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Synthetic modification of the 2-oxypropionic acid moiety in 2-{4-[(7-chloro-2-quinoxalinyl)oxy]phenoxy}propionic acid (XK469), and consequent antitumor effects. Part 4

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Abstract—The criteria for the activity of 2-{4-[(7-chloro-2-quinoxalinyl)oxy]phenoxy}propionic acid (XK469) and 2-{4-[(7-bromo-2-quinolinyl)oxy]phenoxy}propionic acid (SH80) against transplanted tumors in mice established in previous studies, require a (7-halo-2-quinoxalinoxy)- or a (7-halo-2-quinolinoxyl)-residue, respectively, bridged via a 1,4-OC_6H_4O-linker to C_2 of propionic acid. The present work demonstrates that substitution of fluorine at the 3-position of the 1,4-OC_6H_4O-linker of XK469 leads to a 10-fold reduction in activity, whereas the corresponding 2-fluoro analog proved to be 100-fold less active than XK469. Moreover, the latter tolerated substitution of but a single, additional methyl group to the 2-position of the propionic acid moiety, that is, the isobutyric acid analog, without loss of significant in vivo activity. Indeed, an intact 2-oxypropionic acid moiety is a prerequisite for maximum antitumor activity of **1a**.

1. Introduction

Compounds **1a** and **2a**, (R+)-2-{4-[(7-chloro-2-quinoxalinyl)oxy]phenoxy}propionic acid (XK469), and (R+)-2-{4-[(7-bromo-2-quinolinyl)oxy]phenoxy}propionic acid (SH80), respectively (Fig. 1), are two of the most highly and broadly active antitumor agents to have been developed in our laboratories.[1–4] The mechanism(s) of action of these agents remain to be established, though several, disparate pathways of anticancer action (which are very probably similar for both) have been proposed for **1a**.[5a–i] In the absence of a validated target, our endeavor continued to pursue the elaboration of a pharmacophoric pattern for these structures to gain a perception of the binding pocket of the receptor, which, as suggested by Strader,[6] may be inferred from the perspective of the ligand.

Our previous studies[7–9] clearly established that location of a halogen substituent in the benzene (ring-A) of either

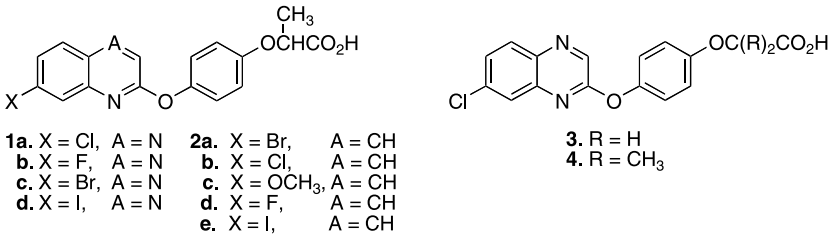

Figure 1.

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1a or **2a**, at other than the 7-position, markedly altered both the in vitro and in vivo activities of corresponding analogs. Thus, the 3-, 5-, 6-, and 8-regioisomers of **1a**, as well as the 6-chloro analog of **2a**, were all essentially inactive. In contrast, all of the 7-halogen derivatives (Fig. 1, **1a**–**d**) proved to be active compounds, with relative antitumor activities of Cl ≈ F ≈ Br > I. Analogs of **2a**, bearing either a 7-halogen or a 7-methoxy substituent (Fig. 1, **2a**–**e**), showed levels of antitumor activities in mice (Br > Cl > CH_3O > F ≈ I), comparable to or greater than those manifested by the corresponding quinoxaline derivatives, **1a**–**e**. Specifically, the order of activity of the 7-halogen substituent in **1** is Cl ≈ F ≈ Br > I, whereas in **2**, Br > Cl > F > I. Moreover, the *R*-enantiomers of both **1a** and **2a** were the more active of the respective antipodes.

The 5-, 6-, 7-, and 8-chloroquinazoline analogs of **1**, and as well the 6- and 7-chloro-[1,2,4]-benzotriazine analogs, were all inactive. Changes in the hydroquinone (1,4) linkage in **1a** to either a resorcinol (1,3), or a catechol (1,2) derivative produced inactive structures, as did replacement of either the 1- or 4-oxygen atoms comprising the hydroquinone bridge by sulfur or nitrogen.

Our preliminary in vitro data indicated[7] that replacement of the lactic acid moiety in **1a** by glycolic acid (**3**) resulted in a loss of antitumor activity, whereas the corresponding 2-hydroxyisobutyric acid analog (**4**) manifested reduced in vitro antitumor activity relative to **1a** (Tables 1 and 2). However, short chain alkyl esters of **1a**, as well as both the unsubstituted and the mono N-alkylamide derivatives of **1a** show only minor decreases in activity, relative to the parent structures.[7]

In summary, the criteria established, to date, for the antitumor activity of **1** and **2** include either a (7-halo-2-quinoxalinoxy)- or a (7-halo-2-quinolinoxyl)-residue, bridged via a 1,4-OC_6H_4O-linker to C_2 of propionic acid. Herein, we describe the antitumor effects in mice consequent to further modification of the 2-(4-oxyphenoxy)propionic acid of **1a**.

2. Results and discussion

2.1. Synthesis

Our endeavor turned first to modifications of the linker of **1a** with syntheses of both 2-{4-[(7-chloro-2-quinoxalinyl)oxy]-2- and 3-fluoro-phenoxy}propionic acids (Scheme 1, **10a** and **10b**, respectively). Preparations of the intermediates, methyl 2-(4-amino-2-fluoro- and 3-fluorophenoxy)propionates (**6a** and **6b**), proceeded from the

Table 1. In vitro cytotoxicity of selected racemic analogues of (*R*,*S*)-XK469 (**1a**) against leukemic cells, solid tumor cells, and normal cells in the disk-diffusion-soft-agar-colony-formation-assay[a,b]

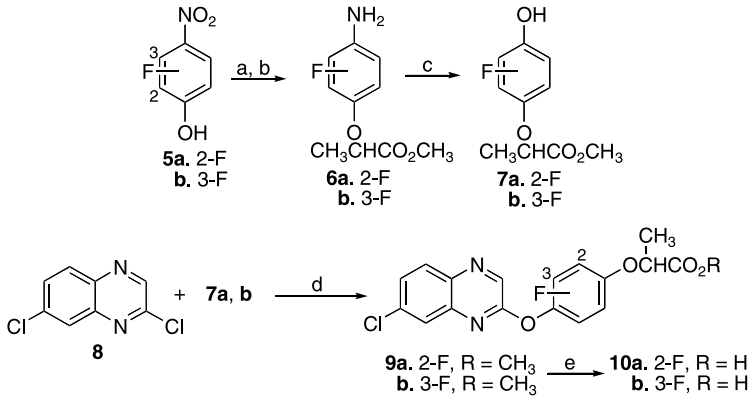
Compound number	μg/disk	Mouse leukemia	Mouse tumors			Human tumors		Normal cells
		L1210	Panc 03	Colon 38	Mam 17/Adr	Colon H116	Colon H15/MDR	Fibroblasts
1a	270	0–600		>800	>850		150–400	500–600
3[c]	225	0–50		40		0–30	0–90	0
4[c]	465	0–400	800–900	500–600		0–100	0–200	0–500
13	305	100–190		0–60		80	0	80
19b	535	0–450	>900	700–800		0–250	0–500	0–600
22	500	0–100	0–250	300–400	200–500	0–100	0–150	0
26b	480	0–380		400		450		200–380
28b	530	200–450		500–900	500–800	100–200	200–400	0–600
30b	470	0–200	600–900	500–600		0–100	0–250	0–600
32b	510	0–450		550–650			0–250	0–250

[a] For a detailed description of the testing methodologies, see Refs. 7–9.
[b] Zone units recorded: 200 units = 6.5 mm.
[c] First prepared and evaluated as a potential herbicide by DuPont Pharmaceutical Company.

