separated, and the aqueous layer was extracted with DCM. The DCM layer was combined and washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatography eluting with DCM:MeOH (50:1) gave the title compound (100 mg, 56%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.72 (d, J = 8.5 Hz, 2H), 7.41 (s, 1H), 7.30 (d, J = 8.6 Hz, 2H), 5.05 (s, 2H), 1.33 (s, 12H).

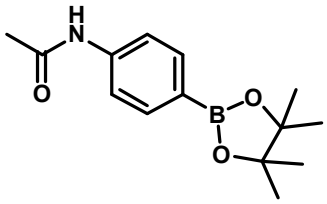
N-(3,5-dichloro-4-((6-hydroxy-4'-ureido-[1,1'-biphenyl]-3-yl)oxy)phenyl)propionamide (**8h**).



To a DME solution of compound **7** (80 mg, 177 μmol, 1.0 equiv) were added $Pd(PPh_3)_4$ (10 mg, 8.7 μmol, 0.05 equiv), an aqueous solution of Na_2CO_3 (400 mg in 1 mL H_2O), and 1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)urea (55.5 mg, 212 μmol, 1.2 equiv) in 1 mL ethanol. This solution was stirred at 71 °C overnight. After cooling to rt, ethyl acetate and 1 M HCl_{aq} were added and extracted 4 times with ethyl acetate. The organic layer was combined and washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The target compound was purified by column chromatography (DCM->DCM:MeOH=30:1), and recrystallized from acetone/DCM/hexane to give the desired product as an off-white powder (11 mg, 14%). TLC R_f=0.25 (DCM:MeOH=30:1); mp 162.0-162.9 °C; IR (neat) 3600-3000 (broad), 1664, 1590, 1535, 1464 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.21 (s, 1H), 9.25 (s, 1H), 8.55 (s, 1H), 7.82 (s, 2H), 7.40 (d, J = 8.7 Hz, 2H), 7.35 (d, J = 8.7 Hz, 2H), 6.84 (d, J = 8.8 Hz, 1H), 6.66 (d, J = 3.2 Hz, 1H), 6.56 (dd, J = 8.8, 3.2 Hz, 1H), 5.84 (s, 2H), 2.34 (q, J = 7.5 Hz, 2H), 1.09 (t, J = 7.5 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 173.0, 156.4, 150.0, 150.0, 142.0, 139.9, 138.1, 131.0, 129.6, 129.1, 128.8, 119.6, 117.7, 117.2, 116.0, 114.0, 30.0, 9.9. HRMS (+) calcd for

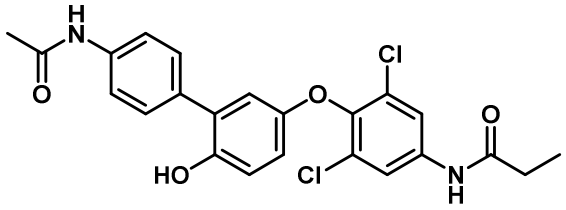
$C_{22}H_{20}Cl_2N_3O_4^+$ $(M-H)^+$ 460.0825. Found 460.0828. Purity (HPLC-UV): 97% (^{t}R=9.11 min). Anal. C 58.46, H 4.61, N 9.06%, calcd for $C_{22}H_{19}Cl_2N_3O_4 \cdot 0.2C_6H_{14}$, C 58.35, H 4.60, N 8.80%.

N-(4-(4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl) phenyl) acetamide.



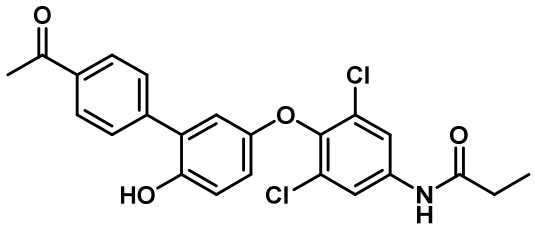
To a MTBE solution of 4-aminophenylboronic acid pinacol ester (100 mg, 457 μmol) was added saturated $NaHCO_3$ aqueous solution, and then to this was added dropwise acetyl chloride (71.7 mg, 914 μmol, 2 equiv) at 0 °C, and stirred for 3 h at rt. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The organic layer was combined and washed with saturated $NaHCO_3$ aqueous solution, 1 M HCl aqueous solution, brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The title compound was recrystallized from DCM to give the desired product as a white powder (88 mg, 74%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.76 (d, J = 8.0 Hz, 2H), 7.51 (d, J = 8.0 Hz, 2H), 7.18 (s, 1H), 2.18 (s, 3H), 1.34 (s, 12H).

N-(4-((4'-acetamido-6-hydroxy-[1, 1'-biphenyl]-3-yl) oxy)-3, 5-dichlorophenyl) propionamide (**8i**).



