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Part 3: Synthesis and biological evaluation of some analogs of the antitumor agents, 2-{4-[(7-chloro-2-quinoxalinyl)-oxy]phenoxy}propionic acid, and 2-{4-[(7-bromo-2-quinolinyl)-oxy]phenoxy}propionic acid

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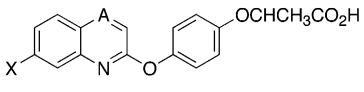
Abstract—2-{4-[(7-Chloro-2-quinoxalinyl)oxy]phenoxy}propionic acid (X469) and 2-{4-[(7-bromo-2-quinolinyl)oxy]phenoxy}propionic Acid (SH80) are among the most highly and broadly active antitumor agents to have been developed in our laboratories. However, the mechanism(s) of action of these agents remain to be elucidated, which prompted our continued endeavor to delineate a pharmacophoric pattern, from which a putative target might be deduced. Herein, we provide additional evidence that intact quinoxaline and quinoline rings in XK469 and SH80, respectively, are fundamental to the activities of these structures against transplanted tumors in mice. The consequence of further modification of the heterocyclic ring system in XK469 and SH80, leading to [1,8]naphthyridine; pyrrolo[1,2-*a*]; imidazo[1,2-*a*]; and imidazo[1,5-*a*] derivatives, all deprive the parent structures of antitumor activity. Introduction of CH_3, CF_3, CH_3O, CO_2H, or C_6H_5 substituents at C_4 of the quinoline ring of SH80 led to weakly active antitumor agents. Similarly, the phenanthridine analog of SH80 manifested only modest cytotoxicity. Lastly, XK469 and SH80 are both significantly more active than the corresponding regioisomeric structures, 2-{4-[(7-halo-4-quinolinyl)oxy]phenoxy)propionic acids.

1. Introduction

2-{4-[(7-Chloro-2-quinoxalinyl)oxy]phenoxy}propionic acid,(XK469, **1a**, Fig. 1) is among the most highly and broadly active antitumor agents to have been developed in our laboratories.[1–4] However, the mechanism of action of **1a** remains to be established, though several, disparate mechanisms of anticancer action have been proposed.[5a–i] In the absence of a validated molecular target, our endeavor focused on the elaboration of a pharmacophoric pattern, from which the nature of a putative receptor might be inferred.[6]



1a. X = Cl, A = N
b. X = F, A = N
c. X = Br, A = N
d. X = I, A = N

2a. X = Br, A = CH
b. X = Cl, A = CH
c. X = OCH_3, A = CH
d. X = F, A = CH
e. X = I, A = CH

Figure 1.

Our initial studies[7–9] indicated that changes in the nature and location of substituents in ring A of **1a** effected significant differences in both the in vitro and in vivo activities of the 2-{4-[(substituted-2-quinoxalinyl)-oxy]phenoxy}propionic acids. The 7-halogeno derivatives (Fig. 1, **1a**–**d**) proved to be the most active compounds with a relative antitumor activity of Cl ≈ F ≈ Br > I. On the other hand, the 3-, 5-, 6-, and 8-regioisomers of **1a** were essentially all inactive. Replacement of the quinoxaline moiety in the lead compound by either a quinazoline or a [1,2,4]-benzotriazine ring system led, in each case, to a complete loss of antitumor activity. By contrast, the quinoline analogs bearing a 7-halo- or a 7-methoxy substituent (Fig. 1, **2a**–**e**), showed levels of antitumor activities in mice

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(Br > Cl > CH_3O > F ≈ I) comparable to, or greater than those manifested by the corresponding quinoxaline analogs. Thus, the observed orders of activity of the 7-halogen substituent in **1** are; Cl ≈ F ≈ Br > I, whereas in **2**; Br > Cl > F > I. Moreover, the *R*-enantiomers of both **1** and **2** proved to be the more active of the two antipodes.

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 1,4-hydroquinone-linkage at C_2 to propionic acid.

Herein, we provide additional evidence that intact quinoxaline and quinoline rings in **1** and **2**, respectively are fundamental to the activities of these structures against transplanted solid tumors in mice. Secondly, it is established that both **2a** and **2b** are significantly more active than the corresponding regioisomeric 2-{4-[(7-halo-4-quinolinyl)oxy]phenoxy}propionic acids, that is, structures **17a** and **b**.

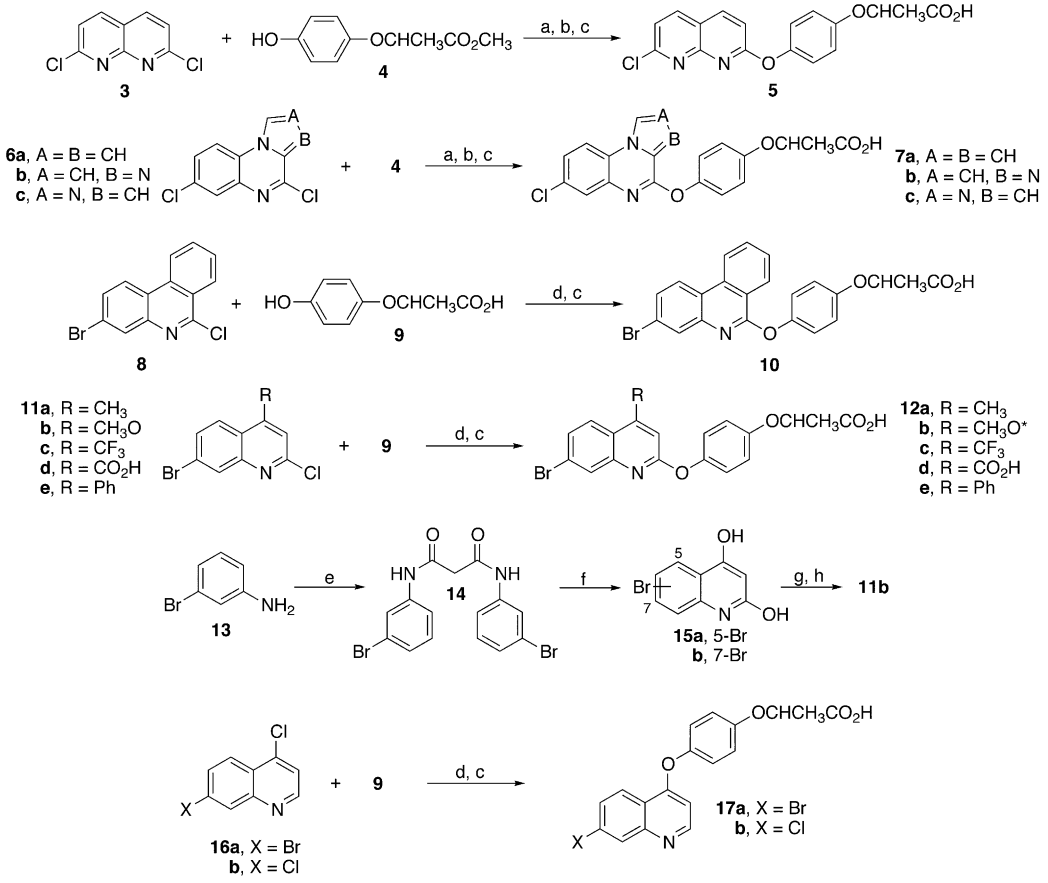
The consequence of further modification of the heterocyclic rings in **1a** and **2a**, relative to their respective activities, was observed from the conversions of the quinoxaline moiety of **1a** to (a) [1,8]naphthyridine; (b) pyrrolo[1,2-*a*]; (c) imidazo[1,2-*a*]; and (d) imidazo[1,5-*a*] derivatives. The significance of an unsubstituted C_3–C_4 bond in ring B of **2** was apparent from the biological evaluation of a corresponding phenanthridine derivative (Scheme 1, **10**). Moreover, the relevance of an unsubstituted site at C_4 of **2** was established by determinations of antitumor activities as a consequence of introduction of substituents of differing electronegativities and/or steric requirements at this position.

2. Results and discussion

2.1. Synthesis

Our synthetic approach utilized one of two methodologies: (A) successive etherification of (*R,S*)-methyl 2-(4-hydroxyphenoxy)propionate (**4**) with the derivatives of 2-chloroquinoxaline, followed by saponification of the intermediate ester, or (B) reaction of selected analogs of 2-chloroquinoline, instead with (*R,S*)-2-(4-hydroxyphenoxy)propionic acid (**9**), as previously described.[7–9] However, if racemic 2-propionic acid derivatives, on biological evaluation, manifested significant antitumor activity, the etherification(s) was repeated with the (*R*)-enantiomer.

2,7-Dichloro[1,8]naphthyridine (**3**), obtained in three steps (64% overall yield) as described by Newkome et al.[10] was converted by Method A to 2-{4-[(7-chloro[1,8]naphthyridin-2-yl)oxy]phenoxy}propionic



Scheme 1. Reagents: (a) K_2CO_3/CH_3CN (method A); (b) aq NaOH/THF; (c) aq HCl; (d) K_2CO_3/DMF (method B); (e) diethyl malonate; (f) Eton's reagent; (g) Me_2SO_4, K_2CO_3/acetone; (h) $POCl_3$. *Via method A.

acid (**5**). Plans to prepare either the 2,7-dichloro or 2,7-dibromo[1,5]naphthyridine analogs of **5** were abandoned as a consequence of the availability of only impractical syntheses of the desired 2,7-dihalo[1,5]naphthyridines.[11a,b] Each method led to complex mixtures of isomeric products, affording the desired starting materials in insufficient yields to provide the isomeric propionic acid derivatives in quantities deemed necessary to conduct meaningful biological evaluations.

4,7-Dichloropyrrolo[1,2-*a*]quinoxaline (**6a**), described by both Guillon et al.[12a] and Cheesman et al.,[12b] was similarly converted to 2-{4-[(7-chloropyrrolo[1,2-*a*]quinoxalin-4-yl)oxy]phenoxy}propionic acid (Scheme 1, **7a**). The synthesis of 2-{4-[(7-chloroimidazo[1,2-*a*]quinoxalin-4-yl)oxy]phenoxy}propionic acid (**7b**) likewise proceeded from 4,7-dichloroimidazo[1,2-*a*]quinoxaline (**6b**), which, in turn, was obtained according to Johnson et al. and Campiani et al.[13a,b]

The preparation of 2-{4-[(7-chloroimidazo[1,5-*a*]quinoxalin-4-yl)oxy]phenoxy}propionic acid (**7c**) utilized the readily accessible intermediate, 7-chloro-2(1*H*)quinoxalinone[7] as starting material. Treatment of the latter with 4-methoxybenzyl chloride in DMF in the presence of NaH, produced the desired *N*-benzylated derivative, together with the readily separable O-tautomer. Interaction of the *N*-benzyl product with tosylmethyl isocyanide (TMI), according to the method described by Barrish and Spergel,[14] followed by successive removal of the 4-methoxybenzyloxy substituent, and chlorination gave 4,7-chloroimidazo[1,5-*a*]quinoxaline (**6c**). Etherification of the latter with **4** gave **7c**.