Table 2. Evaluation of selected analogues of XK-469 (**1a**) against solid tumors of mice[a]

Compound number	SC tumor	No. of injections	Total dose (mg/kg)	Drug deaths	% Body wt. loss at Nadir	*T*/*C* (%)	Log_{10} tumor cell kill	Cures	Activity rating
1a	Colon 38	9	473	0/5	−1.7	0	3.9	2/5	++++
1a	Panc 03	5	300	0/5	−15.0	4	3.3	1/5	++++
4	Panc 03	8 (IV)	480	0/5	−7.4	15	2.2	0/5	+++
10a	Panc 03	5 (IV)	330	0/5	−9.4	18	0.8	0/5	+
10b	Panc 03	8 (PO)[b]	565	0/5	+4.2	14	1.5	0/5	++
19b	Panc 03	8 (IV/PO)[c]	477	0/5	−7.5	30	0.74	0/5	+
28b	Panc 03	11 (IV)	615	0/5	−0.0	>100	0.0	0/5	–
30b	Panc 03	9 (IV)	555	0/5	−0.0	94	0.4	0/5	–

[a] For a detailed description of testing methodologies, see Refs. 7–9.
[b] The indicated dose (60–84 mg/kg/day) was administered as an insoluble suspension by the oral (PO) route. Lower doses were soluble, but 50 mg/kg IV produced pronounced gait disturbances, hyperactivity, and acute agitation. These symptoms resolved within 10 min of IV injection.
[c] The analog was injected IV on days 3–9. The route was changed on day 10 (8th day of treatment) to PO due to tail vein damage.

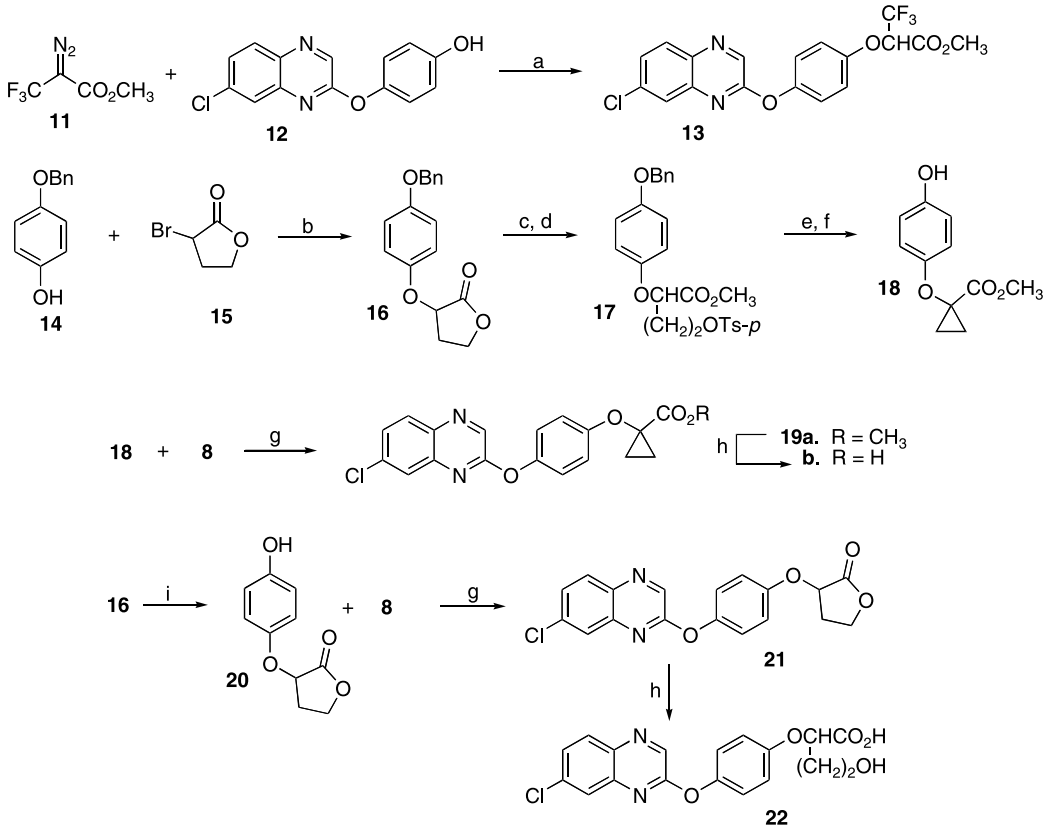


Scheme 1. Reagents: (a) $CH_3CHBrCO_2CH_3/K_2CO_3$/acetone; (b) H_2/Pd–C/CH_3OH; (c) (i) $NaNO_2$/aqueous H_2SO_4; (ii) aqueous $Cu(NO_3)_2/Cu_2O$; (d) K_2CO_3/CH_3CN; (e) (i) aqueous NaOH/THF; (ii) aqueous HCl.

corresponding 4-nitrophenols (**5a** and **5b**), as described by Rogers.[10] Conversion of **6a** and **6b** to the phenol derivatives, **7a** and **7b**, was achieved according to the methodology reported by Cohen et al.[11] Reaction of **7a** and **7b** with 2,7-dichloroquinoxoline (**8**),[7] followed by saponification of the corresponding esters, **9a** and **9b**, provided **10a** and **10b**, respectively.

Efforts then shifted to analogs of the propionic acid moiety in **1a** with the preparation, initially, of methyl 2-{4-[(7-chloro-2-quinoxalinyl)oxy]phenoxy}-3,3,3-trifluoropropionate (Scheme 2, **13**). The carbenoid-intermediate generated from a rhodium-catalyzed-decomposition of methyl 3,3,3-trifluoro-2-diazopropionate (**11**)[12] in toluene, readily reacted[13] with 4-(7-chloro-2-quinoxalinyloxy)phenol (**12**) to afford **13**, though in rather low (21%) yield. However, repeated, attempts to effect the selective saponification of the latter led, instead, to wholesale degradation of the molecule.

The synthesis of 1-{4-[(7-chloro-2-quinoxalinyl)-oxy]-phenoxy}cyclopropanecarboxylic acid (**19b**), an analog of **4**, required the preparation of intermediate, 3-(4-benzyloxyphenoxy)-butyrolactone (**16**). The latter was obtained via the alkylation of 4-benzyloxyphenol (**14**) with α-bromo-γ-butyrolactone (**15**), which was readily



Scheme 2. Reagents: (a) $Rh_2(OAc)_4/PhCH_3$; (b) KF–Celite/CH_3CN; (c) I_2/CH_3OH; (d) *p*-toluenesulfonyl chloride, Et_3N/CH_2Cl_2; (e) NaH/DME; (f) H_2/Pd–C/CH_3OH; (g) K_2CO_3/CH_3CN; (h) (i) aqueous NaOH/THF; (ii) aqueous HCl; (i) H_2/Pd–C/AcOEt.

effected in the presence of KF-coated Celite.[14] Transesterification of **16** with methanol in the presence of iodine, followed by *p*-tosylation yielded methyl 2-(4-benzyloxyphenoxy)-4-*p*-toluenesulfonylbutyrate (**17**). Cyclization of **17** on treatment with NaH in DME, as described by Chan,[15] and catalytic (H_2/Pd–C) debenzylation of the latter yielded methyl 1-(4-hydroxyphenoxy)cyclopropanecarboxylate (**18**). Etherification of **18** with **8**, followed by saponification of **19a**, afforded **19b**.

The route to 2-{4-[(7-chloro-2-quinoxalinyl)oxy]phenoxy}-4-hydroxybutyric acid (**22**), a hydroxyethyl analog of **1a**, proceeded with the debenzylation (H_2/Pd–C) of **16** to give 3-(4-hydroxyphenoxy)butyrolactone (**20**). Reaction of the latter with **8** provided 3-{4-[(7-chloro-2-quinoxalinyl)oxy]phenoxy}butyrolactone (**21**), which was then converted, on alkaline hydrolysis, to **22**.

Preparation of 3-{4-[(7-chloro-2-quinoxalinyl)oxy]-phenyl}-2-methyl-2-propenoic acid (Scheme 3, **26b**) was initiated with 3-(4-hydroxyphenyl)-2-methyl-2-propenoic acid (**25a**), which was obtained by a Knovenaegel condensation reaction, according to that utilized by Papa[16,17] et al. for the synthesis of the corresponding 3,5-diiodo derivative. Thus, condensation of 4-hydroxybenzaldehyde (**23**) and propionic anhydride (**24**), in the presence of sodium propionate, yielded **25a**, which was, then, converted to the corresponding methyl ester (**25b**). Etherification of the latter with **8**, followed by saponification of intermediate **26a**, afforded **26b**.

