Design, Synthesis, and Biological Evaluation of Analogues of the Antitumor Agent, 2-{4-[(7-Chloro-2-quinoxalinyl)oxy]phenoxy}propionic Acid (XK469)

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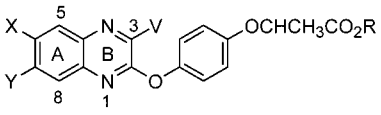
Received December 1, 2000

2-{4-[(7-Chloro-2-quinoxalinyl)oxy]phenoxy}propionic acid (XK469) is among the most highly and broadly active antitumor agents to have been evaluated in our laboratories and is currently scheduled to enter clinical trials in 2001. The mechanism or mechanisms of action of XK469 remain to be elaborated. Accordingly, an effort was initiated to establish a pharmacophore hypothesis to delineate the requirements of the active site, via a comprehensive program of synthesis of analogues of XK469 and evaluation of the effects of structural modification(s) on solid tumor activity. The strategy formulated chose to dissect the two-dimensional parent structure into three regions—I, ring A of quinoxaline; II, the hydroquinone connector linkage; and III, the lactic acid moiety—to determine the resultant in vitro and in vivo effects of chemical alterations in each region. Neither the A-ring unsubstituted nor the B-ring 3-chloro-regioisomer of XK469 showed antitumor activity. The modulating antitumor effect(s) of substituents of differing electronegativities, located at the several sites comprising the A-ring of region I, were next ascertained. Thus, a halogen substituent, located at the 7-position of a 2-{4-[(2-quinoxalinyl)oxy]phenoxy}propionic acid, generated the most highly and broadly active antitumor agents. A methyl, methoxy, or an azido substituent at this site generated a much less active structure, whereas 5-, 6-, 8-chloro-, 6-, 7-nitro, and 7-amino derivatives all proved to be essentially inactive. When the connector linkage (region II) of **1** was changed from that of a hydroquinone to either a resorcinol or a catechol derivative, all antitumor activity was lost. Of the carboxylic acid derivatives of XK469 (region III), i.e., $CONH_2$, $CONHCH_3$, $CON(CH_3)_2$, CONHOH, $CONHNH_2$, CN, or CN_4H (tetrazole), only the monomethyl- and *N*,*N*-dimethylamides proved to be active.

Introduction

2-{4-[(7-Chloro-2-quinoxalinyl)oxy]phenoxy}propionic acid (XK469, **1**, Figure 1) is among the most highly and broadly active antitumor agents to have been evaluated in our laboratories[1−4] (Table 1). The breadth of activity manifested by **1** against transplanted mouse tumors equals or surpasses that of any standard agent against these preclinical models (Table 2). These data prompted the selection of **1** for development as a collaborative effort between the National Cancer Institute (NCI), the DuPont Pharmaceuticals Company (DPC), and our laboratories, the result of which is that this agent is currently scheduled to enter clinical trials in mid-2001.

The discovery and development of the series of compounds is of note. The methyl ester of **1** (Figure 1, *R,S*-**2**) was found to have substantial antileukemic activity at DPC, but it was not developed because of scant human tumor activity in athymic nude mice, poor activity against B16 melanoma, and modest cytotoxicity in culture with short exposure times (1 to 4 h). In 1990/1991, investigators at DPC revived the series and provided us with several analogues. We found excellent



1	XK 469	Y = Cl, V = X = H, R = H
2	XB 947	Y = Cl, V = X = H, R = CH_3
3a	Assure™	X = Cl, V = Y = H, R = C_2H_5
3b	Assure™ analog	X = Cl, Y = Z = H, R = CH_3
3c	Assure™ analog	X = Cl, Y = Z = H, R = H
4	MX 448	X = Y = H, V = Cl, R = CH_3
5	MX 449	X = F, V = Y = H, R = H
6a	MX 450	Y = F, V = X = H, R = H
6b	MX 451	Y = F, V = X = H, R = CH_3
7	MX 453	Y = Br, V = X = H, R = H

Figure 1.

solid tumor selectivity in our in vitro, disk diffusion soft agar colony formation assay[2] for **2** and broad solid tumor activity in tumor-bearing mice.[1−4] However, the water-insoluble ester produced both highly variable toxicity and efficacy with consequent variable oral absorption.[2] Although we were able to improve absorption with

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10.1021/jm0005149 CCC: $20.00
Published on Web 04/28/2001

Table 1. Treatment of Transplanted Tumors of Mouse and Human Origin with XK-469

tumor-sc	XK-469 injection route	no. of injections	total dose, mg/kg	% body wt. loss at nadir	*T/C*, %	log_{10} kill	cures	activity rating
Colon-38	iv	9	546	−3.5	0	>50% cures	3/5	++++
Panc-03	po	4	328	−4	0	>50% cures	4/6	++++
Squam-lung-LC12[a]	iv	8	400	−3	0	all cures	5/5	++++
Mam-16/C	iv	7	525	−9	0	5.2	1/5	++++
Mam-16/C/Taxol	iv	8	480	−11	14	2.7	0/5	+++
Mam-16/C/Adr	iv	8	400	−9	0	4.1	0/5	++++
Mam-17/0	iv	13	620	−12	10	3.4	0/5	++++
Mam-17/Adr	iv	13	620	−4	2	3.9	0/5	++++
Colon-51	po	14	980	−5	0	2.7	1/5	+++
Colon-26	iv	7	300	−12	14	1.3	0/5	++
B16 melanoma	iv	6	300	−11	4	2.6	0/5	+++
Panc-02	iv	8	600	−3	9	2.8	0/6	+++
AML1498 (iv)	iv	4	165	−7	30% ILS	2.0	0/5	+++
L1210 (iv)	iv	5	300	−2	160% ILS	6.4	0/5	+++++
MX-1	iv	8	332	−16	30	0.8	0/5	+
DMS273 sm cell	iv	9	175	−8	14	1.6	0/6	++

[a] Upstaged tumors (median of 288 mg size tumors at first treatment). For conversion of log kill to activity rating, see Biology Methods in text.

Table 2. In Vivo Activity of XK-469 in Comparison with Standard Agents against Transplanted Tumors of Mice

in vivo agent	Colon -38	Mam -16/C	Mam -16/C/ Adr	Mam -16/C/ Taxol	Colon -51	Panc -02	Panc -03	Mam -17	Mam -17/ Adr	Colon -26	Mel B16	Squam-lung-LC12	iv AML Leuk 1498	iv Leuk L1210[b]
Adriamycin	++	++++	±	+++	±	−	+++	++++	−	±	+	++++	++++	+
Taxol	++++	++++	−	−	+	−	++++	++++	−	±	±	−	−	−
Camp/CPT	+	+++	NA	NA	+	−	++++	NA	NA	NA	+	−	NA	NA
VP-16	++	+++	−	+	±	−	++	++	−	−	−	++++	NA	+++++
Vinbl/Vinc	+++	++	−	−	−	−	−	−	−	−	−	−	−[a]	+
5-FU	+++	+++	+++	NA	−	−	+	+	−	++	++	−	+[a]	++++
Ara-C	++	++	NA	NA	−	−	−	++	+++	−	−	−	++++	+++++
Gemzar	+++	++++	NA	NA	NA	NA	NA	NA	NA	+++	NA	−	NA	+++++
Cytoxan	±	+++	++++	NA	++	−	++	+++	+++	++	++	++++	++++	++++
CisDDPt	±	+	+	NA	++	−	++	+++	++++	++	++	++++	NA	++
BCNU	−	−	±	NA	++	−	−	−	−	++++	++++	+	NA	+++++
XK469	++++	++++	++++	+++	+++	++++	++++	++++	++++	++	+++	++++	+++	+++++

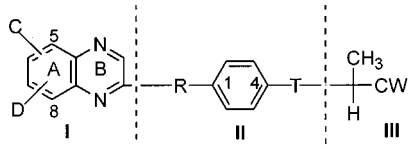
[a] SRI/NCI data. [b] The L1210 activity rating was expanded because of this tumor's higher sensitivity to a variety of agents (including XK469). This expanded rating for L1210 (up to +++++) was used in this (comparison) table and also in Table 1 (see Biology Methods in Experimental Section).

better formulations,[4] it was apparent that a suitable clinical formulation of **2** would be difficult.[2] In search of a more suitable development candidate, DPC provided 337 analogues from their inventory, which comprised, in the main, congeners of the potent herbicidal agent, ASSURE (ethyl 2-{4-[(6-chloro-2-quinoxalinyl)-oxy]phenoxy}propionate), Figure 1, **3a**. Of these analogues, **1** proved to be equally solid-tumor-selective in the in vitro disk assay and even more effective than either **2** or the corresponding ethyl ester in mice.[2−4] Of interest was the comparison of **1** with **3a**. Interestingly, **3a** manifested no antitumor activity, whereas **1** showed no herbicidal activity but instead exhibited impressive antitumor activity. [1−4]

In cell culture, normal fibroblasts and GI epithelial cells have been compared with leukemic cells and solid tumor cells, with GI epithelial cells being the least sensitive to **1**.[3,4] For in vivo treatment and highly active analogues, the most sensitive vital normal cells were the GI epithelial cells, with bone marrow cells being the next most sensitive.[2,4] Historically, a 1.3 to 2.0 log kill of vital normal cells produces lethality in the mouse. Since 6.4 logs of leukemic cells were killed at dosages of **1** that were nonlethal in DBA/2 mice (Table 1) and many solid tumors were as sensitive or more sensitive than the leukemia (Table 1), general tumor selectivity is implied.