The synthesis of 3-bromo-6-chlorophenanthridine (**10**) utilized the methodology developed by Badger and Sasse[15] to obtain the precursory 2-amino-4-bromobiphenyl. The latter was converted, on treatment with triphosgene, to the corresponding isocyanate derivative. Cyclization of the latter was effected with $AlCl_3$ in chlorobenzene,[16] which closely followed the procedure designed for the preparation of the 3-chloro analog. Etherification of **8** with **9**, via procedure B, gave 2-{4-[(3-bromo-6-phenanthridinyl)oxy]phenoxy}propionic acid (**10**).

Davis and co-workers[17] described a facile route to 7-bromo-2-chloro-4-methylquinoline (**11a**), which was utilized in the present study in a reaction with **9** for the preparation of 2-{4-[(7-bromo-4-methyl-2-quinolinyl)-oxy]phenoxy}propionic acid (**12a**).

The synthesis of 7-bromo-2-chloro-4-methoxyquinoline (Scheme 1, **11b**) proceeded according to the methodology of Kappe et al.,[18a] who previously reported the preparation of 7-chloro-2,4-quinolinediol. Accordingly, 3-bromoaniline (**13**), on treatment with ethyl malonate gave the corresponding malondianilide (**14**). However, cyclization of the latter with P_2O_5 in methanesulfonic acid (Eaton's reagent), afforded a 1:1 mixture of 5-bromo (**15a**) and 7-bromo-2,4-quinolinediol (**15b**), rather than the expected[18a] single isomer (**15b**). Treatment of the mixture with methyl sulfate and K_2CO_3 in refluxing acetone[18b] gave the corresponding 4-methoxy-2-quinolinols in near quantitative yield. Reaction of the mixture with $POCl_3$, followed by flash column chromatographic separation of the regioisomeric products, yielded the desired intermediate, **11b**. Reaction of **11b** with **9** led to the anticipated product, 2-{4-[(7-bromo-4-methoxy-2-quinolinyl)oxy]phenoxy}propionic acid (**12b**), but in poor (7%) yield. The major product proved to be 7-bromo-2-chloro-4-quinolinol. A minor improvement in yield was observed in the reaction of **11b** and **4**, followed by saponification to give the acid **12b**.

The unanticipated results of the reaction of **11b** and **9** may be ascribed, in accord with an interpretation provided by Belli et al.,[18c] to the deactivating effect of a CH_3O substituent, *meta* to the reaction center (C_2). The effect is enhanced by direct conjugation of the CH_3O group with a *para* aza function at the one position, with a consequent reduction of the electronegative effect of the nitrogen. In summary, the methoxy group at C_4 deactivates the chlorine substituent at C_2, and accounts, thereby, for resistance of the site to nucleophilic attack.

The synthetic route to 7-bromo-2-chloro-4-trifluoromethylquinoline (**11c**) was based upon a procedure, described by Hamann and co-workers,[19] which is analogous to the preparation of 6-methoxy-4-trifluoromethyl-2-quinolinol. Proceeding, in the present case, from the interaction of 3-bromoaniline and ethyl 4,4′,4″-trifluoroacetoacetate, led to a mixture (11:1; as determined by NMR) of 7- and 5-bromo-4-trifluoromethyl-2-quinolinols after cyclization. Conversion of the mixture to the corresponding 2-chloro derivatives was achieved in the usual manner, which was readily separated by flash column chromatography. Conversion of **11c** to 2-{4-[(7-bromo-4-trifluoromethyl-2-quinolinyl)-oxy]phenoxy}propionic acid (**12c**) was effected by the standard method.

The introduction of a 4-carboxylic acid substituent into 7-bromo-2-chloroquinoline employed the combined methodologies of Tokunaga et al.[20a] and Sadler[20b] to obtain 6-bromoisatin. The latter was then converted to 7-bromocinchonic acid, as described by Wetzel et al.[20c] Treatment of the cinchonic acid derivative with $POCl_3$ provided 7-bromo-2-chloro-4-quinolinecarboxylic acid (**11d**), which was transformed to 2-{4-[(7-bromo-4-carboxy-2-quinolinyl)oxy]phenoxy}propionic acid (**12d**), as described above.

7-Bromo-2-chloro-4-phenylquinoline (**11e**) was obtained via the readily accessible 3-bromo-2-benzoylacetanilide.[21] Cyclization of the latter to 7-bromo-4-phenyl-2-quinolinol was then effected in H_2SO_4 (46% yield) at 100 °C, without (NMR) evidence of the formation of the corresponding 5-bromo isomer. Conversion to **11e**, and then to 2-{4-[(7-bromo-4-phenyl-2-quinolinyl)-oxy]phenoxy}propionic acid (**12e**) was achieved, as described above.

The synthetic route to 2-{4-[(7-bromo-4-quinolinyl)-oxy]phenoxy}propionic acid (**17a**), the positional isomer

of **2a**, required the intermediate, 7-bromo-4-chloroquinoline (**16a**), which has been described by Krogstad and co-workers.[22] Etherification of **16a** with **9** provided **17a** in good yield. Moreover, the same reaction, utilizing the facile conversion of commercially available 4,7-dichloroquinoline (**16b**) to 2-{4-[(7-chloro-4-quinolinyl)oxy]phenoxy}propionic acid (**17b**) was performed in equally good yield.

2.2. Cytotoxic activity and discussion

All new analogs were first evaluated, as previously described[7–9] in our in vitro disk diffusion soft agar colony formation assay to determine cytotoxicity against leukemias, solid tumors, and normal cells (see Experimental section).

It was shown in our prior biological evaluations[7,8] that mouse tumors, such as Panc 03 and Colon 38, responded equally well both in vitro and in vivo to active cytotoxic agents, such as **1a**. However, the naphthyridine derivative (**5**), which manifested interesting in vitro activity against both Colon 38 and Panc 03 tumors, was found to be inactive following high doses in mice bearing transplanted Panc 03 tumors. Neither, the C_3–C_4, five-membered, fused ring, analogs of **1**, that is, **7a**,**b**,**c**, nor the phenanthridine derivative **10**, manifested sufficient activity (see Table 1) to warrant testing in mice. The 7-chloro and 7-bromoquinoline derivatives, **17a** and **b**, with alternative placement of the oxyphenoxy linkage at C_4, that is, the regioisomeric analogs of **2a** and **2b**, respectively, were similarly inactive in culture. The majority of the C_4 substituted derivatives of **2** exhibited only modest cytotoxicity and poor tumor selectivity in culture. Thus, only the 4-methyl (**12a**) and 4-methoxy (**12b**) derivatives of **2** showed sufficient activities in culture to merit in vivo testing (see Table 2). Though active against Colon 38 (1.1 log kill), the racemic form of **12a** was inferior to both **1a** (3.9 log kill) and **2a** (2.2 log kill). The *R*-enantiomer of **12a** was also active, with an efficacy of 2.0 log kill, similar to (*R,S*)-**2a** (2.2 log kill), but required more than twice the total dose. However, neither the end points of toxicity nor maximum tolerated dose (MTD) were reached with either the *R*-enantiomer or the racemic mixture, to permit a direct comparison of efficacy based upon corresponding maximum tolerated doses (MTDs). Moreover, **12b** failed to show in vivo activity; in fact both **12a** and **12b** also had higher dose requirements than **2**, and as such, are not considered as improvements in terms of efficacy and potency (Table 2).

3. Conclusion

Evidence is presented to demonstrate that intact quinoxaline and quinoline rings in **1** and **2**, respectively, are fundamental to the activities of the parent structures against transplanted tumors in mice. Thus, modifications of the heterocyclic ring system in **1a** and **2a**, leading to [1,8]naphthyridine (**5**); pyrrolo[1,2-*a*] (**7a**); imidazo[1,2-*a*] (**7b**); and imidazo[1,5-*a*] (**7c**) derivatives, all deprived the parent structures of antitumor activity. Introduction of CH_3, CF_3, CH_3O, CO_2H, or C_6H_5 substituents at C_4 of the quinoline ring of **2a** led to a group (**12a**–**e**) of weakly active antitumor agents. Similarly, the phenanthridine analog (**10**) of **2a** manifested only modest cytotoxicity. Lastly, **2a** and **2b** are both significantly more active than the corresponding regioisomeric structures, 2-{4-[(7-halo-4-quinolinyl)oxy]phenoxy}propionic acids, **17a** and **b**.

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. Optical rotations were measured on a Jasco DIP-370 polarimeter at room temperature. Nuclear magnetic

Table 1. Cytotoxicity of XK-469 analogs against leukemic cells, solid tumor cells, and normal cells in the disk-diffusion-soft-agar-colony-formation-assay

Compound number	Enantiomeric form	μg/disk	Mouse leukemia	Mouse tumors			Human tumors		Normal cells
			L1210	Panc 03	Colon 38	Mam17/Adr	Colon H116	Colon H15/MDR	Fibroblasts
1a	Racemic	270	0–600		>800	>850		150–400	500–600
1a	*R*	235	0–600		>950	800–900		0–500	400–600
2a	*R*	520	0–750		0–900	0–950		0–500	0–600
5	Racemic	510	0–550	400–800	500–600			0–150	0–200
7a	Racemic	460	0–300		300–450	0–400		0–350	0–350
7b	Racemic	505	0–250		0	150–200		0–50	0–50
7c	Racemic	525	0–300	0–350		0–600	150–300	0–100	0–150
10	Racemic	450	100–220		200–350	0–400		150–300	150–250
12a	Racemic	490	250–650		0–650	0–700		150–300	0–550
12b	Racemic	540	100–450		450–600	0–600		0–250	0–350
12c	Racemic	465	100–250		200	300–400		0–300	0–250
12d	Racemic	470	0	0	0			0	0
12e	Racemic	475	100–250		0–200	0–200		0–200	150–250
17a	Racemic	515	0–250		200–400			0–250	0–100
17b	Racemic	475	100–300			400		0–100	0

Zone units recorded: 200 units = 6.5 mm.