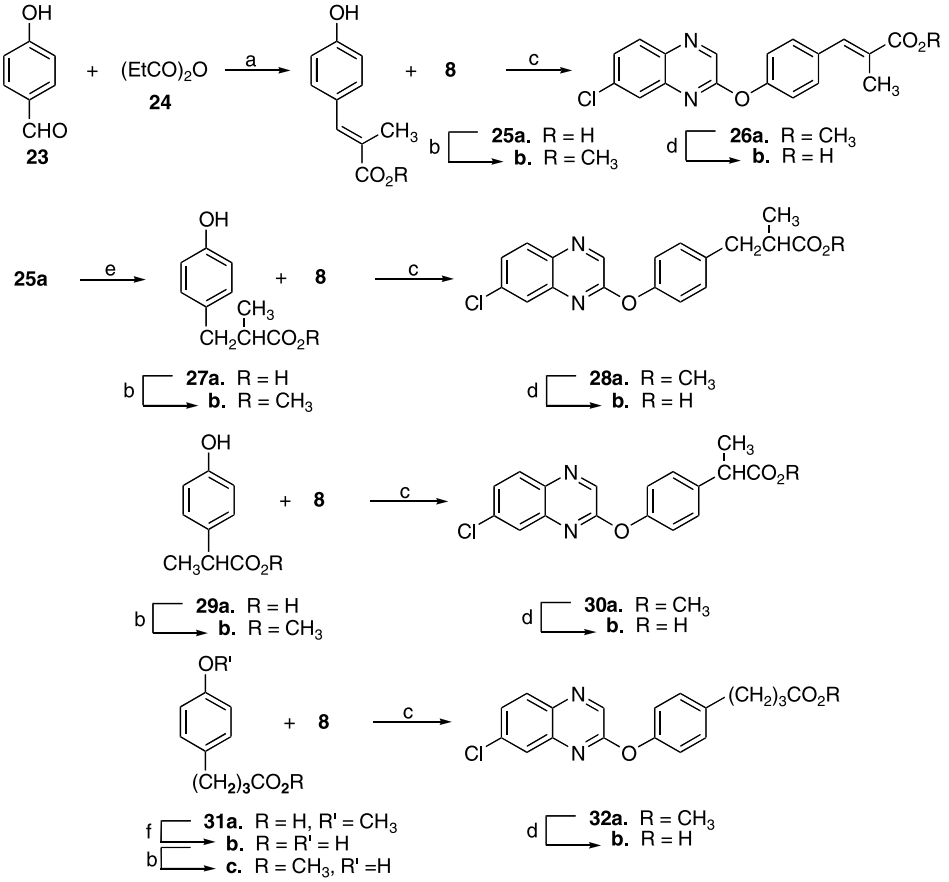
Reduction of **25a** with aluminum–nickel alloy in aqueous alkali[16] gave 3-(4-hydroxyphenyl)-2-methylpropionic acid (**27a**), which on successive esterification with MeOH, O-alkylation with **8**, followed by saponification, yielded the methylene isostere of **1a**, that is, 3-{4-[(7-chloro-2-quinoxalinyl)oxy]phenyl}-2-methylpropionic acid (**28b**).

2-{4-[(7-Chloro-2-quinoxalinyl)oxy]phenyl}propionic acid (**30b**) was obtained by conversion of commercially available 2-(4-hydroxyphenyl)propionic acid (**29a**) to the corresponding methyl ester (**29b**), followed by successive O-alkylation of the latter with **8**, and hydrolysis of the intermediate (**30a**) to **30b**.

Lastly, 4-{4-[(7-chloro-2-quinoxalinyl)oxy]phenyl}-butyric acid (**32b**) was prepared by etherification of methyl 4-(4-hydroxyphenyl)butyrate (**31c**),[18] with **8**, followed by saponification of **32a**.

2.2. Cytotoxic activity

All analogs of **1** were initially evaluated in our in vitro disk diffusion soft agar colony formation assay, as previously described,[7–9] to determine cytotoxicity against



Scheme 3. Reagents: (a) $EtCO_2Na$; (b) CH_3OH/H_2SO_4; (c) K_2CO_3/CH_3CN; (d) (i) aqueous NaOH/THF; (ii) aqueous HCl; (e) (i) Al–Ni/aqueous NaOH; (ii) aqueous HCl; (f) HBr.

mouse leukemia (L1210) cells, Pancreatic Ductal Carcinoma (Panc) 03, Colon 38, and/or multi-drug resistant, Mammary-16/C/Adriamycin-resistant solid tumor cells, human colon cell lines H116 and H15 (multi-drug resistant), in addition to normal-like fibroblast cells. In vivo studies were carried out, as previously described,[7–9] with only those analogs that manifested significant in vitro cytotoxicity, using Panc 03 tumor, transplanted into BDF_1-mice. Tumor-selection was based on the observation that Panc 03 affords responses comparable to that of Colon 38 in the evaluation of **1a** (see Table 2).

The absence of in vitro activity in the glycolic acid analog (**3**) of **1** (see above) is confirmed by the data shown in Table 1. By contrast, substitution of a methyl group at the 2-position of the propionic acid moiety of **1a**, that is, the (isobutyric acid) analog **4**, showed good in vitro activity, albeit with higher dose requirements. Moreover, **4** showed significant in vivo activity (2.2 log kill) without toxicity at an IV total dose of 480 mg/kg (Table 2). However, at individual (IV) doses of 60 mg/kg racemic **4** showed a reversible slowing of nerve conduction velocity, manifested by uncoordinated hind leg movements. This phenomenon was noted previously[8] in the evaluation of much higher doses of racemic and/or (*S*)-analogs of **1a** and **2a**.

The cyclopropyl derivative (**19b**), which was minimally active against Panc 03 (log kill 0.74), also produced the slowing of nerve conduction velocity at lower individual doses than those noted in the treatment of **1a** and **2a**. In addition, **19b**, as apparent in Table 2, was inferior to **4** in terms of tumor efficacy. Both **28b** and **30b** yielded sufficiently interesting in vitro data to warrant in vivo evaluation. However, neither analog was active against Panc 03, even with the injection of elevated, total doses of each (Table 2).

3. Conclusion

The present biological findings clearly indicate that an intact 2-oxypropionic acid moiety is a sine qua non to maximize the antitumor activity of **1a**, and presumably **2a** as well.

4. Experimental

All commercially available solvents and reagents were used without further purification. Melting points were determined on a Thomas–Hoover melting point apparatus and are uncorrected. Infrared spectra were measured on a Perkin–Elmer 1330 spectrometer in KBr pellets. Nuclear magnetic resonance (^1H and ^{13}C NMR) spectra were recorded at room temperature, and referenced to a residual solvent signal, on a Varian Mercury 400 instrument in the Department of Chemistry, Wayne State University, Detroit, MI. Chemical shifts are reported in parts per million downfield from tetramethylsilane (TMS). The splitting pattern abbreviations are as follows: s, singlet; d, doublet; t, triplet; q, quartet; qu, quintet; br, broad; m, unresolved multiplet. Mass spectra were recorded on instruments in the Department of Chemistry, Wayne State University. Flash column chromatography was carried out with silica gel 200–400 mesh, 60 Å (Aldrich), and the crude product was introduced on to the column as a $CHCl_3$ solution. Thin-layer chromatography was performed on Whatman PE SIL G/UV (250 μm) plates. Compounds were visualized by use of 254 or 366 nm light and I_2 vapor. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ and are within ±0.3% of the calculated values.

4.1. General method of the preparation of esters

A mixture of **8**, the phenol, anhydrous K_2CO_3, and CH_3CN was refluxed until the reaction was complete. The hot mixture was filtered, the residue was washed with warm acetone, and the filtrate was evaporated to dryness. The crude residue was purified by flash column chromatography, followed by crystallization.

4.2. General procedure for the hydrolysis of esters

To a solution of the ester dissolved in tetrahydrofuran (THF), was added, in portions, 0.1 M NaOH and the mixture was stirred overnight at room temperature. The reaction mixture was concentrated, filtered to remove insoluble material, and then cooled and adjusted to pH 3–4 with 0.25 M HCl. The solid that deposited on further cooling was collected, washed with ice-water, dried, and crystallized.

4.3. Methyl 2-(2-fluoro-4-nitrophenoxy)propionate[10]

Mp 54–57 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, $J = 2.4$ Hz, 1H), 7.98 (d, $J = 2.4$ Hz, 1H), 6.92 (t, $J = 8.0$ Hz, 1H), 4.92 (q, $J = 6.8$ Hz, 1H), 3.78 (s, 3H), 1.71 (d, $J = 6.4$ Hz, 3H).

4.4. Methyl 2-(4-amino-2-fluorophenoxy)propionate[10] (6a)

^1H NMR (400 MHz, $CDCl_3$) δ 6.81 (t, $J = 8.8$ Hz, 1H), 6.42 (dd, $J = 12.0$, 2.4 Hz, 1H), 6.34–6.29 (m, 1H), 4.59 (q, $J = 6.8$ Hz, 1H), 3.74 (s, 3H), 3.58 (br s, 2H), 1.57 (d, $J = 7.6$ Hz, 3H).