It is of historic interest and, indeed, importance to review the reasons why the series was originally abandoned. Only modest antitumor activity was observed for **2** or **1** in immune-deficient mice.[4] The reason can be ascribed to the intolerance of immune-deficient mice to the granulocyte toxicity of the series, which is also seen with Adriamycin.[2,4] Thus, only 35% of a usual conventional mouse dose of Adriamycin or **1** can be administered without encountering lethality.[2,4] This should not be a concern in most cancer treatment conditions, with the exception of AIDS patients. The poor activity against B16 was a formulation problem, since IV administration of **1** produced excellent activity (see Table 1). However, the agent does require a long exposure time (>12 h) to produce substantial cell killing in culture. This does not pose a problem in either mice or humans, since the half-life of **1** is in excess of 8 h in both species (8 to 18 h half-lives, depending on the assay—NCI data).

A review of other XK469 analogues in the DPC inventory, which were tested in mice, has been published.[2] Most changes resulted in a marked reduction in efficacy. The 3-chloro-regioisomer (**4**), much like ASSURE, as well as the unsubstituted analogue were without antileukemic activity. Replacement of the lactic acid moiety in **1** by 2-hydroxyisobutyric acid leads to a marked reduction in activity, and the corresponding glycolic acid ethyl ester analogue proved to be without



Ring-A, mono- and disubstutited derivatives

II		III	
a,	R = T = O (1, 4)	**a**,	W = O_2H
b,	R = T = O (1, 3)	**b**,	W = O_2H
c,	R = T = O (1, 2)	**c**,	W = O_2H
d,	R = OC_6H_4, T = O	**d**,	W = O_2H
e,	R = NH, T = O	**e**,	W = O_2H
f,	R = O, T = NH	**f**,	W = O_2H
g,	R = S, T = O	**g**,	W = O_2H
h,	R = O, T = S	**h**,	W = O_2H
i,	R = T = O (1, 4)	**i**,	W = $ON(R)_2$
j,	R = T = O (1, 4)	**j**,	W = $ONHNH_2$
k,	R = T = O (1, 4)	**k**,	W = ONHOH
l,	R = T = O (1, 4)	**l**,	CW = CN
m,	R = T = O (1, 4)	**m**,	CW = CHN_4 (tetrazole)

Figure 2.

activity (structures and data not shown). Overall, **1** proved to be the most desirable agent of the series.

The mechanism of action of **1** remains to be elaborated, though common mechanisms of anticancer drug action, including DNA binding, alkylation, scission, tubulin binding, and inhibition of pyrimidine/purine metabolism, have all been previously excluded. In addition, the possibility of **1** being a selective inhibitor of cycloxygenase II was only recently eliminated.[5] By contrast, Snapka and co-workers report[6a] that **1** and, in particular, its *R*(+)-isomer induce protein−DNA cross-links in mammalian cells. They suggested that the primary target of **1** is topoisomerase-IIβ,[6b] which may explain its solid tumor selectivity, but further study of the proposed mechanism is required. In any case, the detailed structure of the putative receptor is presently unknown, which precludes consideration of the option of receptor-based design of structures with enhanced solid tumor selectivity.

Accordingly, an effort was initiated to establish a pharmacophore hypothesis, via a comprehensive program of synthesis of congeners and bioisoteres of **1**. The approach sought not only to delineate the minimal requirements of the active site, by stepwise structural modification and antitumor evaluation, but in addition to optimize solid tumor selectivity and minimize untoward pharmacological effects, e.g., toxicity, of the lead compound.

The strategy formulated in the pursuit of these objectives arbitrarily chose to dissect the two-dimensional parent structure into three regions, as shown in Figure 2, and to determine the resultant in vitro and in vivo effects of chemical alterations in each region. Thus, the modulating antitumor effect(s) of substituents of differing electronegativities, to be located at the several sites comprising the A-ring of region I, would first be ascertained. The importance of both the nature and length of the linker relative to the biological response in region II [i.e., a, (1,4)-hydroquinone; b, (1,3)-resorcinol; c, (1,2)-catechol bridge; d, 4-(4-hydroxyphenyl)phenol; e and f, (1,4- and 4,1-) aminophenol; and g and h, (1,4- and 4,1-) thiophenol] between the 2-heteroaryl and α-substituted propionic acid moieties comprising region II would then be examined. Last, the contribution of the carboxylic acid in XK469 would be evaluated by changes in the biological activities as a consequence of the conversion of the lactic acid moiety (as indicated in Figure 2) to a series of primary, secondary, and tertiary amides, represented by **i**, and hydrazide (**j**), hydroxamide (**k**), nitrile (**l**), and tetrazole (**m**) derivatives.

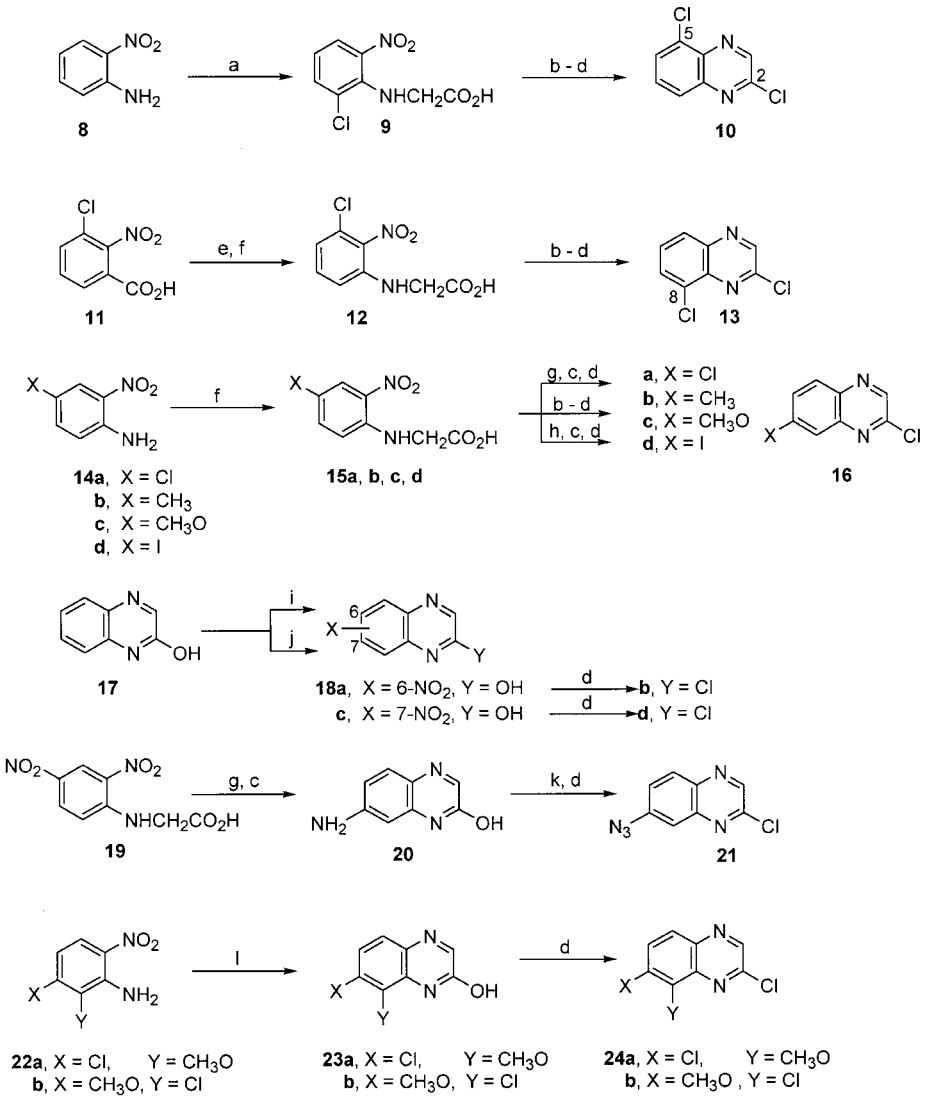
Chemistry

A diverse spectrum of analogues of **1** was prepared, as racemic mixtures, using standard synthetic methodology for a study of structure−activity relationships.

Region I: Quinoxalines. The several synthetic routes to the precursory quinoxalines are illustrated in Scheme 1. The initial objective, that of preparing the 5- and 8-regioisomers of XK469, required the corresponding 2,5- and 2,8-dichloroquinoxalines (Scheme 1, **10** and **13**, respectively).