Table 2. Evaluation of selected analogs of XK-469 against solid tumors of mice

Compound number	Enantiomeric form	SC tumor	Number of IV injections	Total dose, mg/kg	Drug deaths	% Body wt loss at nadir	*T*/*C* (%)	Log_{10} tumor cell kill	Cures	Activity rating
1a	Racemic	Colon 38	9	473	0/5	−1.7%	0	3.9	2/5	++++
1a	Racemic	Panc 03	5	300	0/5	−15.0%	4	3.3	1/5	++++
2a	Racemic	Colon 38	6	360	0/5	0%	23	2.2	0/5	+++
5	Racemic	Panc 03	12	1200	0/5	0%	68	0.3	0/5	–
12a	Racemic	Colon 38	6	696	0/5	−6.6%	5	1.1	0/5	+
12a	*R*	Colon 38	6	840	0/5	−2.0%	7	2.0	0/5	+++
12b	Racemic	Colon 38	6	900	0/3	−7.5%	56	0.4	0/5	–

For a detailed description of testing methodologies, please see Ref. 4. Treatment of Colon 38 or Panc 03 began 3 days postimplant of the tumors. All analogs were water soluble and injected iv. In the case of **12a** and **12b**, the injection route was switched to oral administration (po) after the second injection due to tail vein necrosis. Only three mice were injected for **12b** due to limited drug supply. Treatment was stopped when weight loss was substantial or drug supplies were exhausted. The log kill values were based on tumors that grew (cures were excluded from calculation). The cures represent >4.0 log kill for these tumors.

resonance (^1H and ^{13}C NMR) spectra were recorded at room temperature, and referenced to a residual solvent signal, on either a Varian Unity 300 or Varian Mercury 400 instruments 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; b, broad; m, unresolved multiplet. Mass spectra were recorded on a MS80RFA instrument and other instruments at 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.

4.1. General method of the preparation of esters (procedure A)

A mixture of the 2(4)-chloroheterocycle, **4**, anhydrous K_2CO_3, and an aprotic solvent (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, where required, 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. General direct method for the preparation of acids (procedure B)

A mixture of the 2(4)(6)-chloroheterocycle, **9**, anhydrous K_2CO_3, and DMF was gently refluxed until the reaction was complete. After it was cooled, the reaction mixture was concentrated, water was then added, and the solution was filtered through Celite to remove insoluble material. After it was cooled, the filtrate was acidified with 1 M HCl to pH 3–4, and the solid was collected, washed with ice-water, and dried or extracted with AcOEt. The impure product was dissolved in AcOEt and filtered through silica gel to remove the dark, very polar contaminant. The filtrate was then concentrated, purified by flash column chromatography (if required), and crystallized.

4.4. 2-{4-[(7-Chloro[1,8]naphthyridin-2-yl)oxy]phenoxy}propionic acid (5)

The methyl ester of **5** was prepared by refluxing overnight a mixture of **3** (0.40 g, 2.0 mmol), **4** (0.43 g, 2.2 mmol), anhydrous K_2CO_3 (0.36 g, 2.6 mmol), and CH_3CN (20 mL). Pure material (0.47 g, 66% yield) was obtained after chromatography (2:1 hexanes–AcOEt) and recrystallization from AcOEt–hexanes to give white crystals. Mp 94–96 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.11 (d, J = 8.0 Hz, 1H), 8.03 (d, J = 8.4 Hz, 1H), 7.32 (d, J = 8.8 Hz, 1H), 7.18 (d, J = 8.8 Hz, 1H), 7.17–7.12 (m, 2H), 6.92–6.86 (m, 2H), 4.73 (q, J = 6.4 Hz, 1H), 3.77 (s, 3H), 1.62 (d, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.9, 165.4, 155.2, 154.7, 154.0, 147.2, 139.9, 139.1, 123.0, 121.8, 118.8, 116.4, 114.7, 73.4, 52.7, 18.9. IR (KBr) 1750 (C=O) cm^{-1}. MS (EI) *m*/*z* (%) 358 (M^+, 100), 299 (93), 271 (89), 255 (14), 243 (10), 192 (6), 163 (60), 149 (8), 136 (10), 127 (15), 100 (8), 91 (35), 76 (6), 63 (11), 59 (8), 55 (6), 50 (5). HRMS (EI) *m*/*z* 358.0722 (calcd for $C_{18}H_{15}N_2ClO_4$ 358.0720). Anal. ($C_{18}H_{15}N_2ClO_4$) C, H, N.

The methyl ester of **5** (0.43 g, 1.2 mmol), dissolved in THF (25 mL), was hydrolyzed with 0.1 M NaOH (25 mL, 2.5 mmol) to give **5** (0.42 g, ~100%) as white crystals after recrystallization from $CHCl_3$. Mp ~ 120 °C (dec); ^1H NMR (400 MHz, DMSO-d_6): δ 13.04 (br s, 1H), 8.49 (d, J = 9.2 Hz, 1H), 8.44 (d, J = 8.0 Hz, 1H), 7.55 (d, J = 8.0 Hz, 1H), 7.38 (d, J = 8.8 Hz, 1H), 7.20–7.14 (m, 2H), 6.98–6.92 (m, 2H), 4.84 (q, J = 6.8 Hz, 1H), 1.52 (d, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.8, 165.6, 155.5, 154.3, 153.0, 146.9, 141.7, 141.1, 123.5, 122.0, 119.5, 116.3, 114.8, 72.6, 19.0. IR (KBr) 3420 (OH), 1715

(C=O) cm^{-1}. MS (EI positive ion) *m/z* (%) $727^{(2M+K)}$ (15), $711^{(2M+Na)}$ (26), $706^{(2M+NH_4)}$ (15), $689^{(2M+H)}$ (54), $383^{(M+K)}$ (18), $367^{(M+Na)}$ (55), $362^{(2M+NH_4)}$ (11), $345^{(M+H)}$ (100). Anal. ($C_{17}H_{13}N_2ClO_4$) C, H, N.

4.5. 2-{4-[(7-Chloro-4-pyrrolo[1,2-*a*]quinoxalinyl)-oxy]phenoxy}propionic acid (7a)

The methyl ester of **7a** was prepared by refluxing overnight a mixture of **6a** (0.47 g, 2.0 mmol), **4** (0.43 g, 2.2 mmol), anhydrous K_2CO_3 (0.36 g, 2.6 mmol), and CH_3CN (10 mL). Pure material (0.65 g, 82% yield) was obtained after chromatography (4:1 hexanes–AcOEt) and recrystallization from EtOH to give off-white crystals. Mp 123–125 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86–7.83 (m, 1H), 7.68 (d, J = 8.8 Hz, 1H), 7.61 (d, J = 2.4 Hz, 1H), 7.31 (dd, J = 8.8, 2.4 Hz, 1H), 7.25–7.19 (m, 2H), 7.19–7.15 (m, 1H), 6.98–6.92 (m, 2H), 6.86–6.83 (m, 1H), 4.79 (q, J = 6.8 Hz, 1H), 3.80 (s, 3H), 1.66 (d, J = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.9, 156.1, 155.1, 146.8, 136.1, 130.5, 128.1, 125.8, 125.6, 123.2, 119.2, 116.1, 115.8, 114.7, 114.0, 106.8, 73.4, 52.7, 18.9. IR (KBr) 1730 (C=O) cm^{-1}. MS (EI) *m/z* (%) 396 (M^+, 100), 337 (32), 309 (92), 293 (14), 274 (5), 255 (5), 218 (5), 201 (50), 174 (15), 169 (9), 166 (9), 149 (7), 139 (5), 75 (5), 63 (6), 59 (7). Anal. ($C_{21}H_{17}N_2ClO_4$) C, H, N.

The methyl ester of **7a** (0.44 g, 1.1 mmol), dissolved in THF (20 mL), was hydrolyzed with 0.1 M NaOH (22 mL, 2.2 mmol) to give **7a** (0.41 g, 97% yield) as pale yellow crystals after recrystallization from $CHCl_3$. Mp 184–185 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.08 (br s, 1H), 8.48–8.45 (m, 1H), 8.24 (d, J = 8.8 Hz, 1H), 7.51 (d, J = 2.8 Hz, 1H), 7.47 (dd, J = 8.8, 2.4 Hz, 1H), 7.26–7.20 (m, 2H), 7.09 (d, J = 4.0 Hz, 1H), 6.96–6.90 (m, 3H), 4.83 (q, J = 6.8 Hz, 1H), 1.52 (d, J = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.9, 156.2, 155.5, 146.4, 135.9, 129.9, 127.2, 126.2, 125.9, 123.6, 118.6, 118.4, 116.8, 116.0, 114.6, 107.2, 72.6, 19.0. IR (KBr) 3420 (OH), 1705 (C=O) cm^{-1}. MS (EI) *m/z* (%) 382 (M^+, 81), 337 (9), 323 (6), 309 (100), 293 (8), 274 (9), 218 (6), 201 (63), 174 (21), 168 (7), 166 (13), 149 (10), 139 (7), 83 (5), 81 (5), 75 (7), 69 (8), 63 (9), 57 (9), 55 (10), 50 (5), 45 (6). HRMS (EI) *m/z* 382.0724 (M^+, calcd for $C_{20}H_{15}N_2ClO_4$ 382.0720). Anal. ($C_{20}H_{15}N_2ClO_4$) H, N; C: calcd, 62.75; found 61.39.

4.6. 1-(2-Amino-4-chlorophenyl)-1*H*-imidazole

To a solution of NH_4Cl (1.50 g, 28.0 mmol) in water (15 mL), 1-(4-chloro-2-nitrophenyl)-1*H*-imidazole[13] (3.13 g, 14.0 mmol) in EtOH (50 mL) was added, followed by zinc dust (9.34 g, 140 mmol) and the mixture stirred overnight. The zinc was filtered off, washing with hot EtOH, and the filtrate concentrated to give a dark solid. This was mixed with AcOEt and anhydrous $MgSO_4$ added before filtering off the insoluble material. The filtrate was concentrated to give (~100% crude yield) as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (s, 1H), 7.31 (d, J = 1.6 Hz, 1H), 7.14 (t, J = 1.6 Hz, 1H), 7.01 (d, J = 8.0 Hz, 1H), 6.84 (d, J = 2.4 Hz, 1H), 6.76 (dd, J = 8.4, 2.0 Hz, 1H), 3.89 (br s, 2H).

4.7. 7-Chloro-4-imidazo[1,2-*a*]quinoxalinol

A mixture 1-(2-amino-4-chlorophenyl)-1*H*-imidazole (~14 mmol) and 1,1′-carbonyldiimidazole (2.27 g, 14.0 mmol) in 1,2-Cl_2Ph (100 mL) was heated at reflux for 1.5 h. After cooling the solid was filtered, washed with acetone, and dried to give (2.21 g, 72% yield) as a brown solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.91 (s, 1H), 8.51 (s, 1H), 8.10 (d, J = 9.2 Hz, 1H), 7.58 (d, J = 1.6 Hz, 1H), 7.35 (d, J = 1.6 Hz, 1H), 7.32 (dd, J = 8.4, 2.0 Hz, 1H).