4.5. Methyl 2-(2-fluoro-4-hydroxyphenoxy)propionate[10,11] (7a)

To a solution of **6a** (1.06 g, 4.97 mmol) in 1 M H_2SO_4 (17.5 mL) at 0 °C, $NaNO_2$ (0.36 g, 5.2 mmol) in dissolved in water (5 mL) was added dropwise and the solution stirred for an additional 0.25 h. A solution of $Cu(NO_3)_2{\cdot}2.5H_2O$ (23.26 g, 100 mmol) in water (175 mL) was added followed by Cu_2O (0.81 g, 5.5 mmol) and the mixture stirred vigorously for 0.5 h. AcOEt (50 mL) was added and the insoluble material filtered off. The layers were separated and the aqueous layer extracted with AcOEt (50 mL). The combined extracts were washed with saturated NaCl (10 mL), dried with anhydrous $MgSO_4$ and concentrated to give a brown liquid. This was purified by chromatography (4:1 hexanes–AcOEt) to give a dark yellow liquid

(0.85 g 80% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81 (t, J = 9.2 Hz, 1H), 6.59 (dd, J = 12.4, 2.4 Hz, 1H), 6.49–6.43 (m, 1H), 6.14 (br s, 1H), 4.65 (q, J = 6.8 Hz, 1H), 3.76 (s, 3H), 1.59 (d, J = 6.4 Hz, 3H).

4.6. Methyl 2-(3-fluoro-4-nitrophenoxy)propionate

Using the procedure for the preparation of esters (Section 4.1): **5b** (5.15 g, 32.5 mmol), methyl 2-bromopropionate (4.02 mL, 6.02 g, 35.7 mmol), anhydrous K_2CO_3 (5.61 g, 40.6 mmol), and acetone (75 mL) gave a light yellow liquid (7.67 g, 97% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (t, J = 8.8 Hz, 1H), 6.74–6.67 (m, 2H), 4.83 (q, J = 6.8 Hz, 1H), 3.79 (s, 3H), 1.67 (d, J = 7.2 Hz, 3H).

4.7. Methyl 2-(4-amino-3-fluorophenoxy)propionate (6b)

Using the same procedure[9] as for **6a**: **5b** (1.22 g, 5.02 mmol), 5% Pd–C (0.06 g), and CH_3OH (25 mL) gave a brown liquid (1.07 g, 100% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.73 (dd, J = 10.0, 8.0 Hz, 1H), 6.63 (dd, J = 12.0, 2.4 Hz, 1H), 6.55–6.50 (m, 1H), 4.63 (q, J = 6.8 Hz, 1H), 3.86 (br s, 2H), 3.75 (s, 3H), 1.58 (d, J = 7.6 Hz, 3H).

4.8. Methyl 2-(3-fluoro-4-hydroxyphenoxy)propionate (7b)

Using the same procedure[11] as for **7a**: **6b** (1.07 g, 5.02 mmol) in 1 M H_2SO_4 (17.5 mL), was converted into the diazonium salt with $NaNO_2$ (0.36 g, 5.2 mmol) in water (5 mL). Followed by its decomposition with Cu_2O (0.81 g, 5.5 mmol) and $Cu(NO_3)_2{\cdot}2.5H_2O$ (23.26 g, 100 mmol) in water (175 mL). This gave an orange-yellow liquid (0.45 g 42% yield) after purification by chromatography (4:1 hexanes–AcOEt): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.87 (dd, J = 10.2, 8.7 Hz, 1H), 6.67 (dd, J = 11.7, 2.7 Hz, 1H), 6.58–6.51 (m, 1H), 5.07 (br s, 1H), 4.65 (q, J = 6.9 Hz, 1H), 3.76 (s, 3H), 1.58 (d, J = 6.9 Hz, 3H).

4.9. Methyl 2-{4-[(7-chloro-2-quinoxalinyl)oxy]-2-fluorophenoxy}propionate (9a)

2,7-Dichloroquinoxaline (**8**) (0.72 g, 3.6 mmol), **7a** (0.85 g, 4.0 mmol), anhydrous K_2CO_3 (0.69 g, 5.0 mmol), and CH_3CN (20 mL) were refluxed for 4 h. This was purified by chromatography (4:1 hexanes–AcOEt) to give a white solid. It was recrystallized from EtOH to give **9a** (1.21 g, 89% yield) as white crystals: mp 109–111 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (s, 1H), 7.96 (d, J = 9.2 Hz, 1H), 7.75 (d, J = 2.4 Hz, 1H), 7.54 (dd, J = 8.8, 2.4 Hz, 1H), 7.10 (dd, J = 11.2, 2.4 Hz, 1H), 6.97 (dd, J = 8.8, 8.0 Hz, 1H), 6.96 (dd, J = 9.2, 2.8 Hz, 1H), 4.79 (q, J = 6.4 Hz, 1H), 3.79 (s, 3H), 1.68 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 157.3, 153.2 (d, J = 248 Hz), 146.9 (d, J = 9 Hz), 143.5 (d, J = 10 Hz), 140.6, 139.4, 138.4, 136.6, 130.3, 128.7, 127.0, 118.0 (d, J = 2 Hz), 117.3 (d, J = 4 Hz), 111.2 (d, J = 22 Hz), 75.2, 52.7, 18.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ 52.30 (dd, J = 11.3, 8.3 Hz); IR (KBr) 1735 (C=O) cm^{-1}; MS (EI) m/z (%) 376 (M^+, 38), 317 (24), 290 (17), 262 (39), 219 (9), 205 (14), 163 (33), 136 (17), 129 (12), 100 (12), 97 (13), 95 (16), 91 (22), 81 (45), 73 (26), 69 (100), 67 (22), 60 (22), 57 (31), 55 (46), 45 (15); Anal. ($C_{18}H_{14}N_2ClFO_4$) C, H, N.

4.10. 2-{4-[(7-Chloro-2-quinoxalinyl)oxy]-2-fluorophenoxy}propionic acid (10a)

Ester **9a** (1.17 g, 3.11 mmol), THF (50 mL), and 0.1 M NaOH (62 mL, 6.2 mmol) gave **10a** (0.83 g, 73% yield), after recrystallization from EtOH–heptane, as white crystals: mp 152–153 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.20 (br s, 1H), 8.84 (s, 1H), 8.05 (d, J = 9.2 Hz, 1H), 7.83 (d, J = 2.4 Hz, 1H), 7.69 (dd, J = 8.0, 1.6 Hz, 1H), 7.37 (dd, J = 11.6, 2.8 Hz, 1H), 7.05–6.85 (m, 2H), 4.94 (q, J = 6.8 Hz, 1H), 1.54 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.3, 158.0, 152.0 (d, J = 244 Hz), 146.1 (d, J = 10 Hz), 143.9 (d, J = 10 Hz), 140.8, 140.5, 138.4, 135.8, 131.0, 128.9, 126.8, 118.1 (d, J = 3 Hz), 116.2, 111.5 (d, J = 20 Hz), 73.3, 18.9; ^{19}F NMR (376 MHz, DMSO-d_6) δ 55.02 (m); IR (KBr) 3430 (OH), 1710 (C=O) cm^{-1}. MS (EI) m/z (%) 362 (M^+, 100), 317 (17), 303 (5), 290 (72), 262 (78), 237 (9), 233 (6), 163 (82), 136 (45), 128 (22), 100 (28), 83 (13), 73 (11), 69 (12), 57 (16), 55 (18), 43 (22), 41 (11); HRMS (EI) m/z 362.0465 (M^+, calcd for $C_{17}H_{12}N_2ClFO_4$ 362.0470). Anal. ($C_{17}H_{12}N_2ClFO_4$) C, H, N.