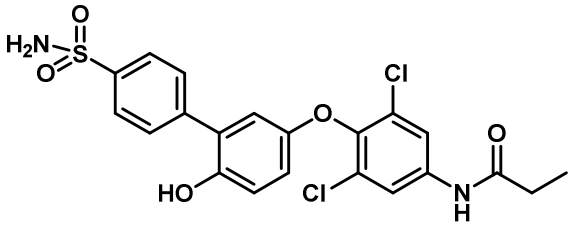
The title compound was synthesized from 7 and N-(4-(4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl) phenyl) acetamide following the general procedure E to give the desired product as an off-white powder (11 mg, 14%); mp 146.8-147.4 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.21 (s, 1H), 9.97 (s, 1H), 9.29 (s, 1H), 7.82 (s, 2H), 7.58 – 7.56 (m, 2H), 7.43 – 7.41 (m, 2H), 6.85 (d, J = 8.8 Hz, 1H), 6.69 (d, J = 3.1 Hz, 1H), 6.57 (dd, J = 8.8, 3.2 Hz, 1H), 2.34 (q, J = 7.5 Hz, 2H), 2.05 (s, 3H), 1.09 (t, J = 7.5 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 172.6, 168.2, 149.6 (2 carbons overlapped), 141.6, 138.1, 137.6, 132.4, 129.2, 128.6, 128.2, 119.1, 118.6, 116.8, 115.8, 113.9, 29.6, 24.0, 9.4. ESI-TOF-MS (-) calcd for $C_{23}H_{19}Cl_2N_2O_4$ $(M-H)^-$ 457.08. Found 457.09. Purity (HPLC-UV): 99% (^{t}R=9.4 min).

N-(4-((4'-acetyl-6-hydroxy-[1, 1'-biphenyl]-3-yl) oxy)-3, 5-dichlorophenyl) propionamide (**8j**).



To a DME solution of compound **7** (80 mg, 177 μmol, 1.0 equiv) were added $Pd(PPh_3)_4$ (10 mg, 8.7 μmol, 0.05 equiv), aqueous solution of Na_2CO_3 (400 mg in 1 mL H_2O), and 4-acetylphenylboronic acid (35 mg, 212 μmol, 1.2 equiv) in 1 mL ethanol. This solution was stirred at 71 °C overnight. After cooling to rt, ethyl acetate and 1 M HCl_{aq} were added and extracted 4 times with ethyl acetate. The organic layer was combined and washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The target compound was purified by column chromatography (DCM-> DCM:EtOAc=10:1), and recrystallized from acetone/DCM/hexane to give the desired product as an off-white powder (10 mg, 13%). TLC R_f=0.3 (DCM:EtOAc=10:1); mp 190.0-193.8 °C; IR (neat) 3311, 3236 (broad), 1667, 1585, 1529, 1466 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ 10.22 (s, 1H), 9.56 (s, 1H), 7.98 – 7.96 (m, 2H), 7.83 (s, 2H), 7.65 – 7.64 (m, 2H), 6.91 (d, J = 8.8 Hz, 1H), 6.76 (d, J = 3.2 Hz, 1H), 6.68 (dd, J = 8.9, 3.2 Hz, 1H), 2.59 (s, 3H), 2.34 (q, J = 7.5 Hz, 2H), 1.09 (t, J = 7.5 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 197.5, 172.6, 149.8, 149.6, 142.6, 141.4, 137.7, 135.1, 129.2, 128.6, 128.0, 127.2, 119.1, 117.2, 115.9, 115.2, 29.6, 26.7, 9.4. HRMS (+) calcd for $C_{23}H_{20}Cl_2NO_4^+$ $(M-H)^+$ 444.0764. Found 444.0757. Purity (HPLC-UV): >99% (^{t}R=10.8 min). Anal. C 62.42, H 4.46, N 3.23%, calcd for $C_{23}H_{19}Cl_2NO_4$, C 62.17, H 4.31, N 3.15%.

N-(3, 5-dichloro-4-((6-hydroxy-4'-sulfamoyl-[1,1'-biphenyl]-3-yl)oxy)phenyl)propionamide (**8k**).



The title compound was synthesized from 7 and 4-sulfamoylbenzeneboronic acid following the general procedure E to give the desired product as an off-white powder (8 mg, 9%); mp 143-144 °C; ^1H NMR (600 MHz, DMSO-d_6) δ 10.22 (s, 1H), 9.57 (s, 1H), 7.83 – 7.82 (m, 4H), 7.68 – 7.67 (m, 2H), 7.35 (s, 2H), 6.91 (d, J = 8.9 Hz, 1H), 6.79 (d, J = 3.2 Hz, 1H), 6.65 (dd, J = 8.9, 3.2 Hz, 1H), 2.35 (q, J = 7.5 Hz, 2H), 1.09 (t, J = 7.6 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 173.0, 150.2, 150.1, 142.8, 141.9, 141.7, 138.2, 129.9, 129.0, 127.5, 125.9, 119.6, 117.5, 116.6, 115.5, 30.0, 9.9. ESI-TOF-MS (-) calcd for $C_{21}H_{17}Cl_2N_2O_5S$ $(M-H)^-$ 479.03. Found 479.04. Purity (HPLC-UV): 95% (^{t}R=9.64 min).

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