The synthesis of **10** proceeded from 2-nitroaniline (**8**), which was converted to 2-chloro-6-nitroaniline on successive reactions with a mixture of fuming and concentrated sulfuric acids at 160 °C, chlorination, and followed by hydrolysis.[7] Cyanomethylation of the latter, according to Harvey,[8] was followed by acid hydrolysis of the intermediate nitrile to the corresponding carboxylic acid (**9**). Catalytic reduction of **9** to an aniline intermediate effected cyclization of the latter to a 3,4-dihydro-2-quinoxalinol, which on oxidation with alkaline H_2O_2 provided 5-chloro-2-quinoxalinol. Treatment of the intermediate with $POCl_3$ gave **10** in high yield. The preparation of **13** utilized commercially available 3-chloro-2-nitrobenzoic acid (**11**) as starting material, which was transformed in 91% yield to 3-chloro-2-nitroaniline, via a Schmidt reaction.[9] The preparation of *N*-(3-chloro-2-nitrophenyl)glycine (**12**) was achieved, though in disappointing (6%) yield, by fusion of the weakly basic 3-chloro-2-nitroaniline and bromoacetic acid. The conversion of **12** to **13** followed the same procedure described above for the preparation of **10**. The *N*-(4-chloro-,[10a] 4-methyl-,[10b] 4-methoxy-,[10a] and 4-iodo-2-nitrophenyl)glycines (**15a**−**d**), each derived by fusion of the corresponding nitroanilines (**14a**−**d**) and bromoacetic acid, followed by reductive cyclization and oxidation in the usual manner, gave the corresponding 7-substituted 2-quinoxalinol. The latter were then converted, on treatment with $POCl_3$ to the 2-chloro derivatives, **16a**−**d**. Treatment of 2-quinoxalinol (**17**) with KNO_3 in H_2SO_4 provided the 6-nitro derivative (**18a**) in high yield,[11] whereas the interaction of **17** with HNO_3 in AcOH gave the 7-regioisomer (**18c**) in equally high yield.[11] Each was converted, without further purification, to 2-chloronitroquinoxalines (**18b** and **d**). Reduction of readily accessible **19** with tin and HCl, followed by oxidation, as described by Atkinson,[12] provided a facile preparation of 7-amino-2-quinoxalinol (**20**). Alternatively, the latter was also obtained by direct reduction of **18c**. Conversion of **20** to a diazonium salt and the reaction of the latter with sodium azide, followed by treatment with $POCl_3$, gave 7-azido-2-chloroquinoxaline (**21**). 3-Chloro-2-methoxy-6-nitroaniline (**22a**) and 2-chloro-3-methoxy-6-nitroaniline (**22b**), previously reported by Mallory,[13,14] were obtained on treatment of the correspondingly substituted benzofuroxans with copper powder and HCl in CH_3OH. Amidation of **22a** and **22b** with cyanoacetic acid[15,16] was

Scheme 1[a]



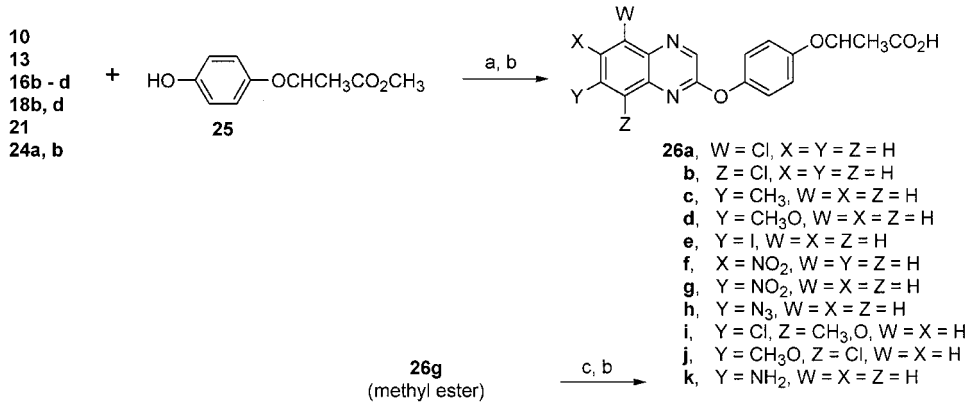
[a] Reagents: (a) (i) H_2SO_4; (ii) Cl_2/AcOH; (iii) H_2O; (iv) $(CH_2O)_n$, KCN, $ZnCl_2$/AcOH; (v) H_2SO_4/AcOH; (b) H_2, 10% Pd/C/CH_3OH; (c) (i) H_2O_2, aq. NaOH; (ii) aq. HCl; (d) $POCl_3$; (e) NaN_3, H_2SO_4; (f) $BrCH_2CO_2H$; (g) Sn, HCl/EtOH; (h) Fe, HCl/EtOH; (i) KNO_3, H_2SO_4; (j) HNO_3/AcOH; (k) (i) $NaNO_2$, aq. HCl, 0 °C; (ii) NaN_3; (l) (i) $NCCH_2CO_2H$, PCl_5/$PhCH_3$; (ii) NaOH/pyridine; (iii) HCl; (iv) $Na_2S_2O_4$/aq. EtOH.

followed by cyclization of the intermediate α-cyano-*ortho*-nitroacetanilides to 2-cyano-3-quinoxalinol-1-oxides. Reduction of the latter with $Na_2S_2O_4$ in aqueous ethanol provided **23a** and **23b**. The conversions of the latter to 2-chloro derivatives, **24a** and **24b**, were readily effected, on treatment with $POCl_3$.

The etherification of (*R*,*S*)-methyl 2-(4-hydroxyphenoxy)propionate (**25**) with each of the 2-chloroquinoxaline derivatives (**10**, **13**, **16b**−**d**, **18b**,**d**, **21**, **24a**,**b**), as shown in Scheme 2, was achieved by method A: (i) K_2CO_3 in acetonitrile; (ii) saponification of the intermediate esters; and (iii) acidification to provide the corresponding 2-{4-[(2-quinoxalinyl)oxy]phenoxy}propionic acids (**26a**−**j**). Reduction of the methyl ester of **26g** with iron powder in acetic acid, followed by hydrolysis of the resulting amino ester, gave **26k**.

Region II: Connector Linkages. The direct linkage of the 7-chloro-2-quinoxalinyloxy-moiety to the 2-position of propionic acid was first undertaken in order to evaluate the contribution of the hydroquinone bridge in XK469 to its antitumor activity. The reaction of 7-chloro-2-quinoxalinol (Scheme 3a, **27**) with methyl 2-bromopropionoate in acetone in the presence of K_2CO_3 (method B) provided methyl 2-[(7-chloro-2-quinoxalinyl)oxy]propionate (**28a**) along with the N-alkylated product (**29**) in a 4:1 ratio. Chromatographic separation and saponification of **28a** yielded the 2-*O*-propionic acid derivative (**28b**). The etherification of resorcinol (**30**) with methyl 2-bromopropionate was achieved with $NaOCH_3$ in CH_3OH[17] (method C). Reaction of the product, **31**, and **16a** (method A) followed by hydrolysis gave the 1,3-linked product, **36**. (2-Benzyloxy)phenol (**32**) was converted to methyl 2-(2-hydroxyphenoxy)-propionate (**33**) by method B, followed by debenzylation (H_2/10% Pd/C in CH_3OH). Substitution of a 2-oxyphenoxy linkage for the hydroquinone bridge in XK469 was achieved by reaction of **16a** with **33** by method D (NaH in DMF) followed by hydrolysis of the intermediate ester to give the catechol analogue (**37**) of XK469. Similarly, the reaction of **16a** and methyl 2-[(4′-hydroxyphenyl)-4-phenoxy]propionate (**35**) (prepared by method C), followed by hydrolysis, yielded a biphenyl analogue (**38**)

Scheme 2[a]



[a] Reagents: (a) K_2CO_3/CH_3CN (method A); (b) (i) aq. NaOH/THF; (ii) aq. HCl; For **26f**, (ii) aq. K_2CO_3/THF; (c) Fe/AcOH.

of XK469. N-Alkylation of 4-aminophenol[18] (**39a**, Scheme 3b) with a mixture of ethyl 2-bromopropionate and Na_2SO_3, afforded **40a** as a crystalline solid. S-Alkylation of 4-mercaptophenol[19] (**39b**) with methyl 2-bromopropionate in DMF in the presence of $KHCO_3$ provided the mercapto derivative, **40b**. Etherification of **40a** and **40b** with **16a** (method A), followed by hydrolysis of the intermediate esters, gave the desired nitrogen and sulfur derivatives, **41a** and **b**, respectively. N-Alkylation[20] of **39a** with **16a** was achieved with HCl in aqueous acetonitrile, whereas S-alkylation of **39b** and **16a** was effected with $KHCO_3$ in DMF. The O-alkylation of both **39a** and **b** and hydrolysis of the intermediate esters led to the respective carboxylic acids, **42a** and **b**, utilizing method B.

Region III: Carboxylic Acid Derivatives. Aminolysis of the methyl ester (**2**) of XK 469 provided the amide (Scheme 4, **43**). Similarly, reaction of **2** with hydrazine in EtOH gave the hydrazide (**44**) in good yield. Conversion of **1** to an acid chloride, followed by reaction of the product with either methyl- or dimethylamine, provided amides, **45a** and **b**, respectively. The acid chloride of **1**, on treatment with $(TMS)_2NOTMS$[21] in toluene, followed by hydrolysis, gave the hydroxamide derivative, **45c**. Reaction of **46** with 2-bromopropionitrile, followed by debenzylation of the intermediate with $BBr_3 \cdot S(CH_3)_2$,[22] gave 2-(4-hydroxyphenoxy)propionitrile (**47**). Etherification of the latter with **16a** (method A) gave the nitrile derivative (**48**) of XK469. Conversion of the latter to a tetrazole derivative (**49**) was readily effected by treatment with NaN_3 and NH_4Cl in DMF.