4.8. 4,7-Dichloroimidazo[1,2-*a*]quinoxaline (6b)

A mixture of 7-chloro-4-imidazo[1,2-*a*]quinoxalinol (2.19 g, 9.97 mmol), $POCl_3$ (9.2 mL, 15 g, 100 mmol), and PCl_5 (4.4 g, 20 mmol) was refluxed overnight. After cooling it was concentrated to give a brown semi-solid, which was added to water and $NaHCO_3$ added slowly until pH 7. The mixture was filtered, washed with water, and dried to give a yellow solid. This was heated with AcOEt, the insoluble material filtered off, and the filtrate concentrated to give (2.15 g, 91% yield) as a yellow solid. Mp 227–229 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (s, 1H), 8.03 (d, J = 2.4 Hz, 1H), 7.85 (s, 1H), 7.83 (d, J = 8.8 Hz, 1H), 7.64 (dd, J = 8.8, 2.4 Hz, 1H).

4.9. 2-{4-[(7-Chloro-4-imidazo[1,2-*a*]quinoxalinyl)-oxy]phenoxy}propionic acid (7b)

The methyl ester of **7b** was prepared by refluxing for 4 h a mixture of **6b** (0.47 g, 2.0 mmol), **4** (0.41 g, 2.1 mmol), anhydrous K_2CO_3 (0.36 g, 2.6 mmol), and CH_3CN (10 mL). Pure material (0.63 g, 79% yield) was obtained after chromatography (4:1 hexanes–AcOEt) and recrystallization from AcOEt to give off-white crystals. Mp 186–188 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (s, 1H), 7.79 (s, 1H), 7.76–7.22 (m, 2H), 7.44 (dd, J = 9.2, 1.6 Hz, 1H), 7.29–7.23 (m, 2H), 6.98–6.92 (m, 2H), 4.79 (q, J = 6.8 Hz, 1H), 3.80 (s, 3H), 1.65 (d, J = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.9, 155.4, 153.5, 146.6, 135.6, 134.3, 132.7, 132.3, 128.5, 126.8, 125.1, 123.2, 116.0, 115.8, 114.1, 73.3, 52.7, 18.9. IR (KBr) 1740 (C=O) cm^{-1}. MS (EI) *m/z* (%) 397 (M^+, 100), 368 (5), 338 (60), 310 (69), 294 (9), 283 (18), 256 (6), 236 (9), 220 (6), 202 (25), 167 (9), 152 (7), 137 (7), 129 (12), 125 (7), 123 (8), 115 (7), 111 (13), 109 (10), 100 (8), 97 (26), 95 (19), 91 (12), 83 (35), 81 (27), 73 (27), 71 (28), 69 (57), 67 (24), 63 (12), 60 (23), 57 (58), 55 (67). Anal. ($C_{20}H_{16}N_3ClO_4$) C, H, N.

The methyl ester of **7b** (0.58 g, 1.5 mmol), dissolved in THF (40 mL), was hydrolyzed with 0.1 M NaOH (29 mL, 2.9 mmol) to give **7b** (0.50 g, 89% yield) as white crystals after recrystallization from EtOH. Mp 244–246 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.08 (br s, 1H), 8.81 (s, 1H), 8.30 (d, J = 8.8 Hz, 1H), 7.81 (s, 1H), 7.64 (d, J = 2.4 Hz, 1H), 7.59 (dd, J = 9.2, 2.4 Hz, 1H), 7.31–7.25 (m, 2H), 6.99–6.92 (m, 2H), 4.85 (q, J = 6.8 Hz, 1H), 1.53 (d, J = 6.4 Hz, 3H). ^{13}C NMR

(100 MHz, DMSO-d_6): δ 173.9, 155.6, 153.7, 146.2, 135.2, 134.3, 132.1, 131.3, 127.3, 126.9, 125.7, 123.5, 117.9, 116.7, 116.1, 72.5, 19.0. IR (KBr) 3430 (OH), 1705 (C=O) cm^{-1}. MS (EI) *m/z* (%) 383 (M^+, 15), 339 (31), 324 (100), 310 (90), 295 (16), 283 (36), 254 (5), 220 (8), 202 (38), 191 (10), 175 (8), 167 (12), 150 (7), 148 (7), 136 (11), 124 (11), 115 (6), 110 (9), 105 (6), 100 (8), 91 (14), 81 (10), 77 (9), 75 (10), 69 (8), 65 (11), 63 (21), 57 (7), 55 (10), 53 (11), 51 (10), 45 (10). HRMS (EI) *m/z* 383.0672 (M^+, calcd for $C_{19}H_{14}N_3ClO_4$ 383.0681). Anal. ($C_{19}H_{14}N_3ClO_4$) C, H, N.

4.10. 1-(4-Methoxybenzyl)-2(1*H*)-7-chloroquinoxalinone and 7-chloro-2-(4-methoxybenzyloxy)quinoxaline

To a mixture of 7-chloro-2-quinolinone[7] (0.89 g, 4.9 mmol) in anhydrous DMF at 0 °C, 60% NaH (0.30 g, 7.5 mmol) was added slowly. After 0.5 h, 4-methoxybenzyl chloride (0.70 mL, 0.81 g, 5.1 mmol) was added and the mixture stirred at room temperature overnight. This was concentrated to give a brown-yellow solid, which was mixed with water (25 mL) and extracted with AcOEt (2 × 50 mL). The combined extracts were washed with saturated NaCl (10 mL), dried over anhydrous $MgSO_4$ and concentrated to give a yellow semi-solid. The regioisomers were separated utilizing column chromatography using 2:1 hexanes–AcOEt as the eluent. The *O*-substituted product eluted first and was recrystallized using hexanes to give (0.24 g, 16% yield) as yellow crystals. Mp 86–88 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.45 (s, 1H), 7.92 (d, J = 8.0 Hz, 1H), 7.85 (d, J = 2.4 Hz, 1H), 7.49 (dd, J = 8.8, 2.4 Hz, 1H), 7.48–7.43 (m, 2H), 6.96–6.91 (m, 2H), 5.45 (s, 2H), 3.82 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.0, 157.8, 141.1, 140.2, 137.6, 136.1, 130.7, 130.3, 128.2, 127.6, 126.6, 114.2, 68.5, 55.5. The *N*-substituted product eluted next and was recrystallized using AcOEt–hexanes to give (0.86 g, 58% yield) as white crystals. Mp 149–150 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (s, 1H), 7.79 (d, J = 8.8 Hz, 1H), 7.32 (d, J = 1.6 Hz, 1H), 7.26 (dd, J = 8.0, 2.4 Hz, 1H), 7.23–7.18 (m, 2H), 6.88–6.83 (m, 2H), 5.36 (s, 2H), 3.77 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.5, 155.1, 150.5, 137.3, 133.7, 132.4, 131.9, 128.7, 126.7, 124.5, 114.8, 114.7, 55.5, 45.4. IR (KBr) 1655 (C=O) cm^{-1}.

4.11. 7-Chloro-5-(4-methoxybenzyl)-4(5*H*)-imidazo[1,5-*a*]quinoxalinone

To a mixture of 60% NaH (0.30 g, 7.5 mmol) in anhydrous THF (5 mL) at 0 °C, a mixture of 1-(4-methoxybenzyl)-2(1*H*)-7-chloroquinoxalinone (0.86 g, 2.9 mmol) and *p*-tosylmethyl isocyanide (0.60 g, 3.0 mmol) in anhydrous THF (10 mL) was added slowly and the mixture stirred for 1 h at room temperature. After adding to water (100 mL) the mixture was filtered, washed with water and ether and dried to give (0.91 g, 94% yield) as a beige solid. Mp 221–223 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.10 (s, 1H), 8.28 (d, J = 8.4 Hz, 1H), 7.96 (s, 1H), 7.42 (s, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.22 (d, J = 8.8 Hz, 2H), 6.86 (d, J = 8.8 Hz, 2H), 5.39 (s, 2H), 3.68 (s, 3H).

4.12. 7-Chloro-4-imidazo[1,5-*a*]quinoxalinol

To solution of 7-chloro-5-(4-methoxybenzyl)-4(5*H*)-imidazo[1,5-*a*]quinoxalinone (0.91 g, 2.7 mmol) in TFA (15 mL) and anisole (6 mL), TfOH (3 mL) was added slowly and the mixture stirred overnight at room temperature. The mixture was concentrated to give a red liquid, which was slowly poured into a mixture of saturated $NaHCO_3$ (25 mL) and AcOEt (25 mL). After mixing it was filtered, washed with water and AcOEt, and dried to give (0.50 g, 85% yield) as a tan solid. Mp >300 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.49 (s, 1H), 9.04 (s, 1H), 8.19 (d, J = 9.2 Hz, 1H), 7.85 (s, 1H), 7.38–7.25 (m, 2H).

4.13. 4,7-Dichloroimidazo[1,5-*a*]quinoxaline (6c)

A mixture of 7-chloro-4-imidazo[1,5-*a*]quinoxalinol (0.49 g, 2.2 mmol) and $POCl_3$ (2.0 mL, 3.4 g, 22 mmol) was refluxed overnight. After cooling it was concentrated to give a brown solid, which was added to water and $NaHCO_3$ added slowly until pH 7. The mixture was filtered, washed with water, and dried to give a brown solid. This was heated with AcOEt, the insoluble material filtered off and the filtrate concentrated to give (0.14 g, 26% yield) as an orange solid. Mp 196–198 °C (dec); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.70 (s, 1H), 7.93 (s, 1H), 7.90 (d, J = 2.4 Hz, 1H), 7.85 (d, J = 8.0 Hz, 1H), 7.56 (dd, J = 8.8, 2.4 Hz, 1H).