4.11. Methyl 2-{4-[(7-chloro-2-quinoxalinyl)oxy]-3-fluorophenoxy}propionate (9b)

Quinoxaline **8** (0.38 g, 1.9 mmol), **7b** (0.45 g, 2.1 mmol), anhydrous K_2CO_3 (0.36 g, 2.6 mmol), and CH_3CN (10 mL) were refluxed for 4 h. This was purified by chromatography (5:1 hexanes–AcOEt) to give a white solid. It was recrystallized from AcOEt–heptane to give **9b** (0.39 g, 54% yield) as white crystals: mp 120–122 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (s, 1H), 7.98 (d, J = 8.8 Hz, 1H), 7.73 (d, J = 2.4 Hz, 1H), 7.54 (dd, J = 8.8, 2.4 Hz, 1H), 7.19 (t, J = 9.2 Hz, 1H), 6.78 (dd, J = 11.2, 3.2 Hz, 1H), 6.73–6.69 (m, 1H), 4.76 (q, J = 6.4 Hz, 1H), 3.81 (s, 3H), 1.66 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 157.0, 156.2 (d, J = 9 Hz), 154.9 (d, J = 249 Hz), 140.7, 138.8, 138.4, 136.6, 134.0 (d, J = 13 Hz), 130.3, 128.7, 127.0, 124.3 (d, J = 2 Hz), 110.8 (d, J = 3 Hz), 104.8 (d, J = 22 Hz), 73.4, 52.8, 18.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ 59.89 (m); IR (KBr) 1740 (C=O) cm^{-1}. MS (EI) m/z (%) 376 (M^+, 100), 317 (82), 289 (18), 273 (14), 262 (53), 163 (55), 136 (28), 128 (14), 124 (5), 100 (18), 87 (6), 82 (7), 75 (6), 73 (5), 59 (19), 55 (8). Anal. ($C_{18}H_{14}N_2ClFO_4$) C, H, N.

4.12. 2-{4-[(7-Chloro-2-quinoxalinyl)oxy]-3-fluorophenoxy}propionic acid (10b)

Ester **9b** (0.42 g, 1.1 mmol), THF (10 mL), and 0.1 M NaOH (22 mL, 2.2 mmol) give **10b** (0.30 g, 74% yield), after recrystallization from EtOH–water, as white crystals: mp 215–217 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.17 (br s, 1H), 8.94 (s, 1H), 8.07 (d, J = 8.8 Hz,

1H), 7.81 (d, $J = 2.8$ Hz, 1H), 7.71 (dd, $J = 8.8$, 2.4 Hz, 1H), 7.39 (t, $J = 8.8$ Hz, 1H), 7.02 (dd, $J = 12.0$, 3.2 Hz, 1H), 6.80 (br dd, $J = 9.2$, 2.0 Hz, 1H), 4.93 (q, $J = 6.8$ Hz, 1H), 1.52 (d, $J = 6.4$ Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.4, 157.3, 156.8 (d, $J = 10$ Hz), 154.7 (d, $J = 246$ Hz), 140.4, 140.1, 138.5, 136.0, 133.3 (d, $J = 13$ Hz), 131.0, 129.0, 126.7, 125.0, 111.6, 104.6 (d, $J = 22$ Hz), 72.7, 18.8; ^{19}F NMR (376 MHz, DMSO-d_6) δ 57.02 (m); IR (KBr) 3410 (OH), 1705 (C=O) cm^{-1}; MS (EI) *m/z* (%) 362 (M^+, 29), 323 (54), 317 (7), 303 (7), 290 (11), 278 (8), 262 (25), 250 (49), 236 (8), 163 (22), 142 (100), 140 (7), 136 (12), 128 (10), 115 (17), 105 (14), 83 (10), 77 (11), 69 (14), 57 (16), 55 (16); HRMS (EI) *m/z* 362.0469 (M^+, calcd for $C_{17}H_{12}N_2ClFO_4$ 362.0470); Anal. ($C_{17}H_{12}N_2ClFO_4$) C, H, N.

4.13. Methyl 3,3,3-trifluoro-2-diazopropionate (11)

By using the reported procedure[12] but using methyl 3,3,3-trifluoro-2-oxypropionate instead of the ethyl variant, this was prepared as a yellow liquid (55% yield): bp 45 °C (50 mmHg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.5, 122.8 (q, $J = 268$ Hz), 52.9.

4.14. Methyl 2-{4-[(7-chloro-2-quinoxalinyl)oxy]phenoxy}-3,3,3-trifluoropropionate (13)

To a mixture of **12** (0.31 g, 1.1 mmol), $Rh_2(OAc)_4$ (5.0 mg, 0.011 mmol), and toluene (50 mL), **11** (0.21 g, 1.2 mmol) dissolved in toluene (5 mL) was added dropwise and the mixture was stirred at room temperature for 0.5 h and at 50 °C for 1 h. Pure material was obtained, after chromatography (4:1 hexanes–AcOEt) to give a light yellow solid, which was recrystallized from EtOH to give **13** (0.10 g, 21% yield) as off white crystals: mp 123–125 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (s, 1H), 7.97 (d, $J = 9.2$ Hz, 1H), 7.74 (d, $J = 2.4$ Hz, 1H), 7.54 (dd, $J = 8.8$, 2.4 Hz, 1H), 7.25–7.20 (m, 2H), 7.08–7.01 (m, 2H), 5.01 (q, $J = 6.4$ Hz, 1H), 3.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 157.6, 154.4, 148.2, 140.6, 139.5, 138.3, 136.6, 130.3, 128.6, 127.0, 123.1, 121.8 (q, $J = 281$ Hz), 117.2, 76.5 (q, $J = 33$ Hz), 53.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ −74.24 (d, $J = 6.0$ Hz); IR (KBr) 1755 (C=O) cm^{-1}; MS (EI) *m/z* (%) 412 (M^+, 100), 384 (9), 272 (7), 255 (12), 243 (69), 208 (6), 192 (5), 163 (28), 136 (15), 109 (6), 100 (7), 81 (5), 69 (10), 45 (34); Anal. ($C_{18}H_{12}N_2ClF_3O_4$) C, H, N.

4.15. 3-(4-Benzyloxyphenoxy)butyrolactone (16)

Phenol **14** (2.02 g, 10.0 mmol), **15** (2.40 mL, 4.28 g, 25.0 mmol), 50% KF–Celite (6.0 g), and CH_3CN (25 mL) were refluxed overnight. After isolating using the standard method used for the esters, it was purified by filtering through silica gel with AcOEt. The filtrate was concentrated to a small volume and recrystallized from AcOEt–hexanes to give **16** (2.70 g, 95% yield) as white crystals: mp 113–115 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.30 (m, 5H), 7.00–6.95 (m, 2H), 6.95–6.88 (m, 2H), 5.02 (s, 2H), 4.84 (t, $J = 8.0$ Hz, 1H), 4.54–4.47 (m, 1H), 4.36–4.29 (m, 1H), 2.72–2.62 (m, 1H), 2.50–2.39 (m, 2H).

4.16. Methyl 2-(4-benzyloxyphenoxy)-4-hydroxybutyrate

Lactone **16** (2.60 g, 9.14 mmol), I_2 (0.05 g), and CH_3OH (50 mL) were refluxed overnight. After the mixture was concentrated, water (25 mL) was added followed by Na_2SO_3 to remove the I_2. The mixture was extracted with AcOEt (2×25 mL) and the extracts washed with saturated NaCl (10 mL), dried with anhydrous $MgSO_4$, and concentrated to a small volume and recrystallized from AcOEt–hexanes (2×) to give unreacted lactone **16** (0.55 g). The combined filtrates were purified by chromatography (2:1 hexanes–AcOEt) to give an addition (0.27 g) of unreacted lactone **16** and the product (1.92 g, 66% yield) as a colorless liquid, which solidified: mp 39–41 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.30 (m, 5H), 6.92–6.82 (m, 4H), 5.01 (s, 2H), 4.79 (t, $J = 6.0$ Hz, 1H), 3.88 (t, $J = 6.0$ Hz, 2H), 3.76 (s, 3H), 2.18 (q, $J = 6.0$ Hz, 2H).

4.17. Methyl 2-(4-benzyloxyphenoxy)-4-*p*-toluenesulfonylbutyrate (17)

To a solution of methyl 2-(4-benzyloxyphenoxy)-4-hydroxybutyrate (1.47 g, 4.65 mmol) and Et_3N (0.82 mL, 0.60 g, 5.8 mmol) in CH_2Cl_2 (10 mL) at 0 °C, *p*-toluenesulfonyl chloride (0.90 g, 4.7 mmol) was added and the mixture stirred overnight at room temperature. Water (10 mL) was added and the mixture extracted with AcOEt (2×50 mL) and the extracts washed with saturated NaCl (10 mL), dried with anhydrous $MgSO_4$, and concentrated to give **17** as a brown-yellow liquid (2.00 g, 91% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74–7.70 (m, 2H), 7.44–7.30 (m, 5H), 7.23 (d, $J = 8.0$ Hz, 2H), 6.87–6.82 (m, 2H), 6.72–6.68 (m, 2H), 5.01 (s, 2H), 4.61 (dd, $J = 8.8$, 4.4 Hz, 1H), 4.24 (dd, $J = 7.6$, 4.0 Hz, 2H), 3.72 (s, 3H), 2.39 (s, 3H), 2.35–2.26 (m, 1H), 2.24–2.15 (m, 1H).