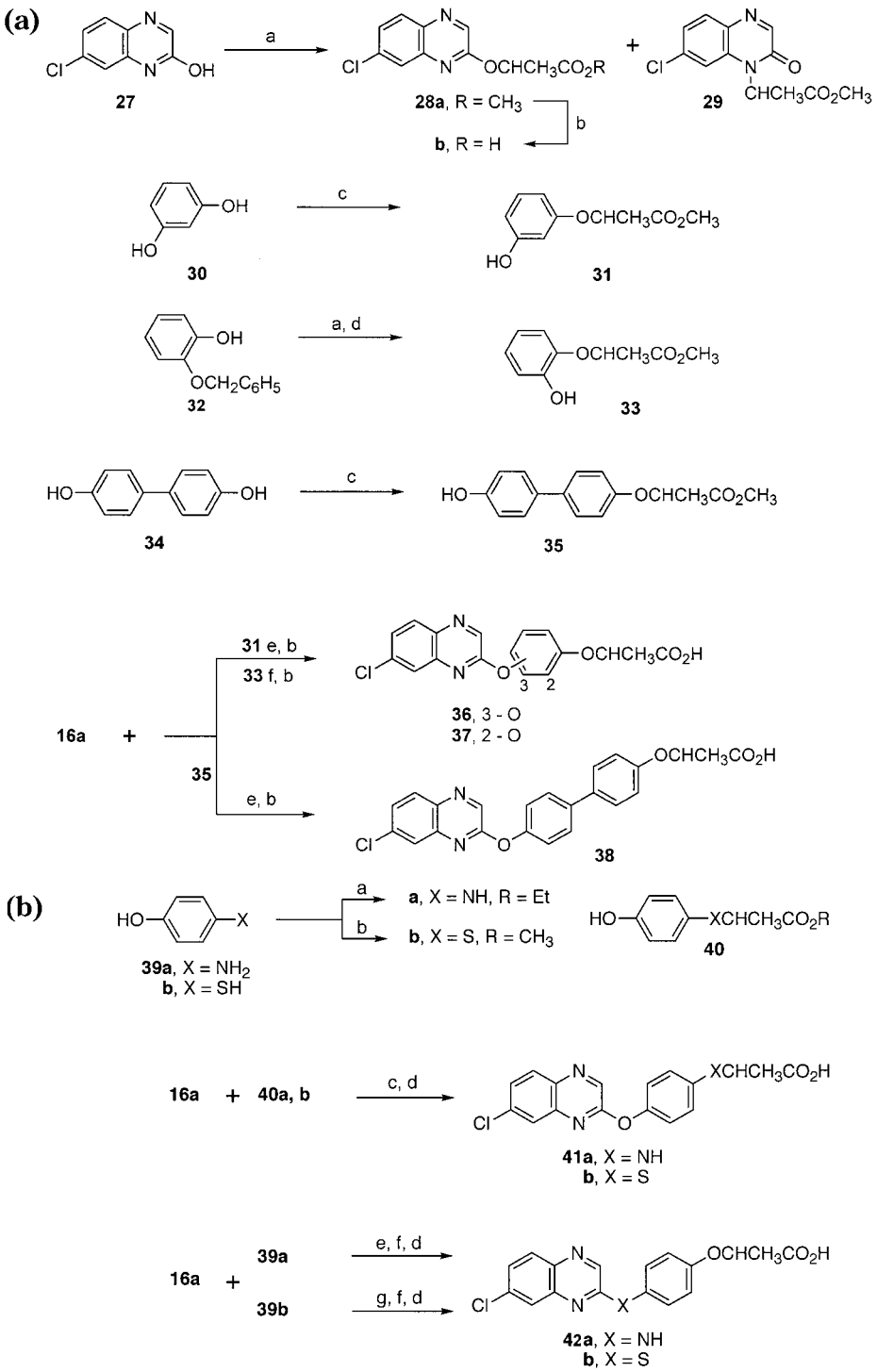
Biological Results and Discussion

In Vitro Testing of Analogues. All newly synthesized analogues of XK469 were initially evaluated in our in vitro, disk diffusion soft agar colony formation assay, to determine cytotoxicity against leukemias, solid tumors, and normal cells. Many of the analogues of **1** that were tested in mice (Tables 3−5) exhibited only modest cytotoxicity and unimpressive tumor selectivity in tissue culture. These analogues, based on historic results with other classes of agents, had only a low probability of being active, though one, obviously, cannot be certain of this. On the other hand, analogues without meaningful cytotoxicity were excluded from testing in tumor-bearing mice. Those manifesting activity in a first tumor were evaluated against a second tumor as well, if supplies permitted.

In Vivo Efficacy Evaluations in Tumor-Bearing Mice. Region I: The exceptionally high activity of racemic XK469 is evident in Tables 1−3. The enantiomers of **1** were compared for efficacy and toxicity in C3H mice bearing Mammary Adenocarcinoma-17/Adr tumors. The schedule was daily × 7, beginning the day after tumor implant (QD1−6), with intravenous (iv) injections in a volume of 0.2 mL/injection. The top dose (62 mg/kg/injection) was planned for 7 days, but we stopped at six injections (372 mg/kg total) because of two of five drug deaths. An explanation of this rationale has been provided by one us (T.H.C.) in an earlier work.[27] Additional information to explain dose schedules and routes are incorporated in the legends to tables.

The *R*-form produced a −18% body weight loss, whereas the *S*-form effected a −14% body weight loss in these mice (20.8 g average at the start of the posttreatment). The next lower dose (301 mg/kg total on a QD1−7 schedule IV) for both enantiomers was not toxic, and the efficacies were essentially identical: 2.9 log kill for the *R*- and 2.7 log kill for the *S*-form against Mammary Adenocarcinoma-17/Adr, a *p*-glycoprotein positive multidrug resistant tumor. The equal activity of the *R*- and *S*-forms is not surprising, since the two are interconverted in the liver of the mouse, with 90% *R* (the clinical agent) produced at equilibrium (personal communication, Drs. B. Jasti and Ralph Parchment, Wayne State University/Karmanos Cancer Institute). The methyl ester of the *R*-form (**2**) was also highly active (Table 3), but had variable absorption and variable efficacy due to poor formulation properties, as previously discussed. The 6-chloro carboxylic acid (**3c**), like Assure (**3a**), proved to be inactive. Moreover, the 5- and 8-regioisomers of XK469, i.e., structures **26a** and **b**, respectively, were also without antitumor activity, though **26b** produced severe neurotoxicity, limiting the total dose that could be administered to 351 mg/kg (Table 3). The readily soluble (pH 8) 7-fluoro analogue (**6a**) was well tolerated by the mice and highly active, producing cures against Colon Adenocarcinoma-38 (Table 3). The drawback was a markedly higher dose requirement than that of the chloro analogue. The 7-fluoro methyl ester (**6b**) could only be administered orally as a suspension, which undoubtedly gave rise to absorption problems and compromised its activity (Table 3). The 6-fluoro car-

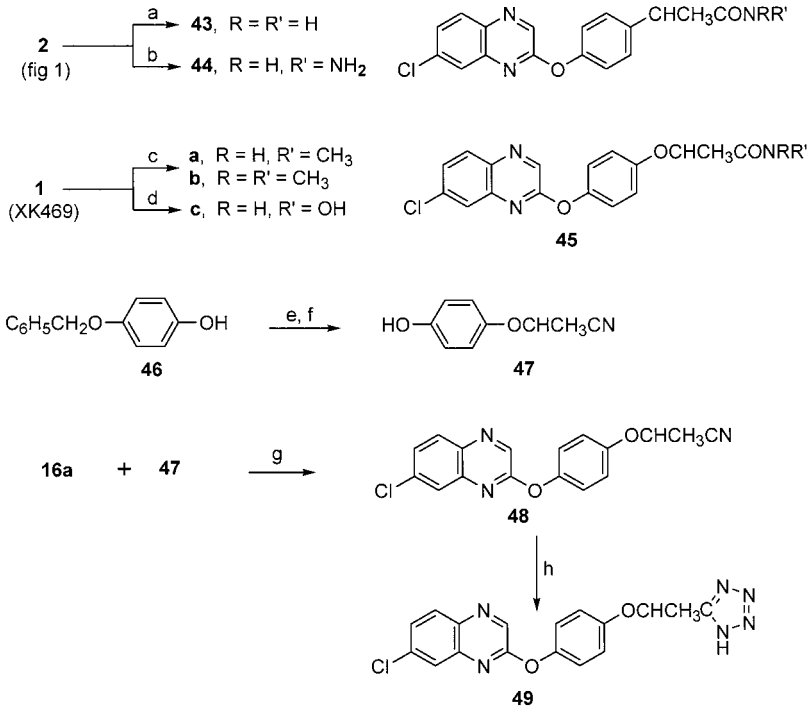
Scheme 3[a,b]



[a] Reagents for Scheme 3a: (a) $BrCHCH_3CO_2CH_3$, K_2CO_3/acetone (method B); (b) (i) aq. NaOH/THF; (ii) aq. HCl; (c) $BrCHCH_3CO_2CH_3$, $NaOCH_3/CH_3OH$ (method C); (d) H_2, 10% Pd/C/CH_3OH; (e) method A; (f) NaH/DMF (method D). [b] Reagents for Scheme 3b: (a) $BrCHCH_3CO_2Et$, Na_2SO_3; (b) $BrCHCH_3CO_2CH_3$, $KHCO_3$/DMF; (c) method A; (d) (i) aq. NaOH/THF; (ii) aq. HCl; (e) aq. HCl/CH_3CN; (f) method B; (g) $KHCO_3$/DMF.

boxylic acid (**5**), rather surprisingly, showed activity, albeit marginal (0.9 log kill, see Table 3). However, this agent, provided by DPC, was not derived via a regiospecific synthesis, which suggested possible contamination with the active 7-fluoro derivative (**6a**). However, comparison of ^{1}H NMR spectra of **5** and **6a** failed to confirm the presence of the suspected contaminant, though >1% of an as yet unidentified impurity was seen in the spectrum of **5**. The 7-bromo analogue (**7**) of **1** was also highly active and curative. Furthermore, the dose requirement was no higher than that of XK469. The limitation was the substantially reduced water solubility of **7**. The 7-iodo derivative (**26e**) was active (1.8 log kill) and not toxic at a total dose of 530 mg/kg, iv. However, **26e** required higher doses than **1** and had substantially reduced activity. Likewise, the 7-azido analogue (**26h**) was active (2.0 log kill Panc-03 and 1.0 log kill Mam-17/Adr) but obviously inferior to **1**. It is also worthy of