4.14. 2-{4-[(7-Chloro-4-imidazo[1,5-*a*]quinoxalinyl)-oxy]phenoxy}propionic acid (7c)

The methyl ester of **7c** was prepared by refluxing for 4 h a mixture of **6c** (0.14 g, 0.59 mmol), **4** (0.12 g, 0.61 mmol), anhydrous K_2CO_3 (0.11 g, 0.80 mmol) and CH_3CN (5 mL). Pure material (0.15 g, 65% yield) was obtained after recrystallization from CH_3OH to give off-white crystals. Mp 195–197 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.69 (s, 1H), 7.94 (s, 1H), 7.80 (d, J = 9.2 Hz, 1H), 7.63 (d, J = 2.4 Hz, 1H), 7.38 (dd, J = 9.2, 2.0 Hz, 1H), 7.23–7.18 (m, 2H), 6.97–6.92 (m, 2H), 4.79 (q, J = 7.2 Hz, 1H), 3.80 (s, 3H), 1.66 (d, J = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.8, 155.5, 155.4, 146.1, 136.6, 132.6, 130.6, 128.5, 126.7, 126.6, 123.1, 122.9, 118.2, 116.1, 115.4, 73.3, 52.7, 18.9. IR (KBr) 1735 (C=O) cm^{-1}. MS (EI) *m/z* (%) 397 (M^+, 100), 338 (62), 310 (86), 294 (15), 284 (6), 255 (7), 202 (28), 175 (26), 169 (9), 148 (12), 139 (5), 124 (6), 111 (7), 101 (7), 97 (14), 95 (10), 91 (15), 86 (9), 83 (18), 81 (15), 71 (14), 69 (26), 67 (16), 63 (11), 59 (13), 57 (29), 55 (35), 51 (7), 45 (6). Anal. ($C_{20}H_{16}N_3ClO_4$) C, H, N.

The methyl ester of **7c** (0.11 g, 0.27 mmol), dissolved in THF (10 mL), was hydrolyzed with 0.1 M NaOH (5.5 mL, 0.55 mmol) to give **7c** (0.10 g, 95% yield) as off-white crystals after recrystallization from EtOH–water. Mp 234–236 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.10 (br s, 1H), 9.29 (s, 1H), 8.33 (d, J = 8.4 Hz, 1H), 7.96 (s, 1H), 7.56–7.52 (m, 3H), 7.28–7.23 (m, 2H), 6.97–6.91 (m, 2H), 4.84 (q, J = 6.8 Hz, 1H), 1.52 (d, J = 6.4 Hz, 3H). ^{13}C NMR (100 MHz,

DMSO-d_6): δ 173.8, 155.7, 145.9, 136.3, 131.6, 127.3, 126.8, 123.6, 117.6, 116.1, 72.5, 19.0. IR (KBr) 3450 (OH), 1720 (C=O) cm^{-1}. MS (EI) *m/z* (%) 383 (M^+, 97), 338 (15), 324 (8), 310 (100), 294 (7), 275 (5), 255 (9), 202 (30), 175 (29), 169 (7), 148 (13), 136 (5), 124 (6), 110 (6), 100 (5), 91 (6), 75 (7), 69 (5), 65 (6), 63 (9), 55 (7), 50 (6), 45 (5). HRMS (EI) *m/z* 383.0672, (M^+, calcd for $C_{19}H_{14}N_3ClO_4$ 383.0673). Anal. ($C_{19}H_{14}N_3ClO_4$), C: calcd, 59.46; found, 58.37. H: calcd, 3.68; found 4.37. N: calcd, 10.95, found, 10.44.

4.15. 4-Bromobiphenyl 2-isocyanate

To a solution of 2-amino-4-bromobiphenyl[15] (3.72 g, 15.0 mmol) in toluene (50 mL), triphosgene (1.66 g, 5.5 mmol) was added slowly and the mixture refluxed for 1 h. After cooling it was concentrated to give (4.08 g, 99% yield) as a light yellow liquid. ^1H NMR (400 MHz, $CDCl_3$): δ 7.50–7.37 (m, 6H), 7.35 (d, J = 1.6 Hz, 1H), 7.20 (d, J = 9.2 Hz, 1H).

4.16. 3-Bromo-6-phenanthridinol

To a mixture of anhydrous $AlCl_3$ (2.4 g, 18 mmol) and PhCl (25 mL) at 100 °C, 4-bromobiphenyl 2-isocyanate (4.52 g, 16.5 mmol) in PhCl (10 mL) was added and the mixture refluxed for 1 h. After cooling it was added to water and the mixture boiled to remove the PhCl. After the aqueous mixture had cooled it was filtered, washed with water and ether, and dried to give (2.56 g, 57% yield) as a white solid. ^1H NMR (400 MHz, DMSO-d_6): δ 11.76 (s, 1H), 8.48 (d, J = 8.0 Hz, 1H), 8.33 (d, J = 8.8 Hz, 1H), 8.29 (dd, J = 8.0, 1.6 Hz, 1H), 7.85 (dt, J = 8.0, 1.6 Hz, 1H), 7.65 (t, J = 8.4 Hz, 1H), 7.52 (d, J = 1.6 Hz, 1H), 7.40 (dd, J = 8.4, 2.0 Hz, 1H).

4.17. 3-Bromo-6-chlorophenanthridine (8)

A mixture of 3-bromo-6-phenanthridinol (4.44 g, 16.2 mmol) and $POCl_3$ (7.4 mL, 12.4 g, 80.8 mmol) was refluxed for 1 h. After cooling it was concentrated to give a brown solid, which was added to water and $NaHCO_3$ added slowly until pH 7. The mixture was filtered, washed with water, and dried to give an off-white solid. This was heated with $CHCl_3$, the insoluble material filtered off, and the filtrate concentrated and recrystallized to give (4.37 g, 92% yield) as off-white crystals. Mp 192–194 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.52 (d, J = 8.0 Hz, 1H), 8.45 (d, J = 8.0 Hz, 1H), 8.33 (d, J = 9.2 Hz, 1H), 8.21 (d, J = 2.4 Hz, 1H), 7.93–7.88 (m, 1H), 7.77 (dd, J = 7.2, 1.6 Hz, 1H), 7.74 (dd, J = 8.8, 2.0 Hz, 1H).

4.18. 2-{4-[(3-Bromo-6-phenanthridinyl)oxy]phenoxy}-propionic acid (10)

A mixture of **8** (0.58 g, 2.0 mmol), **9** (0.36 g, 2.0 mmol), anhydrous K_2CO_3 (0.69 g, 5.0 mmol), and DMF (10 mL) were refluxed overnight. (Note: aqueous solution not filtered due to low solubility.) The pure product (0.44 g, 51% yield) was obtained after recrystallization from $CHCl_3$ as off-white crystals: ^1H NMR (400 MHz, DMSO-d_6): δ 13.08 (br s, 1H), 8.78 (d, J = 8.0 Hz, 1H), 8.60 (d, J = 8.0 Hz, 1H), 8.46 (d, J = 8.0 Hz, 1H), 7.99 (t, J = 7.6 Hz, 1H), 7.84 (t, J = 7.6 Hz, 1H), 7.75 (d, J = 2.4 Hz, 1H), 7.67 (dd, J = 8.8, 2.4 Hz, 1H), 7.29–7.24 (m, 2H), 6.99–6.93 (m, 2H), 4.85 (q, J = 6.8 Hz, 1H), 1.53 (d, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.9, 159.9, 155.4, 147.2, 143.8, 134.9, 132.9, 130.1, 129.2, 128.6, 125.4, 123.7, 123.3, 122.6, 122.2, 119.6, 116.1, 72.5, 19.1. IR (KBr) 3430 (OH), 1700 (C=O) cm^{-1}. MS (EI) *m/z* (%) 437 (M^+, 11), 393 (7), 364 (9), 273 (100), 256 (13), 229 (24), 212 (8), 195 (5), 182 (39), 177 (25), 166 (28), 164 (9), 139 (24), 137 (15), 110 (68), 97 (9), 83 (12), 81 (16), 74 (20), 69 (24), 65 (11), 60 (15), 57 (21), 55 (23), 45 (7). HRMS (EI) *m/z* 437.0261 (M^+, calcd for $C_{22}H_{16}N^{79}BrO_4$ 437.0263). Anal. ($C_{22}H_{16}NBrO_4$) C, H, N.

4.19. 2-{4-[(7-Bromo-4-methyl-2-quinolinyl)oxy]phenoxy}propionic acid (12a)

A mixture of **11a** (0.51 g, 2.0 mmol), **9** (0.36 g, 2.0 mmol), anhydrous K_2CO_3 (0.69 g, 5.0 mmol), and DMF (5 mL) were refluxed overnight. The pure product (0.45 g, 56% yield) was obtained after chromatography (1:1 hexanes–AcOEt) and recrystallization from $CHCl_3$–hexanes as off-white crystals. Mp 168–170 °C; ^1H NMR (400 MHz, DMSO-d_6): δ 13.07 (br s, 1H), 7.91 (d, J = 8.8 Hz, 1H), 7.77 (d, J = 1.6 Hz, 1H), 7.59 (dd, J = 9.2, 1.6 Hz, 1H), 7.16–7.10 (m, 3H), 6.92–6.88 (m, 2H), 4.82 (q, J = 6.8 Hz, 1H), 2.63 (s, 3H), 1.51 (d, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.9, 162.9, 155.2, 149.5, 147.3, 147.2, 130.0, 128.2, 126.8, 125.0, 123.7, 123.3, 116.1, 113.7, 72.5, 19.1, 18.8. IR (KBr) 3420 (OH), 1715 (C=O) cm^{-1}. MS (EI) *m/z* (%) 401 (M^+, 68), 356 (17), 342 (23), 328 (49), 314 (8), 300 (5), 250 (11), 220 (65), 204 (6), 141 (100), 114 (21), 109 (6), 102 (5), 81 (5), 75 (5), 69 (5), 63 (11), 57 (5), 55 (6), 51 (5), 45 (6). HRMS (EI): *m/z* 401.0265 (M^+, calcd for $C_{19}H_{16}N^{79}BrO_4$ 401.0263). Anal. ($C_{19}H_{16}NBrO_4$) C, H, N. (*R*) enantiomer: $[\alpha]_D$ +33.4 (*c* 0.50, 0.1 MNaOH), 84% yield. Chiral HPLC separation ((*S*) enantiomer 9.4 min (*R*) enantiomer 12.3 min) using Astec Chirobiotic T 250 × 4.6 mm, 65% H_2O, 35% CH_3OH, 20 mM NH_4NO_3 at 1 mL/min with detection at 250 nm.

4.20. *N,N′*-Bis-(3-bromophenyl)malonamide (14)

A mixture of 3-bromoanaline (2.78 mL, 4.30 g, 25.0 mmol) and diethyl malonate (1.92 mL, 2.00 g, 12.5 mmol) was heated at 220 °C for 18 h. The resulting brown solid was dissolved in AcOEt and filtered through silica gel. The filtrate was concentrated to a small volume and recrystallized from AcOEt–hexanes to give (3.87 g, 75% yield) as cream-colored crystals. Mp 168–170 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 9.34 (s, 2H), 7.88 (s, 2H), 7.43 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 8.4 Hz, 2H), 7.20 (t, J = 8.0 Hz, 2H), 3.61 (s, 2H).