4.18. Methyl 1-(4-benzyloxyphenoxy)cyclopropanecarboxylate

NaH (60%, 0.42 g, 10.5 mmol) was added to **17** (2.00 g, 4.2 mmol) in DME (25 mL) and the mixture stirred at room temperature for 2 days. It was filtered and the solid washed with AcOEt. The solid was dissolved in water and acidified to pH 3 to give 2-(4-benzyloxyphenoxy)-4-hydroxybutyric acid, which can be recycled to **17** via the ester. To the filtrate, water (10 mL) was added and the layers separated. The aqueous layer was extracted with AcOEt (25 mL) and the combined organic liquids washed with saturated NaCl (10 mL), dried with anhydrous $MgSO_4$, and concentrated to give a light yellow liquid. This was purified by chromatography (4:1 hexanes–AcOEt) to give the product (0.56 g, 45% yield) as a colorless liquid, which solidified, mp 67–69 °C and unreacted **17**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.30 (m, 5H), 6.91–6.82 (m, 4H), 5.01 (s, 2H), 3.73 (s, 3H), 1.61–1.55 (m, 2H), 1.32–1.28 (m, 2H).

4.19. Methyl 1-(4-hydroxyphenoxy)cyclopropanecarboxylate (18)

A mixture of methyl 1-(4-benzyloxyphenoxy)cyclopropanecarboxylate (0.68 g, 2.3 mmol), 10% Pd–C (0.04 g), concentrated HCl (one drop), and CH_3OH (50 mL) were shaken under 50 psi of H_2 in a Parr shaker for 6 h. The catalyst was removed, and the filtrate concentrated, and purified by chromatography (2:1 hexanes–AcOEt) to give **18** (0.45 g, 96% yield) as a colorless liquid that solidified: mp 95–100 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.82–6.70 (m, 4H), 4.85 (s, 1H), 3.73 (s, 3H), 1.61–1.57 (m, 2H), 1.32–1.28 (m, 2H).

4.20. Methyl 1-{4-[(7-chloro-2-quinoxalinyl)oxy]phenoxy}cyclopropanecarboxylate (19a)

Quinoxaline **8** (0.42 g, 2.2 mmol), **18** (0.45 g, 2.2 mmol), anhydrous K_2CO_3 (0.38 g, 2.8 mmol), and CH_3CN (10 mL) were refluxed for 6 h. This was purified by chromatography (4:1 hexanes–AcOEt) to give a colorless liquid that solidified. It was recrystallized from EtOH to give **19a** (0.54 g, 68% yield) as white crystals: mp 105–106 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (s, 1H), 7.93 (d, J = 8.0 Hz, 1H), 7.72 (d, J = 2.4 Hz, 1H), 7.50 (dd, J = 8.8, 2.4 Hz, 1H), 7.19–7.13 (m, 2H), 7.00–6.94 (m, 2H), 3.75 (s, 3H), 1.66–1.61 (m, 2H), 1.38–1.33 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 157.8, 155.0, 146.7, 140.7, 139.6, 138.2, 136.4, 130.2, 128.4, 127.0, 122.5, 116.3, 58.6, 52.9, 17.8; IR (KBr) 1720 cm^{-1} (C=O); MS (EI) *m*/*z* (%) 370 (M$^+$, 100), 311 (84), 283 (43), 269 (38), 255 (17), 243 (55), 228 (11), 208 (7), 192 (8), 163 (73), 136 (39), 131 (12), 124 (5), 110 (5), 100 (21), 75 (9), 63 (9), 59 (21), 55 (10), 50 (8); Anal. ($C_{19}H_{15}N_2ClO_4$) C, H, N.

4.21. 1-{4-[(7-Chloro-2-quinoxalinyl)oxy]phenoxy}cyclopropanecarboxylic acid (19b)

Ester **19a** (0.51 g, 1.4 mmol), THF (25 mL), and 0.1 M NaOH (28 mL, 2.8 mmol) gave **19b** (0.45 g, 92% yield), after recrystallization from EtOH–water, as off white crystals: mp 225–227 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.02 (br s, 1H), 8.83 (s, 1H), 8.04 (d, J = 9.2 Hz, 1H), 7.80 (d, J = 2.4 Hz, 1H), 7.67 (dd, J = 8.8, 2.4 Hz, 1H), 7.27–7.22 (m, 2H), 7.01–6.95 (m, 2H), 1.55–1.50 (m, 2H), 1.29–1.25 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.5, 158.3, 155.4, 146.6, 140.9, 140.6, 138.2, 135.7, 130.9, 128.6, 126.7, 123.1, 116.6, 58.2, 16.9; IR (KBr) 3410 (OH), 1695 (C=O) cm^{-1}; MS (EI) *m*/*z* (%) 356 (M$^+$, 100), 311 (48), 283 (18), 269 (15), 256 (48), 243 (53), 241 (16), 228 (9), 215 (5), 208 (6), 192 (6), 163 (70), 136 (41), 131 (7), 124 (5), 109 (9), 105 (10), 100 (22), 81 (5), 77 (7), 75 (9), 65 (7), 63 (9), 55 (7), 50 (8), 45 (6); HRMS (EI) *m*/*z* 356.0570 ($C_{18}H_{13}N_2ClO_4$: 356.0570); Anal. ($C_{18}H_{13}N_2ClO_4$) C, H, N.

4.22. 3-(4-Hydroxyphenoxy)butyrolactone (20)

A mixture of **16** (0.56 g, 2.0 mmol), 10% Pd–C (0.02 g), concentrated HCl (one drop), and AcOEt (25 mL) were shaken under 50 psi of H_2 in a Parr shaker for 6 h. The catalyst was removed, and the filtrate concentrated and purified by chromatography (1:1 hexanes–AcOEt) to give **20** (0.39 g, 100% yield) as a colorless liquid that solidified: mp 96–97 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96–6.91 (m, 2H), 6.79–6.74 (m, 2H), 4.82 (t, J = 7.6 Hz, 1H), 5.01 (s, 2H), 4.54–4.48 (m, 1H), 4.37–4.30 (m, 1H), 2.72–2.63 (m, 1H), 2.51–2.40 (m, 1H).

4.23. 3-{4-[(7-Chloro-2-quinoxalinyl)oxy]phenoxy}butyrolactone (21)

Quinoxaline **8** (0.42 g, 2.2 mmol), **20** (0.39 g, 2.0 mmol), anhydrous K_2CO_3 (0.35 g, 2.5 mmol), and CH_3CN (10 mL) were refluxed for 4 h. This was purified by chromatography (1:1 hexanes–AcOEt) to give an off white solid. It was recrystallized from AcOEt–heptane to give **21** (0.59 g, 83% yield) as off white crystals. Mp 179–181 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (s, 1H), 7.96 (d, J = 9.2 Hz, 1H), 7.74 (d, J = 2.8 Hz, 1H), 7.53 (dd, J = 8.8, 2.4 Hz, 1H), 7.23–7.17 (m, 2H), 7.15–7.09 (m, 2H), 4.97 (t, J = 7.6 Hz, 1H), 4.58–4.51 (m, 1H), 4.41–4.34 (m, 1H), 2.80–2.70 (m, 1H), 2.57–2.46 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 157.8, 155.1, 147.3, 140.7, 139.5, 138.3, 136.5, 130.3, 128.5, 127.0, 122.8, 117.2, 73.3, 65.6, 30.1; IR (KBr) 1775 (C=O) cm^{-1}; MS (EI) *m*/*z* (%) 356 (M$^+$, 100), 298 (3), 271 (14), 243 (72), 208 (4), 163 (31), 136 (13), 110 (4), 100 (6), 81 (5), 69 (9); Anal. ($C_{18}H_{13}N_2ClO_4$) C, H, N.

4.24. 2-{4-[(7-Chloro-2-quinoxalinyl)oxy]phenoxy}-4-hydroxybutyric acid (22)

Ester **21** (0.54 g, 1.5 mmol), THF (25 mL), and 0.1 M NaOH (30 mL, 3.0 mmol) gave **22** (0.52 g, 91% yield), as an off white solid; mp 167–168 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.04 (br s, 1H), 8.83 (s, 1H), 8.05 (d, J = 9.2 Hz, 1H), 7.81 (d, J = 2.0 Hz, 1H), 7.68 (dd, J = 8.4, 2.0 Hz, 1H), 7.27–7.21 (m, 2H), 6.98–6.92 (m, 2H), 4.79 (dd, J = 8.8, 4.0 Hz, 1H), 4.69 (br s, 1H), 3.59 (br t, J = 6.0 Hz, 2H), 2.08–1.92 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.6, 158.3, 156.1, 146.5, 140.8, 140.6, 138.2, 135.7, 130.9, 128.6, 126.7, 123.2, 116.4, 73.6, 57.2, 36.3; IR (KBr) 3420 (OH), 3170 (OH), 1715 (C=O) cm^{-1}; MS (EI negative ion) *m*/*z* (%) 747 (2M−H, 6), 373 (M−H, 100), 322 (2), 271 (69), 249 (2), 111 (7), 101 (39), 98 (4), 80 (3), 69 (15). Anal. ($C_{18}H_{15}N_2ClO_5$) C, H, N.