Scheme 4[a]



[a] Reagents: (a) NH_3/CH_3OH; (b) $NH_2NH_2/EtOH$; (c) (i) $(COCl)_2/THF$; (ii) RR′NH; (d) (i) $SOCl_2$; (ii) TMS_2NOTMS/toluene; (iii) H_2O; (e) $BrCHCH_3CN$, K_2CO_3/acetone; (f) $BBr_3{\cdot}S(CH_3)_2/CH_2Cl_2$; (g) method A; (h) NaN_3, NH_4Cl/DMF.

note that, whereas the dose requirement for **26h** was low (144 to 216 mg/kg), higher dosages produced deaths from marrow toxicity. The 7-nitro derivative (**26g**) was inactive (note the large dosage used; 1310 mg/kg total, Table 3). The 6-nitro derivative (**26f**) was similarly inactive. The 7-amino analogue (**26k**) was not cytotoxic in tissue culture and, therefore, not tested in mice. The 7-methyl analogue (**26c**) of XK469 was only marginally active and had a large dose requirement (750 to 1250 mg/kg, total). The 7-methoxy derivative (**26d**) was well tolerated in mice and highly active against multidrug resistant tumors, Mam-17/Adr (*p*-glycoprotein positive) and Mam-16/C/Adr (*p*-glycoprotein negative) (2.7 to 3.0 log kill). Thus, **26d** was essentially as active as the chloro analogue against these tumors, but it exhibited a slightly higher dose requirement. It was also active against Colon Adenocarcinoma-38 (1.7 log kill), but at a level substantially lower than that of **1** against the same tumor. Higher dosages of **26d** produced lethality from GI epithelial damage, essentially identical to that seen with lethal dosages of XK469. The 7-chloro-8-methoxyquinoxaline compound (**26i**) exhibited significant activity against Panc-03 (3.0 log kill), Mam-17/Adr (1.5 log kill), and Mam-16/C/Adr (1.7 log kill). Moreover, the dose requirement for **26i** was low (162 to 324 mg/kg total), which is about half that of the requirement for **1**. However, the activities of **26i** were less than that elicited by **1**, and the dose−response relationship was very steep (see Panc-03 data in Table 3). In contrast, the 7-methoxy-8-chloroquinoxaline derivative (**26j**) was inactive.

In summary, it is apparent that there is clear requirement for a group in the 7-position for significant antitumor activity, with Cl = Br = F > OCH_3 > N_3 > I. In addition, a Cl substituent in the 7-position and OCH_3 substitution in the 8-position also produced high antitumor activity together with a lower dose requirement, though the dose−response relationship was excessively steep.

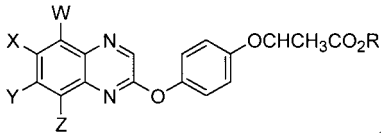
Region II: The importance of the hydroquinone linkage to the activity of XK469 is indicated by the changes to the connector linkage summarized in Table 4. Thus, the direct linkage of the propionic acid moiety, via oxygen, at the 2 position of 7-chloroquinoxaline (**28b**) results in a complete loss of antitumor activity. A similar effect is observed on substitution of catechol (**37**), resorcinol (**36**), or 4-(4-hydroxyphenyl)phenol (**38**) linkages for hydroquinone. Last, structures bearing the bioisoteric substitutions, i.e., **41a** and **b**, as well as **42a** and **b**, all proved to be inactive.

Region III: The doses selected for all analogues listed in Table 5 were derived from multiple dose−level testing (two to three dosages per agent). Dosages were escalated daily until some evidence of toxicity was noted or a very high total dose was obtained.

Of the derivatives presented in Table 5, only the amides **43**, **45a**, and **45b** showed interesting activities. Thus, **43** is clearly active (1.9 log kill) but showed a high dosage requirement. Dosages over 600 mg/kg total within a 10 day time period are considered to be a high dosage,[23,28] which has discouraged the development of agents that show this requirement.

The $-NHCH_3$ derivative (**45a**) appears to be more active than **43**, though both the weight loss and the dose (2300 mg/kg) were higher in the former. The evaluation of **45b**, as indicated in Table 5, was performed on a prior occasion with the tumor Colon-38 and utilized a sample of the agent derived from the DPC inventory. A comparison of the physical properties of the latter with those of a sample of **45b**, prepared in the present study, showed them to be identical.

Table 3. Structure−In Vivo Activity Relationships for Some 2-{4-[(2-Quinoxalinyl)oxy]phenoxy}propionic Acids and Derivatives against Murine Tumors



compd no.[a]	W	X	Y	Z	R[a]	tumor	no. of injections	total dose, mg/kg	% body wt. loss	*T/C*, %	$\log_{10}$ kill	activity rating
1	H	H	Cl	H	H	Panc-03	4	328	−4.0	0	2.1[b]	++++
												4/6 cures
1	H	H	Cl	H	H	Mam-17/ADR	13	620	−4.0	2	3.9	++++
1 (*R*)	H	H	Cl	H	H	Mam-17/ADR	7	301	−8.0	2	2.9	++++
1 (*S*)	H	H	Cl	H	H	Mam-17/ADR	7	301	−3.0	0	2.7	++++
2 (*R*)	H	H	Cl	H	CH_3	Colon-38	30	495	0	0	3.5[b]	++++
												3/5 cures
3a	H	Cl	H	H	C_2H_5	Colon-38	19	2686	0	61	0.42	−
3b	H	Cl	H	H	CH_3	Colon-38	15	2770	0	>100	none	−
3c	H	Cl	H	H	H	Colon-38	14	1590	−4	>100	none	−
5	H	F	H	H	H	Colon-38	7	769	+1.0	34	0.9	+
6a	H	H	F	H	H	Panc-03	12	1085	−13	0	3.7[b]	++++
												3/5 cures
6b[c]	H	H	F	H	CH_3	Colon-38	10	1433	+1.0	34	0.8	+
7	H	H	Br	H	H	Colon-38	8	753	−12.0	0	3.0[b]	++++
							8	466	−7.0	0	2.1[b]	2/5 cures
												+++
												3/5 cures
26a	Cl	H	H	H	H	Panc-03	9	1010	−2.0	59	0.27	−
							9	561	+2.0	>100	none	−
26b	H	H	H	Cl	H	Panc-03	7	351	−4.0	74	0	−
							10	287	−3.9	69	0.1	−
26c	H	H	CH_3	H	H	Mam-17/ADR	7	1250	+7.1	21	0.63	±
							7	750	+4.3	47	0.38	−
26d	H	H	OCH_3	H	H	Mam-17/ADR	7	679	−4.6	4.6	3.0	++++
							7	407.4	0.0	6.4	1.7	++
26d	H	H	OCH_3	H	H	Mam-16c/ADR	6	582	−13.6	0	2.7	+++
							7	455	−1.2	8	2.1	+++
26d	H	H	OCH_3	H	H	Colon-38	9	585	0	23	1.73	++
							9	195	0	90	0.12	−
26e	H	H	I	H	H	Panc-03	13	530	0	15	1.8	++
26f	H	NO_2	H	H	H	Panc-03	7	700	−1.4	41	0.42	−
26g	H	H	NO_2	H	H	Panc-03	14	1310	-3.5	52	0.6	−
26h	H	H	N_3	H	H	Panc-03	6	144	+2.9	17	2.0	+++
26h	H	H	N_3	H	H	Mam-17/ADR	8	216	+4.3	30	1.0	+
26i	H	H	Cl	OCH_3	H	Panc-03	12	324	−15.0	0	3.0	++++
							12	180	−5.0	33	0.64	±
26i	H	H	Cl	OCH_3	H	Mam-16c/ADR	7	164	−6.2	7.5	1.7	++
26i	H	H	Cl	OCH_3	H	Mam-17/ADR	6	162	−16.4	7	1.5	++
							6	99	−1.5	13	1.2	+
26j	H	H	OCH_3	Cl	H	Panc-03	14	939	+11.1	76	0	−
26k[d]	H	H	NH_2	H	H							

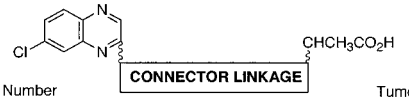
[a] In cases in which R = H, these analogues were water-soluble in aqueous $NaHCO_3$ and were injected iv. In cases in which R = CH_3, these analogues were water-insoluble and were injected orally (po). A dose-escalation schedule was followed as presented in ref 27. Treatment was stopped when weight loss was substantial or drug supply was exhausted. Dosages of >1100 mg/kg indicate an agent with no clinical promise.[23,28] Treatment of Colon-38 or Panc-03 began 3 days post-implant of the tumors. The other tumors were faster growing (1. 0 to 1. 2 day doubling), and treatment began the day after tumor implant. [b] The log kill values were based on tumors that grew (cures excluded from the calculation). The cures represent >4.0 log kill for these tumors. [c] Made a poor suspension and gave poor oral absorption which may account for the limited activity. [d] Inactive in vitro, not tested in vivo.

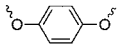
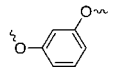
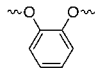
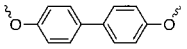
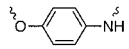
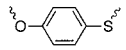
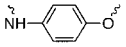
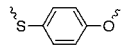
An evaluation of **45b** against Panc-03 is currently in progress. Moreover, the activity of **45b** against Colon-38 has also prompted (an in-progress) synthesis of the *R*- and *S*-forms of this agent to ascertain whether the anticipated activity against the tumors, Panc-03 as well as Colon-38, is a property of one or both enantiomers.