4.21. 5-Bromo-4-hydroxy-2-quinolinol (15a) and 7-bromo-4-hydroxy-2-quinolinol (15b)

N,*N*′-Bis-(3-bromophenyl)malonamide (4.51 g, 10.9 mmol) was dissolved in 7.7% P_2O_5/CH_3SO_3H (10 mL) and heated at 160 °C for 1.5 h. The resulting dark brown solution was poured on ice, filtered, and washed with water. The crude product was dissolved in 0.5 M NaOH, the insoluble material was filtered off, and the filtrate was acidified with concentrated HCl to pH 5. The precipitated solid was filtered and washed with cold water to give (2.59 g, 98% yield) as a white solid (1:1 7-Br:5-Br). Mp ~ 340 °C; 5-Bromo-4-hydroxy-2-quinolinol; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.50 (s, 1H), 11.40 (s, 1H), 7.31–7.23 (m, 3H), 5.77 (s, 1H). 7-Bromo-4-hydroxy-2-quinolinol; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.39 (s, 1H), 11.26 (s, 1H), 7.66 (d, J = 8.4 Hz, 1H), 7.41 (d, J = 1.6 Hz, 1H), 7.36 (dd, J = 7.6, 1.6 Hz, 1H), 5.72 (s, 1H).

4.22. 5-Bromo-4-methoxy-2-quinolinol and 7-bromo-4-methoxy-2-quinolinol

A mixture of 7-bromo-(5-bromo)-4-hydroxy-2-quinolinol (1.99 g, 8.29 mmol) and acetone (350 mL), K_2CO_3 (2.29 g, 16.6 mmol), and $(CH_3)_2SO_4$ (0.95 mL, 1.3 g, 10 mmol) was refluxed for 2.5 h. After removing the solvent, the yellow solid was mixed with water, and neutralized with 1 M HCl. The light yellow solid (2.1 g, ≈ 100% yield) was filtered and washed with water. 5-Bromo-4-methoxy-2-quinolinol; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.54 (s, 1H), 7.35–7.26 (m, 3H), 5.93 (s, 1H), 3.90 (s, 3H). 7-Bromo-4-methoxy-2-quinolinol; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.42 (s, 1H), 7.65 (d, J = 9.2 Hz, 1H), 7.43 (d, J = 2.8 Hz, 1H), 7.40 (dd, J = 7.2, 1.6 Hz, 1H), 5.90 (s, 1H), 3.86 (s, 3H).

4.23. 5-Bromo-2-chloro-4-methoxyquinoline and 7-bromo-2-chloro-4-methoxyquinoline (11b)

The mixture of 7-bromo-(5-bromo)-4-methoxy-2-quinolinol (2 g, 8 mmol) and $POCl_3$ (3.6 mL, 39 mmol) was refluxed for 1 h. After the removal of excess $POCl_3$, the dark brown viscous liquid was added to water, and $NaHCO_3$ added slowly until pH 7, followed by extracted using AcOEt (2 × 50 mL). The organic layer was washed with saturated NaCl (10 mL), dried over anhydrous $MgSO_4$, and concentrated to give a yellow solid. The solid was purified by filtering through silica gel with $CHCl_3$ and the regioisomers were separated utilizing column chromatography using toluene as the elutent. Both regioisomers were recrystallized using hexanes eluting first as white, needle-like crystals of 5-bromo-2-chloro-4-methoxyquinoline (0.50 g, 23% yield). Mp 119–120 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (d, J = 7.6 Hz, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.46 (t, J = 8.0 Hz, 1H), 6.78 (s, 1H) and followed by white shorter crystals of 7-bromo-2-chloro-4-methoxyquinoline (0.65 g, 30% yield). Mp 147–148 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (d, J = 2.4 Hz, 1H), 7.98 (d, J = 8.8Hz, 1H), 7.58 (dd, J = 8.8, 2.0 Hz, 1H), 6.74 (s, 1H), 4.05 (s, 3H).

4.24. 2-{4-[(7-Bromo-4-methoxy-2-quinolinyl)oxy]phenoxy}propionic acid (12b)

The methyl ester of **12b** was prepared by refluxing for several days a mixture of **11b** (0.27 g, 1.0 mmol), **4** (0.20 g, 1.0 mmol), anhydrous K_2CO_3 (0.17 g, 1.3 mmol), and CH_3CN (10 mL). Pure material (0.07 g, 19% yield) was obtained after chromatography (toluene→4:1 hexanes–AcOEt) and recrystallization from AcOEt–hexanes to give white crystals. Mp 140–142 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (d, J = 8.8 Hz, 1H), 7.86 (d, J = 1.6 Hz, 1H), 7.43 (dd, J = 9.2, 1.6 Hz, 1H), 7.17–7.11 (m, 2H), 6.95–6.89 (m, 2H), 6.38 (s, 1H), 4.77 (q, J = 6.8 Hz, 1H), 4.00 (s, 3H), 3.79 (s, 1H), 1.64 (d, J = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.0, 164.9, 164.2, 154.8, 147.9, 130.0, 127.5, 124.6, 123.4, 122.9, 118.4, 116.2, 91.3, 73.4, 56.2, 52.7, 18.9. IR (KBr) 1740 (C═O) cm^{-1}. MS (EI) *m*/*z* (%) 431 (M^+, 58), 372 (27), 344 (35), 328 (5), 266 (7), 256 (8), 236 (34), 221 (9), 213 (6), 171 (16), 149 (47), 137 (7), 129 (29), 127 (10), 114 (17), 112 (12), 98 (28), 95 (15), 87 (12), 85 (18), 83 (31), 81 (35), 79 (10), 73 (44), 71 (36), 69 (82), 67 (24), 60 (44), 57 (100), 55 (79). Anal. ($C_{20}H_{18}BrNO_5$) C, H, N.

The methyl ester of **12b** (0.11 g, 0.25 mmol), dissolved in THF (5 mL), was hydrolyzed with 0.1 M NaOH (5 mL, 0.5 mmol) to give **12b** (0.08 g, 76% yield) as white crystals after recrystallization from $CHCl_3$–hexanes. Mp 145–146 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.28 (br s, 1H), 7.91–7.86 (m, 2H), 7.42 (dd, J = 8.8, 2.4 Hz, 1H), 7.11–7.06 (m, 2H), 6.96–6.90 (m, 2H), 6.27 (s, 1H), 4.76 (q, J = 6.8 Hz, 1H), 3.95 (s, 3H), 1.67 (d, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.7, 165.1, 164.4, 154.7, 147.8, 147.5, 129.6, 127.6, 124.9, 123.5, 123.0, 118.3, 116.4, 91.1, 73.1, 56.3, 18.7. IR (KBr) 3440 (OH), 1730 (C═O) cm^{-1}. MS (EI) *m*/*z* (%) 417 (M^+, 83), 372 (24), 358 (34), 344 (74), 338 (5), 330 (11), 315 (5), 304 (5), 266 (16), 236 (100), 221 (31), 208 (8), 195 (6), 178 (5), 157 (8), 127 (22), 114 (59), 109 (9), 102 (6), 100 (7), 97 (8), 91 (7), 88 (8), 83 (11), 81 (11), 75 (15), 69 (16), 63 (22), 57 (19), 55 (20), 45 (13). HRMS (EI) *m*/*z* 419.0196 (M^+, calcd for $C_{19}H_{16}{}^{81}BrNO_5$, 419.0191). Anal. ($C_{19}H_{16}BrNO_5$) C, H, N. Chiral HPLC separation ((*S*) enantiomer 6.7 min (*R*) enantiomer 7.7 min) using Astec Chirobiotic T 250 × 4.6 mm, 100 CH_3OH, 0.1 AcOH, 0.1 Et_3N at 0.5 mL/min with detection at 236 nm.

4.25. *N*-(3-Bromophenyl)-3-(3-bromophenylamino)-4,4,4-trifluoro-2-butenamide and ethyl 3-(3-bromophenylamino)-4,4,4-trifluoro-2-butenoate

A mixture of 3-bromoaniline (3.7 mL, 5.8 g, 33 mmol), ethyl 4,4,4-trifluoroacetoacetate (5.0 mL, 6.3 g, 33 mmol), and $PhCH_3$ (25 mL) were heated at 110 °C overnight. After cooling it was concentrated to give an orange-yellow liquid, which was purified by column chromatography using 10:1→4:1 hexanes–AcOEt as the elutent. Ethyl 3-(3-bromophenylamino)-4,4,4-trifluoro-2-butenoate eluted first as a light yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.80 (br s, 1H), 7.39–7.04 (m, 4H), 5.39 (s, 1H), 4.25–4.17 (m, 2H), 1.34–1.25 (m,

3H). *N*-(3-Bromophenyl)-3-(3-bromophenylamino)-4,4,4-trifluoro-2-butenamide eluted next and was recrystallized using hexanes to give (4.08 g, 50% yield) as white crystals. Mp 114–115 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.57 (br s, 1H), 7.79 (br s, 1H), 7.38–7.33 (m, 3H), 7.25–7.10 (m, 5H), 5.33 (s, 1H). ^{19}F NMR (376 MHz, $CDCl_3$): δ −63.5 (s).

4.26. 5-Bromo-4-trifluoromethyl-2-quinolinol and 7-bromo-4-trifluoromethyl-2-quinolinol

Cold concentrated H_2SO_4 (10 mL) was added to *N*-(3-bromophenyl)-3-(3-bromophenylamino)-4,4,4-trifluoro-2-butenamide (3.62 g, 7.80 mmol) and the mixture allowed to warm to room temperature. After all of the solid had dissolved it was heated at 100 °C for 1 h. After cooling it was poured onto ice and filtered, washing with water, and dried to give (1.57 g, 69% yield) as a white solid (11:1 7-Br:5-Br). 5-Bromo-4-trifluoromethyl-2-quinolinol; ^{1}H NMR (400 MHz, DMSO-d_6) (Partial): δ 12.53 (br s, 1H), 7.64 (t, J = 4.4 Hz, 1H), 7.15 (s, 1H). ^{19}F NMR (376 MHz, $CDCl_3$): δ −54.3 (s). 7-Bromo-4-trifluoromethyl-2-quinolinol; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.36 (br s, 1H), 7.61–7.56 (m, 2H), 7.45 (dd, J = 8.8, 1.6 Hz, 1H), 7.00 (s, 1H). ^{19}F NMR (376 MHz, $CDCl_3$): δ −63.1 (s).