4.25. 3-(4-Hydroxyphenyl)-2-methyl-2-propenoic acid (25a)[16]

Mp 207–208 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.25 (br s, 1H), 9.81 (br s, 1H), 7.48 (s, 1H), 7.34–7.29 (m, 2H), 6.82–6.77 (m, 2H), 2.00 (s, 3H).

4.26. Methyl 3-(4-hydroxyphenyl)-2-methyl-2-propenoate (25b)

Acid **25a** (0.89 g, 5.0 mmol), concentrated H_2SO_4 (0.1 mL), and CH_3OH (10 mL) were refluxed overnight. After the mixture was concentrated, water (25 mL) was added followed by $NaHCO_3$ until pH 8. The mixture was extracted with AcOEt (2 × 25 mL) and the extracts

washed with saturated NaCl (10 mL), dried with anhydrous $MgSO_4$, and purified by filtering through silica gel to give **25b** (0.91 g, 95% yield) as a pale yellow solid after concentrating: mp 100–102 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (s, 1H), 7.35–7.30 (m, 2H), 6.89–6.84 (m, 2H), 5.25 (s, 1H), 3.81 (s, 3H), 2.12 (d, J = 1.6 Hz, 1H).

4.27. Methyl 3-{4-[(7-chloro-2-quinoxalinyl)oxy]phenyl}-2-methylacrylate (26a)

Quinoxaline **8** (0.20 g, 1.0 mmol), **25b** (0.20 g, 1.0 mmol), anhydrous K_2CO_3 (0.18 g, 1.3 mmol), and CH_3CN (5 mL) were refluxed together for 4 h. This was purified by chromatography (4:1 hexanes–AcOEt) to give a white solid. It was recrystallized from hexanes to give **26a** (0.30 g, 86% yield) as white crystals. Mp 120–122 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (s, 1H), 7.98 (d, J = 8.8 Hz, 1H), 7.77 (d, J = 2.4 Hz, 1H), 7.71 (s, 1H), 7.55 (dd, J = 8.8, 2.4 Hz, 1H), 7.52–7.47 (m, 2H), 7.33–7.29 (m, 2H), 3.84 (s, 3H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 157.4, 152.5, 140.7, 139.6, 138.4, 138.2, 136.6, 133.5, 131.3, 130.3, 128.7, 128.6, 127.0, 121.6, 52.4, 14.4; IR (KBr) 1720 (C═O) cm^{-1}; MS (EI) *m/z* (%) 354 (M^+, 100), 326 (8), 323 (13), 295 (15), 266 (21), 163 (8), 136 (10), 131 (5), 115 (17), 100 (5); Anal. ($C_{19}H_{15}N_2ClO_3$) C, H, N.

4.28. 3-{4-[(7-Chloro-2-quinoxalinyl)oxy]phenyl}-2-methylacrylic acid (26b)

Ester **26a** (0.26 g, 0.73 mmol), THF (15 mL), and 0.1 M NaOH (15 mL, 1.5 mmol) gave **26b** (0.19 g, 76% yield), after recrystallization from AcOEt–heptane to give off white crystals: mp 206–208 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.45 (br s, 1H), 8.88 (s, 1H), 8.07 (d, J = 8.0 Hz, 1H), 7.79 (d, J = 2.4 Hz, 1H), 7.70 (dd, J = 8.8, 2.4 Hz, 1H), 7.62 (s, 1H), 7.62–7.56 (m, 2H), 7.42–7.37 (m, 2H), 2.06 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.1, 157.8, 152.7, 140.9, 140.5, 138.4, 137.2, 135.8, 133.7, 131.9, 131.0, 129.6, 128.9, 126.7, 122.3, 14.7; IR (KBr) 3430 (OH), 1655 (C═O) cm^{-1}; MS (EI) *m/z* (%) 340 (M^+, 100), 312 (31), 296 (27), 267 (17), 241 (7), 163 (16), 136 (21), 131 (6), 115 (21), 103 (6), 100 (13), 77 (9), 63 (5), 51 (5); HRMS (EI) *m/z* 340.0618 ($C_{18}H_{13}N_2ClO_3$: 340.0615); Anal. ($C_{18}H_{13}N_2ClO_3$) C, H, N.

4.29. 3-(4-Hydroxyphenyl)-2-methylpropionic acid (22a)[16]

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.05 (br s, 1H), 9.17 (br s, 1H), 6.96–6.91 (m, 2H), 6.65–6.60 (m, 2H), 2.74 (dd, J = 12.4, 6.0 Hz, 1H), 2.53–2.40 (m, 2H), 0.97 (d, J = 6.8 Hz, 3H).

4.30. Methyl 3-(4-hydroxyphenyl)-2-methylpropionate (27b)

Acid **27a** (0.68 g, 3.8 mmol), concentrated H_2SO_4 (0.1 mL), and CH_3OH (10 mL) were refluxed overnight. The mixture was isolated as in **25b** to give **27b** (0.72 g, 99% yield) as a brown liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03–6.98 (m, 2H), 6.75–6.60 (m, 2H), 5.12 (s, 1H), 3.64 (s, 3H), 2.93 (dd, J = 13.2, 7.2 Hz, 1H), 2.74–2.65 (m, 2H), 2.61 (dd, J = 13.8, 7.2 Hz, 1H), 1.14 (d, J = 7.2 Hz, 3H).

4.31. Methyl 3-{4-[(7-chloro-2-quinoxalinyl)oxy]phenyl}-2-methylpropionate (28a)

Quinoxaline **8** (0.40 g, 2.0 mmol), **27a** (0.41 g, 2.1 mmol), anhydrous K_2CO_3 (0.36 g, 2.6 mmol), and CH_3CN (10 mL) were refluxed together for 4 h. This was purified by chromatography (4:1 hexanes–AcOEt) to give a colorless liquid. It was recrystallized from hexanes to give **28a** (0.65 g, 92% yield) as off white crystals. Mp 69–70 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (s, 1H), 7.96 (d, J = 9.2 Hz, 1H), 7.75 (d, J = 2.4 Hz, 1H), 7.53 (dd, J = 8.8, 2.4 Hz, 1H), 7.27–7.22 (m, 2H), 7.19–7.15 (m, 2H), 3.67 (s, 3H), 3.07 (dd, J = 12.4, 6.0 Hz, 1H), 2.82–2.69 (m, 2H), 1.21 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.7, 157.7, 151.1, 140.8, 139.6, 138.3, 137.0, 136.5, 130.4, 130.2, 128.5, 127.0, 121.5, 51.9, 41.7, 39.3, 17.1; IR (KBr) 1730 (C═O) cm^{-1}; MS (EI) *m/z* (%) 356 (M^+, 65), 341 (10), 325 (6), 297 (100), 269 (94), 241 (95), 205 (5), 163 (20), 136 (19), 115 (7), 107 (22), 100 (12), 91 (9), 77 (11), 69 (7), 51 (5); Anal. ($C_{19}H_{17}N_2ClO_3$) C, H, N.

4.32. 3-{4-[(7-Chloro-2-quinoxalinyl)oxy]phenyl}-2-methylpropionic acid (28b)

Ester **28a** (0.65 g, 1.8 mmol), THF (35 mL), and 0.1 M NaOH (36 mL, 3.6 mmol) gave **28b** (0.55 g, 89% yield), after recrystallization from EtOH–water to give off white crystals: mp 155–157 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.19 (br s, 1H), 8.83 (s, 1H), 8.05 (d, J = 8.8 Hz, 1H), 7.76 (d, J = 2.4 Hz, 1H), 7.69 (dd, J = 8.8, 2.4 Hz, 1H), 7.31–7.26 (m, 2H), 7.25–7.20 (m, 2H), 2.93 (dd, J = 16.0, 10.8 Hz, 1H), 2.70–2.61 (m, 2H), 1.07 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 177.5, 158.0, 151.2, 140.9, 140.6, 138.3, 137.7, 135.7, 131.0, 130.8, 128.7, 126.7, 121.9, 41.3, 39.0, 17.5; IR (KBr) 3420 (OH), 1720 (C═O) cm^{-1}; MS (EI) *m/z* (%) 342 (M^+, 73), 327 (8), 307 (6), 297 (54), 269 (100), 241 (95), 163 (16), 136 (17), 107 (23), 100 (10), 91 (6), 89 (5), 77 (9); HRMS (EI) *m/z* 342.0771 ($C_{18}H_{15}N_2ClO_3$: 342.0771); Anal. ($C_{18}H_{15}N_2ClO_3$) C, H, N.