Summary

Without knowledge of a target structure for **1**, we elected to delineate the putative requirements of the active site via a comprehensive structure−activity study of analogues of **1**. The investigation focused on relationships of in vitro and in vivo antitumor activities to (a) changes in the nature and location of substituents in ring A of region I; (b) alterations in hydroquinone moiety, the connector linkage comprising region II; and (c) to derivatives of the carboxylic acid function. The order of the relative activities of the 7-halogen derivatives was found to be F ≈ Cl ≈ Br > I. On the other hand, the 3,5,6- and 8-regioisomers of **1** were essentially all inactive. Changes in the hydroquinone (1,4) linkage to that of either a resorcinol (1,3) or a catechol (1,2) derivative all resulted in inactive structures, as did replacement of either the 1- or 4-oxygen atom comprising the hydroquinone bridge by sulfur or nitrogen. By contrast, simple alkyl ester and amide derivatives of **1b** showed relatively minor changes in activities relative to **1**.

Table 4. Importance of the Connector Linkage to the Antitumor Activity of XK469



Compound Number	CONNECTOR LINKAGE	Tumor	Activity Rating
1		Panc 03	++++
28b		a	NA
36		Panc 03	(-)
37		a	NA
38		a	NA
41a		Panc 03	(-)[b]
41b		Panc 03 Mam 17/Adr	(-) (-)
42a		a	NA
42b		a	NA

[a] Inactive in culture; not tested in mice. [b] Total iv: 330mg/kg; *T*/*C* = 100%; no log kill.

Clearly, the components and topology of **1** combine to give the optimum solid tumor selectivity, relative to the majority of analogues prepared and evaluated in this study. Our ongoing work, which will be the subject of later reports, includes a study of changes in the antitumor activity of **1** as a consequence of the bioisosteric replacement of the $C_3 = N_4$ comprising ring B of the quinoxaline ring by (1) quinazoline ($N_3 = C_4$), (2) 1,2,4-trazine ($N_3 = N_4$), and (3) quinoline ($C_3 = C_4$) ring systems.

Experimental Section

Chemistry. 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, Nujol mull, or as a thin film. Magnetic resonance (^{1}H and ^{13}C NMR) spectra were recorded at room temperature on either a Varian Unity 300, Varian Mercury 400, or GE Q300 instruments in the chemistry department at Wayne State University, Detroit, MI, and referenced to a residual solvent signal. Chemical shifts are reported in ppm downfield from 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 in the chemistry department at Wayne State University, Detroit, MI. Flash column chromatography was carried out unless otherwise indicated with silica gel 200−400 mesh, 60 Å (Aldrich), and the crude product was introduced onto 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. All the compounds are racemic mixtures.

2-Chloroquinoxaline Derivatives. *N*-(2-Chloro-6-nitrophenyl)glycine (9). 2-Chloro-6-nitroaniline[7] (1.73 g, 10.0 mmol), paraformaldehyde (0.90 g, 30 mmol), KCN (1.96 g, 30.0 mmol), $ZnCl_2$ (13.63 g, 100.0 mmol), AcOH (25 mL), and concentrated H_2SO_4 (1 drop) were heated at 50 °C overnight. After cooling, the mixture was poured into ice−water (100 mL) and extracted with AcOEt (4 × 50 mL). The extracts were washed with saturated $NaHCO_3$ (50 mL portions), followed by saturated NaCl (50 mL), then dried ($MgSO_4$), and concentrated to give a yellow solid, purified by chromatography (2:1 hexanes:AcOEt) to give 2-chloro-*N*-cyanomethyl-6-nitroaniline as a yellow solid (0.54 g, 25% yield): mp 82−83 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (dd, J = 8.4, 1.2 Hz, 1 H), 7.56 (dd, J = 8.1, 1.2 Hz, 1 H), 6.97 (t, J = 8.1 Hz, 1 H), 6.89 (bt, J = 7.2 Hz, 1 H), 4.38 (d, J = 7.2 Hz, 2 H).

2-Chloro-*N*-cyanomethyl-6-nitroaniline (0.54 g, 2.6 mmol), AcOH (10 mL), and 50% H_2SO_4 (25 mL) were heated at 100 °C for 2 h. After cooling, the mixture was added to ice (100 mL), filtered, washed with ice−water, and dried to give **9** as a yellow solid (0.47 g): mp 134−137 °C. Additional product was obtained by extracting the filtrate with AcOEt (2 × 50 mL) and washing the extracts with water (4 × 100 mL) and then saturated NaCl (50 mL). The extracts were dried ($MgSO_4$) and concentrated under high vacuum to remove the remaining AcOH to give 0.14 g of product (∼100% total yield): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.93 (bs, 1 H), 7.87 (dd, J = 8.4, 1.2 Hz, 1 H), 7.56 (dd, J = 7.8, 1.2 Hz, 1 H), 7.00 (bt, J = 5.7 Hz, 1 H), 6.89 (t, J = 8.4 Hz, 1 H), 4.02 (d, J = 5.7 Hz, 2 H).

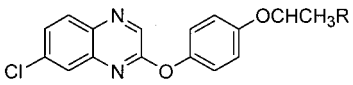
2,5-Dichloroquinoxaline (10). The precursory intermediate **9** (0.61 g, 2.6 mmol), 10% Pd/C (0.03 g) in CH_3OH (50 mL), was shaken with H_2 (30 psi) in a Parr apparatus for 6 h. The mixture was then filtered and concentrated, to which 1 N NaOH (6 mL) and 3% H_2O_2 (6 mL) were added and heated for 1 h. After cooling, the solution was acidified to pH 5 with HCl, filtered, washed with ice−water, and dried to give 5-chloro-2-quinoxalinol as a light tan solid (0.31 g, 65% yield): mp ∼295 °C (dec); ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.59 (bs, 1 H), 8.22 (s, 1 H), 7.50 (t, J = 8.1 Hz, 1 H), 7.41 (dd, J = 7.8, 0.9 Hz, 1 H), 7.24 (dd, J = 8.1, 0.9 Hz, 1 H).

5-Chloro-2-quinoxalinol (0.31 g, 1.7 mmol) and $POCl_3$ (2.0 mL, 3.3 g, 21 mmol) were refluxed for 1 h and then concentrated, and water (25 mL) and $NaHCO_3$ were added until pH 7. The mixture was then extracted with AcOEt (4 × 25 mL), and the extracts were washed with saturated NaCl (25 mL), dried ($MgSO_4$), and evaporated to dryness. After the residue was dissolved in $CHCl_3$, the solution was filtered through silica gel and the filtrate concentrated to give **10** as a pale yellow solid (0.24 g, 70% yield): mp 131−134 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.88 (s, 1 H), 7.97 (dd, J = 8.7, 0.9 Hz, 1 H), 7.89 (dd, J = 7.5, 0.9 Hz, 1 H), 7.74 (t, J = 8.1 Hz, 1 H).

***N*-(3-Chloro-2-nitrophenyl)glycine (12).** 3-Chloro-2-nitroaniline[9] (5.12 g, 29.7 mmol) was heated with bromoacetic acid (4.25 g, 29.7 mmol) at 125 °C for 1 h with air passing over the mixture to remove the HBr. Methanol was then added and the mixture heated until all the solid dissolved. Dilute NH_4OH was added in portions to maintain the pH > 8 while the mixture was concentrated by heating. The cooled mixture was filtered and then washed with dilute NH_4OH, and the filtrate was washed with ether (50 mL). The aqueous layer was then concentrated to a small volume and acidified while hot to pH 3 with concentrated HCl. After cooling, the product was collected, washed with ice−water, and dried to give **12** as a yellow-brown solid: mp 195−197 °C (dec). Additional product was obtained by extracting the filtrate with AcOEt (2 × 25 mL) and washing the extracts with saturated NaCl (25 mL). After the extract was dried ($MgSO_4$), it was concentrated to give a yellow solid (total 0.42 g, 6% total yield): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.83 (bs, 1 H), 7.30 (t, J = 8.4 Hz, 1 H), 6.82 (d, J = 7.8 Hz, 1 H), 6.73 (d, J = 8.7 Hz, 1 H), 6.54 (bt, J = 6.0 Hz, 1 H), 3.92 (d, J = 6.0 Hz, 2 H).

2,8-Dichloroquinoxaline (13): prepared as described above for **10** from **12** (0.27 g, 1.2 mmol), using 10% Pd/C (0.01 g) and CH_3OH (50 mL) followed by 1 N NaOH (3 mL) and 3% H_2O_2 (3 mL) to give 8-chloro-2-quinoxalinol as a light tan solid

Table 5. Some Carboxylic Acid Derivatives of 2-{4-[(7-Chloro-2-quinoxalinyl)oxy]phenoxy}propionic Acid (XK469) against Murine Tumors



compd no.[a]	R	tumor	no. of injections	total dosage, mg/kg	% body wt. loss	*T*/*C*, %	$\log_{10}$ kill[b]	activity rating
43	$CONH_2$	Panc-03	13	1320	−3.6	7.3	1.9	++
44	$CONHNH_2$	Panc-03	4	800	−6.5	27	0.75	+
45a	$CONHCH_3$	Panc-03	10	2300	−14.5	4	4.2**	++++ 1/5 cures
			4	480	−9.3	39	1.2	+
45b	$CON(CH_3)_2$	Panc-03	9	1530	- 3. 8	16	2. 2	+++
45c	CONHOH	*c*						
48	CN	*c*						
49	CHN_4[d]	Panc-03	7	477	+8.7	>100	none	−

[a] These agents were all water-insoluble and were injected orally (po) beginning 3 days after tumor implantation. Two to three dosages were tested, with the highest nontoxic dosage shown. A dose-escalation schedule was administered as per ref 27. Treatment was stopped when weight loss was substantial (as with 45a) or the drug supply was exhausted. [b] The log kill values were based on tumors that grew (cures excluded from the calculation). The cures represent >4.0 log kill for these tumors. [c] Inactive in vitro, not tested in vivo. [d] Tetrazole.