4.27. 7-Bromo-2-chloro-4-trifluoromethylquinoline (11c) and 5-bromo-2-chloro-4-trifluoro-methylquinoline

The mixture of 7-bromo-(5-bromo)-4-trifluoromethyl-2-quinolinol (1.80 g, 6.17 mmol) and $POCl_3$ (2.9 mL, 4.9 g, 31 mmol) was refluxed for 1 h. After the removal of excess $POCl_3$, the dark brown viscous liquid was added to water, and $NaHCO_3$ added slowly until pH 7, and the mixture was extracted using AcOEt (2 × 50 mL). The organic layer was washed with saturated NaCl (10 mL), dried over anhydrous $MgSO_4$, and concentrated to give a brown-yellow solid. The solid was purified by filtering through silica gel with $CHCl_3$ and the regioisomers were separated utilizing column chromatography using 20:1 hexanes–AcOEt as the elutent. 7-Bromo-2-chloro-4-trifluoromethylquinoline eluted first as a light yellow liquid that solidified. (1.60 g, 84% yield). Mp 45–46 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30 (d, J = 2.4 Hz, 1H), 7.99–7.94 (m, 1H), 7.78 (dd, J = 8.8, 2.4 Hz, 1H), 7.70 (s, 1H). ^{19}F NMR (376 MHz, $CDCl_3$): δ −62.1 (s). 5-Bromo-2-chloro-4-trifluoromethylquinoline as a light yellow liquid that solidified. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14–8.08 (m, 2H), 7.90 (s, 1H), 7.63 (t, J = 8.0 Hz, 1H). ^{19}F NMR (376 MHz, $CDCl_3$): δ −52.3 (s).

4.28. 2-{4-[(7-Bromo-4-trifluoromethyl-2-quinolinyl)-oxy]phenoxy}propionic acid (12c)

A mixture of **11c** (0.31 g, 1.0 mmol), **9** (0.18 g, 1.0 mmol), anhydrous K_2CO_3 (0.35 g, 2.5 mmol), and DMF (2 mL) were refluxed overnight. The pure product (0.11 g, 24% yield) was obtained after chromatography (1:1 hexanes–AcOEt) and recrystallization from $CHCl_3$–hexanes as off-white crystals. Mp 166–168 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.08 (br s, 1H), 7.95 (d, J = 1.6 Hz, 1H), 7.90 (bd, J = 7.2 Hz, 1H), 7.77 (dd, J = 8.8, 1.6 Hz, 1H), 7.74 (s, 1H), 7.24–7.18 (m, 2H), 6.97–6.91 (m, 2H), 4.83 (q, J = 6.4 Hz, 1H), 1.52 (d, J = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.8, 162.1, 155.6, 148.0, 146.7, 137.2 (q, J = 32 Hz), 130.7, 130.3, 125.8, 125.2, 123.2, 123.2 (q, J = 273 Hz), 119.0, 116.2, 113.0 (d, J = 5 Hz), 72.6, 19.0. ^{19}F NMR (376 MHz, DMSO-d_6): δ −61.45. IR (KBr) 3420 (OH), 1745 (C=O) cm^{-1}. MS (EI) *m*/*z* (%) 455 (M^+, 97), 410 (23), 396 (20), 382 (60), 366 (10), 304 (18), 274 (54), 254 (19), 195 (20), 176 (8), 145 (8), 109 (5), 91 (5), 63 (7). HRMS (EI). *m*/*z* 456.9955 (M^+, calcd for $C_{19}H_{13}N^{81}BrF_3O_4$ 456.9960). Anal. ($C_{19}H_{13}NBrF_3O_4$) C, H, N.

4.29. 7-Bromo-2-hydroxy-4-quinolinecarboxylic acid

A mixture of 6-bromoisatin[20a,b] (2.86 g, 12.7 mmol), malonic acid (6.61 g, 63.5 mmol), and AcOH (125 mL) was refluxed overnight. After cooling it was concentrated to give a brown solid to which water (100 mL) was added. The mixture was filtered and washed with water to give a brown solid. This was heated with $NaHCO_3$ solution and the insoluble material filtered off. The filtrate was acidified to pH 1 with concentrated HCl and the mixture filtered, washed with water, and dried to give (2.54 g, 75% yield) as a brown-yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.14 (br s, 2H), 8.12 (d, J = 9.2 Hz, 1H), 7.54 (d, J = 2.4 Hz, 1H), 7.38 (dd, J = 8.8, 2.4 Hz, 1H), 6.90 (s, 1H).

4.30. 7-Bromo-2-chloro-4-quinolinecarboxylic acid (11d)

A mixture of 7-bromo-2-hydroxy-4-quinolinecarboxylic acid (2.53 g, 9.44 mmol) and $POCl_3$ (4.3 mL, 7.2 g, 47 mmol) was refluxed for 1 h. After cooling it was concentrated to give a black solid, which was added to water and $NaHCO_3$ added slowly until pH 8. The insoluble material was filtered off and the filtrate was acidified to pH 3 with concentrated HCl. The solid was filtered, washed with water, and dried to give an off-white solid. The solid was purified by filtering through silica gel with hot AcOEt, and the filtrate concentrated and recrystallized to give (1.56 g, 58% yield) as off-white crystals. Mp 218–220 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.61 (d, J = 8.8 Hz, 1H), 8.28 (d, J = 2.4 Hz, 1H), 7.95 (s, 1H), 7.90 (dd, J = 9.2, 2.0 Hz, 1H).

4.31. 2-{4-[(7-Bromo-4-carboxy-2-quinolinyl)oxy]phenoxy}propionic acid (12d)

A mixture of **11d** (0.43 g, 1.5 mmol), **9** (0.27 g, 1.5 mmol), anhydrous K_2CO_3 (0.73 g, 5.3 mmol), and DMF (5 mL) were refluxed overnight. The pure product (0.53 g, 82% yield) was obtained after recrystallization from acetone–$CHCl_3$ as light yellow crystals. Mp 230–231 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.40 (br s, 2H), 8.51 (d, J = 8.8 Hz, 1H), 7.87 (d, J = 2.4 Hz, 1H), 7.68 (dd, J = 9.2, 2.0 Hz, 1H), 7.59 (s, 1H), 7.22–7.16 (m, 2H), 6.96–6.90 (m, 2H), 4.83 (q, J = 6.8 Hz, 1H), 1.52 (d, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.8, 167.1, 162.6, 155.4, 148.1, 147.1,

141.3, 130.1, 129.5, 128.2, 124.5, 123.3, 121.7, 116.3, 115.2, 72.6, 19.0. IR (KBr) 3420 (OH), 1725 (C=O), 1705 (C=O) cm^{-1}. MS (EI) *m/z* (%) 431 (M^+, 100), 386 (26), 372 (22), 358 (61), 342 (14), 314 (21), 287 (6), 280 (18), 267 (12), 250 (41), 236 (5), 206 (23), 194 (11), 191 (5), 182 (9), 178 (11), 175 (31), 171 (7), 143 (11), 127 (42), 115 (18), 110 (19), 100 (14), 94 (16), 91 (15), 84 (17), 81 (15), 76 (16), 73 (20), 69 (27), 65 (17), 63 (18), 59 (72), 57 (31), 55 (47), 51 (15), 45 (30). HRMS (EI) *m/z* 432.9984 (M^+, calcd for $C_{19}H_{14}N^{81}BrO_6$ 432.9984). Anal. ($C_{19}H_{14}NBrO_6$) C, H, N.

4.32. *N*-(3-Bromophenyl)-3-oxo-3-phenylpropionamide

A mixture of 3-bromoaniline (2.25 mL, 3.6 g, 20 mmol), ethyl benzoylacetate (3.6 mL, 4.0 g, 20 mmol), and $PhCH_3$ (10 mL) were heated at 110 °C overnight. After cooling it was concentrated to give an orange-yellow solid, which was purified by washing with 10:1 hexanes–AcOEt followed by recrystallization from hexanes–AcOEt to give (3.01 g, 47% yield) as white crystals. Mp 120–121 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.48 (br s, 1H), 8.03 (d, J = 8.0 Hz, 2H), 7.89–7.86 (m, 1H), 7.66 (t, J = 8.0 Hz, 1H), 7.54 (d, J = 8.0 Hz, 1H), 7.53–7.47 (m, 2H), 7.25 (d, J = 5.6 Hz, 1H), 7.19 (t, J = 8.0 Hz, 1H), 4.12 (s, 2H).

4.33. 7-Bromo-4-phenyl-2-quinolinol

Cold concentrated H_2SO_4 (10 mL) was added to *N*-(3-Bromophenyl)-3-oxo-3-phenyl-propionamide (3.00 g, 9.43 mmol) and the mixture allowed to warm to room temperature. After all of the solid had dissolved it was heated at 100 °C for 1 h. After cooling it was poured onto ice and filtered, washing with water, and dried to give (1.30 g, 46% yield) as a light brown solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.95 (br s, 1H), 7.8–7.2 (m, 8H), 6.41 (s, 1H).

4.34. 7-Bromo-2-chloro-4-phenylquinoline (11e)

A mixture of 7-bromo-4-phenyl-2-quinolinol (1.29 g, 4.30 mmol) and $POCl_3$ (2.0 mL, 3.4 g, 22 mmol) was refluxed for 1 h. After the removal of excess $POCl_3$, the dark brown semi-solid was added to water and $NaHCO_3$ added slowly until pH 7, followed by extracted using AcOEt (2 × 50 mL). The organic layer was washed with saturated NaCl (10 mL), dried over anhydrous $MgSO_4$ and concentrated to give a brown liquid. The mixture was purified by filtering through silica gel with $CHCl_3$ followed by column chromatography using 10:1 hexanes–AcOEt as the elutent. The product eluted first and was recrystallized using 2-PrOH to give (0.75 g, 53% yield) as white crystals. Mp 121–122 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (d, J = 1.6 Hz, 1H), 7.74 (d, J = 9.2 Hz, 1H), 7.58 (dd, J = 9.2, 2.4 Hz, 1H), 7.56–7.52 (m, 3H), 7.48–7.44 (m, 2H), 7.35 (s, 1H).