4.33. Methyl 2-(4-hydroxyphenyl)propionic acid (29b)

Acid **29a** (0.85 g, 5.0 mmol), concentrated H_2SO_4 (0.1 mL), and CH_3OH (10 mL) were refluxed overnight. The mixture was isolated as in **25b** to give **29b** (0.89 g, 99% yield) as a brown liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18–7.12 (m, 2H), 6.80–6.74 (m, 2H), 5.40 (br s, 1H), 3.67 (q, J = 7.2 Hz, 1H), 3.66 (s, 3H), 1.47 (d, J = 7.2 Hz, 3H).

4.34. Methyl 2-{4-[(7-chloro-2-quinoxalinyl)oxy]phenyl}propionate (30a)

Quinoxaline **8** (0.40 g, 2.0 mmol), **29b** (0.40 g, 2.2 mmol), anhydrous K_2CO_3 (0.38 g, 2.7 mmol), and

CH_3CN (10 mL) were refluxed together for 4 h. This was purified by chromatography (4:1 hexanes–AcOEt) to give a colorless liquid that solidified. It was recrystallized from hexanes to give **30a** (0.65 g, 96% yield) as off white crystals. Mp 107–108 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (s, 1H), 7.97 (d, J = 9.2 Hz, 1H), 7.76 (d, J = 1.6 Hz, 1H), 7.54 (dd, J = 8.8, 2.4 Hz, 1H), 7.41–7.36 (m, 2H), 7.25–7.20 (m, 2H), 3.79 (q, J = 7.2 Hz, 1H), 3.70 (s, 3H), 1.55 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.1, 157.6, 151.7, 140.7, 139.6, 138.3, 138.0, 136.5, 130.3, 129.0, 128.6, 127.0, 121.7, 52.4, 18.9; IR (KBr) 1730 (C=O) cm^{-1}; MS (EI) *m/z* (%) 342 (M^+, 54), 283 (100), 255 (36), 163 (6), 136 (8), 121 (5), 103 (6), 100 (5), 91 (5), 77 (7), 69 (8), 57 (7), 55 (5); Anal. ($C_{18}H_{15}N_2ClO_3$) C, H, N.

4.35. 2-{4-[(7-Chloro-2-quinoxalinyl)oxy]phenyl}propionic acid (30b)

Ester **30a** (0.65 g, 1.9 mmol), THF (25 mL), and 0.1 M NaOH (38 mL, 3.8 mmol) gave **30b** (0.57 g, 92% yield), after recrystallization from EtOH–water to give off white crystals: mp 170–172 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.40 (br s, 1H), 8.85 (s, 1H), 8.06 (d, J = 8.8 Hz, 1H), 7.82 (d, J = 2.4 Hz, 1H), 7.69 (dd, J = 8.8, 2.4 Hz, 1H), 7.41–7.36 (m, 2H), 7.31–7.26 (m, 2H), 3.74 (q, J = 7.2 Hz, 1H), 1.39 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.0, 157.9, 151.7, 140.9, 140.5, 139.1, 138.3, 135.8, 130.9, 129.5, 128.7, 126.7, 122.1, 44.8, 19.2; IR (KBr) 3430 (OH), 1685 (C=O) cm^{-1}; MS (EI) *m/z* (%) 328 (M^+, 95), 283 (100), 255 (75), 163 (12), 142 (7), 138 (5), 136 (16), 121 (9), 103 (9), 100 (10), 91 (9), 83 (6), 77 (13), 71 (5), 69 (8), 57 (10), 55 (8); HRMS (EI) *m/z* 328.0618 ($C_{17}H_{13}N_2ClO_3$: 328.0615); Anal. ($C_{17}H_{13}N_2ClO_3$) C, H, N.

4.36. 4-(4-Hydroxyphenyl)butyric acid (31b)[18]

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.99 (br s, 1H), 9.13 (br s, 1H), 6.96–6.91 (m, 2H), 6.67–6.62 (m, 2H), 2.44 (t, J = 7.2 Hz, 2H), 2.16 (t, J = 7.6 Hz, 2H), 1.71 (qu, J = 7.2 Hz, 2H).

4.37. Methyl 4-(4-hydroxyphenyl)butyrate (31c)

Acid **31b** (0.90 g, 5.0 mmol), concentrated H_2SO_4 (0.1 mL), and CH_3OH (10 mL) were refluxed overnight. The mixture was isolated as in **25b** to give **31c** (0.94 g, 97% yield) as a brown liquid: ^{1}H NMR (400 MHz, $CDCl_3$) 7.06–7.00 (m, 2H), 6.78–6.72 (m, 2H), 4.98 (s, 1H), 3.67 (s, 3H), 2.57 (t, J = 7.2 Hz, 2H), 2.32 (t, J = 7.2 Hz, 2H), 1.91 (qu, J = 7.2 Hz, 2H).

4.38. Methyl 4-{4-[(7-chloro-2-quinoxalinyl)oxy]phenyl}butyrate (32a)

Quinoxaline **8** (0.20 g, 1.0 mmol), **31c** (0.20 g, 1.0 mmol), anhydrous K_2CO_3 (0.18 g, 1.3 mmol), and CH_3CN (5 mL) were refluxed together for 4 h. This was purified by chromatography (4:1 hexanes–AcOEt) to give a white solid. It was recrystallized from hexanes to give **32a** (0.32 g, 89% yield) as white crystals. Mp 96–97 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (s, 1H), 7.96 (d, J = 9.2 Hz, 1H), 7.76 (d, J = 2.4 Hz, 1H), 7.53 (dd, J = 8.8, 2.4 Hz, 1H), 7.28–7.24 (m, 2H), 7.19–7.15 (m, 2H), 3.69 (s, 3H), 2.70 (t, J = 8.0 Hz, 2H), 2.38 (t, J = 7.6 Hz, 2H), 2.01 (quintet, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 157.8, 150.8, 140.8, 139.6, 139.0, 138.3, 136.4, 130.2, 129.9, 128.5, 127.0, 121.5, 51.8, 34.8, 33.6, 26.7; IR (KBr) 1730 (C=O) cm^{-1}; MS (EI) *m/z* (%) 356 (M^+, 28), 325 (12), 283 (100), 269 (7), 254 (23), 241 (20), 163 (10), 136 (10), 107 (10), 100 (6), 91 (6), 77 (6), 74 (5), 69 (8), 57 (7), 55 (6); Anal. ($C_{19}H_{17}N_2ClO_3$) C, H, N.

4.39. 4-{4-[(7-Chloro-2-quinoxalinyl)oxy]phenyl}butyric acid (32b)

Ester **32a** (0.29 g, 0.81 mmol), THF (15 mL), and 0.1 M NaOH (16 mL, 1.6 mmol) gave **32b** (0.25 g, 89% yield), after recrystallization from EtOH–water to give white crystals: mp 132–134 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.08 (br s, 1H), 8.83 (s, 1H), 8.04 (d, J = 9.2 Hz, 1H), 7.76 (d, J = 2.4 Hz, 1H), 7.68 (dd, J = 8.8, 2.4 Hz, 1H), 7.30–7.26 (m, 2H), 7.24–7.20 (m, 2H), 2.62 (t, J = 7.6 Hz, 2H), 2.25 (t, J = 7.6 Hz, 2H), 1.82 (quintet, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 175.0, 158.1, 151.0, 140.9, 140.6, 139.7, 138.3, 135.7, 131.0, 130.3, 128.7, 126.7, 122.0, 34.5, 33.8, 27.0; IR (KBr) 3420 (OH), 1690 (C=O) cm^{-1}; MS (EI) *m/z* (%) 342 (M^+, 30), 283 (100), 269 (12), 254 (24), 241 (39), 163 (13), 136 (14), 107 (14), 100 (9), 91 (7), 77 (9), 69 (6), 60 (6), 57 (7), 55 (7); HRMS (EI) *m/z* 342.0771 ($C_{18}H_{15}N_2ClO_3$: 342.0771); Anal. ($C_{18}H_{15}N_2ClO_3$) C, H, N.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2005.04.011.

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