(0.12 g, 57% yield); mp 190−195 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.00 (bs, 1 H), 8.18 (s, 1 H), 7.30 (dd, J = 8.1, 0.9 Hz, 1 H), 7.66 (dd, J = 7.8, 0.9 Hz, 1 H), 7.27 (t, J = 8.1 Hz, 1 H).

8-Chloro-2-quinoxalinol (0.12 g, 0.66 mmol) on treatment with $POCl_3$ (1.0 mL, 1.6 g, 10 mmol) gave **13** as a white solid (0.12 g, 92% yield): mp 120−122 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.83 (s, 1 H), 8.05 (dd, J = 8.4, 0.9 Hz, 1 H), 7.90 (dd, J = 7.5, 0.9 Hz, 1 H), 7.71 (t, J = 8.1 Hz, 1 H).

2,7-Dichloroquinoxaline[10a] **(16a):** ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.78 (s, 1 H), 8.07 (d, J = 9.0 Hz, 1 H), 8.03 (d, J = 2.1 Hz, 1 H), 7.75 (dd, J = 9.0, 2.1 Hz, 1 H).

2-Chloro-7-methylquinoxaline[10b] **(16b):** (reductive cyclization of **16b** performed using H_2, 10% Pd/C, CH_3OH instead of tin, HCl, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.71 (s, 1 H), 8.00 (d, J = 8.4 Hz, 1 H), 7.79 (s, 1 H), 7.28 (dd, J = 8.7, 1.8 Hz, 1 H), 2.60 (s, 3 H).

2-Chloro-7-methoxyquinoxaline[10a] **(16c):** (reductive cyclization of **16c** performed using H_2, 10% Pd/C, CH_3OH instead of tin, HCl, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.62 (s, 1 H), 7.96 (d, J = 9.3 Hz, 1 H), 7.40 (dd, J = 9.3, 3.0 Hz, 1 H), 7.28 (d, J = 2.7 Hz, 1 H), 3.95 (s, 3 H).

***N*-(4-Iodo-2-nitrophenyl)glycine (15d):** prepared as described above for **12** from **14a** (34.87 g, 132.1 mmol) and bromoacetic acid (18.92 g, 132.1 mmol) to give **15d** as a brown-red solid (2.90 g, 7% yield); mp 189−190 °C (dec); ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.07 (bs, 1 H), 8.37 (bt, J = 5.6 Hz, 1 H), 8.29 (d, J = 2.4 Hz, 1 H), 7.74 (dd, J = 9.2, 1.6 Hz, 1 H), 6.76 (t, J = 10.0 Hz, 1 H), 4.14 (d, J = 5.6 Hz, 2 H).

2-Chloro-7-iodoquinoxaline (16d). To a refluxing solution of **15d** (2.29 g, 7.11 mmol), concentrated HCl (1.8 mL), and CH_3OH (75 mL) was added iron powder (2.08 g, 35.6 mmol) in portions over 2 h, and the mixture was refluxed for an additional 2 h. The mixture was filtered immediately and washed with hot CH_3OH. To the filtrate, 1 N NaOH (50 mL) and 3% H_2O_2 (20 mL) were added, and the mixture was heated for 1 h before filtering hot and washing with dilute NaOH and CH_3OH. The mixture was then refiltered through Celite and concentrated to ∼100 mL before acidifying pH 5 with concentrated HCl. After cooling, the mixture was filtered, washed with ice−water, and dried to give crude 7-iodo-2-quinoxalinol as a brown solid (1.67 g, 86% crude yield). A sample was heated with CH_3OH, the insoluble material was removed, and the filtrate was concentrated to give a brown solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.40 (bs, 1 H), 8.15 (s, 1 H), 7.62 (d, J = 1.6 Hz, 1 H), 7.58 (d, J = 9.2 Hz, 1 H), 7.50 (d, J = 8.4 Hz, 1 H).

Crude 7-iodo-2-quinoxalinol (1.67 g, 6.1 mmol) and $POCl_3$ (2.8 mL, 4.6 g, 30 mmol) (as described above for **10**) gave **16d** as a yellow solid (0.64 g, 36% yield): mp 148−150 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.77 (s, 1 H), 8.43 (d, J = 1.8 Hz, 1 H), 8.03 (dd, J = 8.4, 1.8 Hz, 1 H), 7.81 (d, J = 8.7 Hz, 1 H); MS (EI) m/z (%) 290 (M^+, 100), 255 (14), 163 (42), 128 (22), 101 (24), 75 (27), 50 (18).

2-Chloro-6-nitroquinoxaline[11] **(18b):** (PCl_5 was not required for conversion of 2-OH to 2-Cl); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.02 (d, J = 2.4 Hz, 1 H), 8.94 (s, 1 H), 8.59 (dd, J = 9.2, 2.8 Hz, 1 H), 8.19 (d, J = 9.2 Hz, 1 H).

2-Chloro-7-nitroquinoxaline[11] **(18d):** (PCl_5 was not required for conversion of 2-OH to 2-Cl); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.94 (s, 1 H), 8.92 (d, J = 2.4 Hz, 1 H), 8.56 (dd, J = 9.0, 2.4 Hz, 1 H), 8.30 (d, J = 9.0 Hz, 1 H).

7-Azido-2-chloroquinoxaline (21). A mixture of **20**[12] (0.16 g, 1.0 mmol) and HCl (3 mL) was stirred together overnight before cooling to 0 °C. A cold solution of $NaNO_2$ (0.08 g, 1.2 mmol) in water (2 mL) was added dropwise, and the mixture was stirred an additional 1 h. NaN_3 (0.07 g, 1.1 mmol) in water (2 mL) was added, and the mixture was allowed to warm to room temperature. The solid was dissolved in 1 N NaOH; the solution was filtered, acidified to pH 5 with HCl, and cooled; and the product was collected, washed with ice−water, and dried to give 7-azido-2-quinoxalinol as a light brown solid (0.13 g, 70% yield): mp >300 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.34 (bs, 1 H), 8.04 (s, 1 H), 7.73 (d, J = 8.4 Hz, 1 H), 6.99 (d, J = 7.8 Hz, 1 H), 6.87 (s, 1 H); IR (Nujol) 2130 (N_3) cm^{-1}.

7-Azido-2-quinoxalinol (0.12 g, 0.64 mmol) was treated with $POCl_3$ (0.60 mL, 0.99 g, 6.4 mmol) (as described for **10**) to give **21** as a light brown solid (0.09 g, 69% yield): mp 144−147 °C (dec); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.70 (s, 1 H), 8.07 (d, J = 9.0 Hz, 1 H), 7.61 (d, J = 2.1 Hz, 1 H), 7.41 (dd, J = 9.0, 2.4 Hz, 1 H); IR (Nujol) 2140 (N_3) cm^{-1}.

7-Chloro-8-methoxy-2-quinoxalinol (23a): To a mixture of **22a**[13] (2.03 g, 10.0 mmol), cyanoacetic acid (1.72 g, 20.0 mmol), and toluene (100 mL) was added PCl_5 (4.39 g, 20.0 mmol) in small portions, and the mixture was refluxed while passing air over the mixture. After 2 h, additional cyanoacetic acid (0.21 g, 2.5 mmol) and PCl_5 (0.55 g, 2.5 mmol) were added, and the refluxing continued until the yellow color disappeared. After concentration, the solid was dissolved in AcOEt (200 mL) and washed with saturated NaCl (50 mL), a mixture of saturated NaCl (50 mL), and saturated $NaHCO_3$ (25 mL) followed by saturated NaCl (50 mL). The dried solution ($MgSO_4$) was then concentrated and recrystallized from EtOH−heptane to give α-cyano-3-chloro-2-methoxy-6-nitroacetanilide as off-white crystals (2.55 g, 94% yield): mp 170−172 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37 (bs, 1 H), 7.77 (d, J = 9.0 Hz, 1 H), 7.46 (d, J = 9.3 Hz, 1 H), 3.99 (s, 3 H), 3.63 (s, 2 H).

To this intermediate (2.55 g, 9.45 mmol), dissolved in pyridine (10 mL), was added 1 N NaOH (9.5 mL, 9.5 mmol), and the mixture was stirred overnight. Water (75 mL) was added, and the mixture was filtered and washed with water. The filtrate was acidified to pH 6 with concentrated HCl. After cooling, the product was collected, washed with ice−water, and dried to give 6-chloro-2-cyano-5-methoxy-3-quinoxalinol-1-oxide as a yellow solid (2.38 g, ∼100% yield): mp ∼280 °C (dec);

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.81 (bs, 1 H), 7.86 (d, J = 9.3 Hz, 1 H), 7.47 (d, J = 9.3 Hz, 1 H), 3.83 (s, 3 H).

A mixture of this second intermediate (1.06 g, 4.21 mmol), sodium dithionite (2.59 g, 12.6 mmol), EtOH (25 mL), and water (50 mL) was refluxed for 2 h. After cooling, concentrated HCl was added to pH 1 and the mixture was concentrated prior to the addition of NaOH to pH > 12. The hot solution was filtered, the residue washed with 1 N NaOH, and the filtrate acidified to pH 6 with concentrated HCl. After cooling, the solid was collected, washed with ice−water, and dried to give **23a** as a brown-yellow solid (0.70 g, 79% yield): mp ∼225 °C (dec); ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.29 (bs, 1 H), 8.15 (s, 1 H), 7.50 (d, J = 9.0 Hz, 1 H), 7.34 (d, J = 8.7 Hz, 1 H), 3.81 (s, 3 H).