4.35. 2-{4-[(7-Bromo-4-phenyl-2-quinolinyl)oxy]phenoxy}propionic acid (12e)

A mixture of **11e** (0.32 g, 1.0 mmol), **9** (0.18 g, 1.0 mmol), anhydrous K_2CO_3 (0.35 g, 2.5 mmol), and DMF (2 mL) were refluxed overnight. The pure product (0.38 g, 83% yield) was obtained after chromatography (1:2 hexanes–AcOEt) and recrystallization from $CHCl_3$–hexanes as yellow crystals. Mp 152–154 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.07 (br s, 1H), 7.87 (d, J = 1.6 Hz, 1H), 7.64 (d, J = 8.8 Hz, 1H), 7.61–7.51 (m, 6H), 7.22–7.16 (m, 3H), 6.96–6.90 (m, 2H), 4.83 (q, J = 6.8 Hz, 1H), 1.52 (d, J = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.9, 162.7, 155.3, 152.5, 147.9, 147.2, 137.1, 130.1, 129.9, 129.7, 129.5, 128.8, 128.0, 124.1, 123.4 (2C), 116.2, 113.5, 72.5, 19.1. IR (KBr) 3430 (OH), 1725 (C=O) cm^{-1}. MS (EI) *m/z* (%) 463 (M^+, 93), 418 (22), 404 (25), 390 (44), 385 (5), 374 (7), 312 (16), 299 (8), 282 (66), 254 (5), 203 (100), 190 (6), 176 (18), 165 (8), 151 (5), 110 (6), 77 (9), 69 (5), 63 (6), 57 (5), 55 (7), 51 (5). HRMS (EI) *m/z* 463.0414 (M^+, calcd for $C_{24}H_{18}N^{79}BrO_4$ 463.0419). Anal. ($C_{24}H_{18}NBrO_4$) C, H, N.

4.36. 2-{4-[(7-Bromo-4-quinolinyl)oxy]phenoxy}propionic acid (17a)

A mixture of **16a** (0.49 g, 2.0 mmol), **7** (0.37 g, 2.0 mmol), anhydrous K_2CO_3 (0.69 g, 5.0 mmol), and DMF (5 mL) were refluxed overnight. The pure product (0.56 g, 72% yield) was obtained after recrystallization from AcOEt as white crystals. Mp 197–198 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.05 (br s, 1H), 8.67 (d, J = 4.8 Hz, 1H), 8.23 (d, J = 8.8 Hz, 1H), 8.21 (d, J = 1.6 Hz, 1H), 7.76 (dd, J = 8.8 Hz, 1.6 Hz, 1H), 7.26–7.20 (m, 2H), 7.03–6.97 (m, 2H), 6.54 (d, J = 5.6 Hz, 1H), 4.86 (q, J = 6.8 Hz, 1H), 1.52 (d, J = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.7, 162.3, 156.0, 153.5, 150.4, 147.6, 131.3, 130.0, 124.4, 124.3, 122.9, 120.1, 117.1, 104.9, 72.6, 19.0. IR (KBr) 3430 (OH), 1720 (C=O) cm^{-1}. MS (EI) *m/z* (%) 387 (M^+, 2), 256 (14), 236 (9), 213 (10), 199 (5), 194 (5), 185 (10), 171 (6), 157 (6), 152 (6), 143 (5), 138 (6), 129 (26), 125 (9), 123 (9), 115 (12), 111 (19), 101 (11), 97 (39), 95 (23), 87 (15), 85 (31), 83 (53), 81 (31), 73 (78), 71 (51), 69 (81), 67 (32), 60 (71), 57 (99), 55 (100), 45 (12). HRMS (EI) *m/z* 387.0102 (M^+, calcd for $C_{18}H_{14}{}^{79}BrNO_4$, 387.0106). Anal. ($C_{18}H_{14}BrNO_4$) H, N; C: calcd, 55.69, found 53.62. (*R*) enantiomer: $[\alpha]_D$ +44.4° (c = 0.50, 0.1 M NaOH), mp 203–204 °C, 81% yield. Chiral HPLC separation ((*S*) enantiomer 6.6 min (*R*) enantiomer 8.0 min) using Astec Chirobiotic T 250 × 4.6 mm, 100 CH_3OH, 0.1 AcOH, 0.1 Et_3N at 0.5 mL/min with detection at 232 nm.

4.37. 2-{4-[(7-Chloro-4-quinolinyl)oxy]phenoxy}propionic acid (17b)

A mixture of **16b** (0.40 g, 2.0 mmol), **9** (0.36 g, 2.0 mmol), anhydrous K_2CO_3 (0.69 g, 5.0 mmol), and DMF (5 mL) was refluxed overnight. The pure product (0.33 g, 48% yield) was obtained after recrystallization from AcOEt–heptane to give off-white crystals. Mp 197–198 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.08 (br s, 1H), 8.68 (d, J = 4.8 Hz, 1H), 8.31 (d, J = 8.8 Hz, 1H), 8.05 (d, J = 2.4 Hz, 1H), 7.65 (dd, J = 9.2, 1.6 Hz, 1H), 7.26–7.20 (m, 2H), 7.03–6.97 (m, 2H), 6.53 (d, J = 4.8 Hz, 1H), 4.85 (q, J = 6.8 Hz, 1H),

1.52 (d, $J = 7.2$ Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.7, 162.2, 156.0, 153.5, 150.2, 147.6, 135.6, 128.0, 127.4, 124.3, 122.9, 119.8, 117.1, 104.8, 72.7, 19.0. IR (KBr) 3420 (OH), 1720 (C=O) cm^{-1}. MS (EI) *m/z* (%) 343 (M^+, 100), 298 (10), 270 (89), 242 (5), 235 (9), 219 (6), 162 (54), 149 (6), 135 (24), 127 (10), 110 (12), 99 (17), 97 (9), 91 (7), 83 (10), 81 (8), 74 (6), 71 (8), 69 (16), 67 (6), 63 (6), 57 (16), 55 (16). HRMS (EI) *m/z* 343.0616 (M^+, calcd for $C_{18}H_{14}NClO_4$ 343.0611). Anal. ($C_{18}H_{14}NClO_4$) C, H, N. (*R*) isomer: $[\alpha]_D$ +37.2° ($c = 0.50$, 0.1 M NaOH), mp 194–195 °C, 81% yield. Chiral HPLC separation ((*S*) enantiomer 6.7 min (*R*) enantiomer 8.5 min) using Astec Chirobiotic T 250 × 4.6 mm, 100 CH_3OH, 0.1 AcOH, 0.1 Et_3N at 0.5 mL/min with detection at 228 nm.

4.38. Biologic evaluation methods: in vitro

A brief description of the methods follows. All materials were initially tested in a disk diffusion soft agar colony formation assay (disk assay). The disk assay is designed to compare the relative cytotoxicity of an agent against leukemia cells, solid tumor cells (including multidrug resistant solid tumors), and normal cells. The inhibition is expressed in zone units, with 200 units = 6.5 mm. On average, a 10-fold dilution of a cytotoxic agent produces a 330 zone unit change. Activity against a drug sensitive leukemia (L1210 or P388) provides the reference point. The leukemic cell can represent antiproliferative leukemic active agents of past discoveries. The agent needs greater activity against the drug insensitive solid tumors than against the leukemia cells. Normal fibroblasts were also used in current studies. For the operation of the assay, the tumor cells are isolated from live tissue, that is, a tumor growing in a mouse. The cells are then seeded in the soft agar. The drug is placed on a filter paper disk (standard hole punch of Whatman no 1), which is then placed on top of the soft agar (60 mm plate). The drug diffuses off the disk as the tumor cells are replicating, creating a zone of inhibition of colony formation. Those materials with sufficient cytotoxicity (>400 units) and tumor selectivity progressed to in vivo evaluation in tumor-bearing mice as described below.

4.39. In vivo

Treatment was carried out against early stage pancreatic ductal adenocarcinoma-03, and/or early colon adenocarcinoma 38. All are sensitive to **1**.

4.39.1. Tumor and animal maintenance. Mouse tumors were maintained in the mouse strain of origin and were transplanted into the appropriate F_1 hybrid (or the inbred mouse of origin) for therapy trials. Individual mouse body weights for each experiment were within 5 g, and all mice were over 17 g at the start of therapy. The mice were supplied food and water ad libitum.

4.39.2. Chemotherapy of solid tumors. The animals were pooled, implanted subcutaneously with 30–60 mg tumor fragments by a 12 gauge trocar, and again pooled before unselective distribution to the various treatment and control groups (five or six mice per group). For early stage treatment, chemotherapy was started 1–3 days after tumor implantation while the number of cells is relatively small (10^7 to 5×10^7 cells). Tumors were measured with a caliper twice weekly, or three times weekly for the more rapidly growing tumors. Mice were sacrificed when their tumors reached 1500 mg (i.e., before they could cause the animal discomfort). Tumor weights were estimated from two-dimensional measurements. Dose schedules were adjusted for toxicity; accordingly, doses reported in Table 2 are not the same, because of the toxicity encountered at the top dose(s), at which time treatment was terminated for all doses. Therefore, the highest, achieved dose is reported.

4.39.3. Tumor weight. The tumor weight (in mg) = $(a \times b^2)/2$, where a and b are the tumor length and width (in mm), respectively.

4.39.4. Quantified end points for assessing antitumor activity for solid tumors. The following quantified end points are used to assess antitumor activity.

4.39.4.1. Tumor growth delay ($T - C$ value). T is the median time (in days) required for the treatment group tumors to reach a predetermined size (e.g., 1000 mg), and C is the median time (in days) for the control group tumors to reach the same size. Tumor-free survivors are excluded from these calculations (cures are tabulated separately). In our judgment, this value is the single most important criterion of antitumor effectiveness because it allows the quantification of tumor cell kill.

4.39.4.2. Calculation of tumor cell kill. For subcutaneously (SC) growing tumors, the log cell kill is calculated from the following formula: log cell kill total (gross) $T - C$ value in days (3.32) (T_d), where $T - C$ is the tumor growth delay as described above and T_d is the tumor volume doubling time in days, estimated from the best fit straight line from a log-linear growth plot of the control group tumors in exponential growth (100–800 mg range). The conversion of the $T - C$ values to log cell kill is possible because the T_d of tumors regrowing post treatment (R_x) approximates the T_d values of the tumors in untreated control mice.

Duration of treatment of solid tumor, 5–20 days		
Antitumor activity		Gross log tumor cell kill
Highly active	++++	>2.8
	+++	2.0–2.8
	++	1.3–1.9
	+	0.7–1.2
Inactive	–	<0.7

4.39.4.3. Nonquantitative determination of antitumor activity by tumor growth inhibition (*T*/*C* value). The treatment and control groups are measured when the control group tumors reach approximately 700–1200 mg in size (median of group). The median tumor weight of each group is determined, including zeros. The *T*/*C* value in percent is an indication of antitumor

effectiveness. A *T*/*C* equal to or less than 42% is considered significant antitumor activity by the Drug Evaluation Branch of the Division of Cancer Treatment (NCI). A *T*/*C* value <10% is considered to indicate highly significant antitumor activity, and is the level used by NCI to justify a clinical trial if toxicity, formulation, and certain other requirements are met (termed DN-2 level activity). A body weight loss nadir (mean of group) of greater than 20% or greater than 20% drug deaths is considered to indicate an excessively toxic dosage in a single course trial.

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