2,7-Dichloro-8-methoxyquinoxaline (24a). Compound **23a** (0.69 g, 3.3 mmol) was reacted with $POCl_3$ (1.6 mL, 2.6 g, 17 mmol) (as described above for **10**) to give **24a** as an off-white solid (0.55 g, 73% yield): mp 136−138 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.76 (s, 1 H), 7.83 (d, J = 9.0 Hz, 1 H), 7.76 (d, J = 9.0 Hz, 1 H), 4.21 (s, 3 H).

8-Chloro-7-methoxy-2-quinoxalinol (23b). The method described above for the preparation of **23a** was applied. Thus **22b**[14] (2.06 g, 10.2 mmol), cyanoacetic acid (1.75 g, 20.4 mmol), toluene (100 mL), and PCl_5 (4.47 g, 20.4 mmol) gave α-cyano-3-chloro-2-methoxy-6-nitroacetanilide as off-white crystals following recrystallization from EtOH−heptane (2.48 g, 91% yield): mp 226−228 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.63 (bs, 1 H), 8.04 (d, J = 9.3 Hz, 1 H), 7.27 (d, J = 9.3 Hz, 1 H), 3.97 (s, 3 H), 3.96 (s, 2 H).

This intermediate derivative (2.48 g, 9.20 mmol) was dissolved in pyridine (30 mL), and treated with 1 N NaOH (9.2 mL, 9.2 mmol) to give a mixture of 6-chloro-2-cyano-5-methoxy-3-quinoxalinol-1-oxide and 6-chloro-2-cyano-5-methoxy-3-quinoxalinol as a yellow solid (2.32 g).

The mixture (0.25 g) was treated with sodium dithionite (0.51 g, 2.5 mmol), EtOH (5 mL), and water (10 mL) to give **23b** as a brown solid (0.11 g): mp ∼220 °C (dec); ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.83 (bs, 1 H), 8.00 (s, 1 H), 7.72 (d, J = 9.0 Hz, 1 H), 7.15 (d, J = 9.0 Hz, 1 H), 3.93 (s, 3 H).

2,7-Dichloro-8-methoxyquinoxaline (24b). A mixture of crude **23b** (1.4 g, ∼6.8 mmol) and $POCl_3$ (3.0 mL, 4.9 g, 32 mmol) (as described above for **10**) gave **24b** as a pale yellow solid (0.69 g): mp 164−167 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.68 (s, 1 H), 8.06 (d, J = 9.3 Hz, 1 H), 7.58 (d, J = 9.3 Hz, 1 H), 4.12 (s, 1 H).

General Preparation of Quinoxaline Esters (Method A). A mixture of the 2-chloroquinoxaline, the phenol, anhydrous K_2CO_3, and CH_3CN was refluxed until the reaction was complete. The mixture was filtered hot, the residue washed with hot acetone, and the filtrate evaporated to dryness. The residue was dissolved in CH_2Cl_2, filtered through silica gel, and washed with ether. The filtrate was shaken with saturated NaCl, containing a small amount of 1 N NaOH, followed by saturated NaCl. The dried solution ($MgSO_4$) was evaporated and the crude residue purified by flash column chromatography. If the product was a solid, it was recrystallized; if it was an oil, it was hydrolyzed.

General Preparation of Quinoxaline Carboxylic Acids. To a solution of the ester dissolved in THF was added 0.1 N base in portions, and the mixture was stirred overnight at room temperature. After the mixture was concentrated and filtered to remove insoluble material, the filtrate was cooled and acidified to pH 3−4 with 0.25 N HCl. After recooling, the solid was collected, washed with ice−water, and recrystallized, if required.

2-{4-[(5-Chloro-2-quinoxalinyl)oxy]phenoxy}propionic Acid (26a). The methyl ester of **26a** was prepared from **10** (0.25 g, 1.3 mmol), **25** (0.27 g, 1.4 mmol), anhydrous K_2CO_3 (0.24 g, 1.7 mmol), and CH_3CN (10 mL) for 6 h (method A). Pure material (0.31 g, 69% yield) was obtained after chromatography (4:1 hexanes:AcOEt) and recrystallization from EtOH−heptane to give white crystals: mp 111−112 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.76 (s, 1 H), 7.73−7.65 (m, 2 H), 7.56 (t, J = 7.8 Hz, 1 H), 7.23−7.16 (m, 2 H), 6.99−6.91 (m, 2 H), 4.79 (q, J = 6.9 Hz, 1 H), 3.79 (s, 3 H), 1.65 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 157.5, 155.1, 146.6, 141.2, 139.4, 136.2, 132.9, 130.1, 127.5, 126.7, 122.4, 116.1, 73.1, 52.3, 18.6; IR (KBr) 1740 (C=O) cm^{-1}; MS (EI) *m*/*z* (%) 358 (M$^+$, 27), 299 (19), 243 (12), 163 (10), 149 (16), 137 (18), 123 (9), 121 (9), 109 (9), 107 (6), 97 (9), 95 (15), 93 (8), 85 (7), 83 (12), 81 (51), 73 (9), 71 (13), 69 (100), 67 (11), 60 (7). Anal. ($C_{18}H_{15}N_2ClO_4$) C, H, N.

The methyl ester of **26a** (0.26 g, 0.72 mmol), dissolved in THF (10 mL), was hydrolyzed with 0.1 N NaOH (14.5 mL, 1.45 mmol) to give **26a** (0.24 g, 96% yield) as off-white crystals after recrystallization from EtOH−water: mp 144−145 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.08 (bs, 1 H), 8.90 (s, 1 H), 7.81 (dt, J = 4.5, 0.9 Hz, 1 H), 7.66 (d, J = 4.2 Hz, 2 H), 7.27−7.19 (m, 2 H), 6.97−6.89 (m, 2 H), 4.83 (q, J = 6.6 Hz, 1 H), 1.50 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 173.5, 157.9, 155.4, 146.3, 141.0, 140.6, 135.8, 132.4, 131.1, 127.9, 126.9, 122.9, 116.1, 72.4, 18.7; IR (KBr) 3400 (OH), 1685 (C=O) cm^{-1}; MS (EI) *m*/*z* (%) 344 (M$^+$, 100), 299 (16), 285 (12), 272 (31), 255 (7), 243 (82), 215 (6), 208 (8), 193 (12), 181 (6), 163 (61), 152 (5), 136 (26), 127 (22), 124 (8), 116 (10), 109 (18), 100 (40), 85 (11), 81 (17), 75 (13), 69 (11), 63 (13), 57 (14), 55 (24), 45 (26), 43 (24), 41 (17), 39 (15); HRMS (EI) *m*/*z* 344.0558 (M$^+$, calcd for $C_{17}H_{13}N_2ClO_4$ 344.0564). Anal. ($C_{17}H_{13}N_2ClO_4$) C, H, N.

2-{4-[(8-Chloro-2-quinoxalinyl)oxy]phenoxy}propionic Acid (26b). The methyl ester of **26b** was prepared from **13** (0.16 g, 0.80 mmol), **25** (0.17 g, 0.87 mmol), anhydrous K_2CO_3 (0.15 g, 1.1 mmol), and CH_3CN (5 mL) for 6 h (method A). Pure material (0.19 g, 66% yield) was obtained after chromatography (4:1 hexanes:AcOEt) and recrystallization from EtOH−hexanes to give pale yellow crystals: mp 86−88 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.69 (s, 1 H), 7.98 (dd, J = 8.4, 1.2 Hz, 1 H), 7.77 (dd, J = 7.8, 0.9 Hz, 1 H), 7.52 (dd, J = 8.1, 7.8 Hz, 1 H), 7.39−7.32 (m, 2 H), 7.01−6.93 (m, 2 H), 4.80 (q, J = 6.6 Hz, 1 H), 3.79 (s, 3 H), 1.66 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 156.9, 155.0, 146.9, 140.3, 139.7, 137.0, 131.2, 130.3, 127.8, 126.9, 122.1, 116.1, 73.3, 52.2, 18.5; IR (KBr) 1740 (C=O) cm^{-1}; MS (EI) *m*/*z* (%) 358 (M$^+$, 100), 299 (51), 271 (20), 255 (11), 243 (50), 215 (4), 208 (3), 192 (6), 179 (3), 163 (36), 149 (6), 136 (17), 127 (11), 110 (6), 100 (13), 91 (5), 75 (7), 63 (7), 59 (12), 55 (7). Anal. ($C_{18}H_{15}N_2ClO_4$) C, H, N.

The methyl ester of **26b** (0.17 g, 0.47 mmol), dissolved in THF (5 mL), was hydrolyzed with 0.1 N NaOH (9.5 mL, 0.95 mmol) to give **26b** (0.13 g, 81% yield) as off-white-yellow crystals after recrystallization from EtOH−water: mp 133−136 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 13 (bs, 1 H), 8.77 (s, 1 H), 7.93 (dd, J = 8.1, 0.9 Hz, 1 H), 7.82 (dd, J = 7.5, 0.9 Hz, 1 H), 7.57 (t, J = 8.1 Hz, 1 H), 7.35−7.27 (m, 2 H), 6.99−6.91 (m, 2 H), 4.82 (q, J = 6.6 Hz, 1 H), 1.50 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 173.5, 157.3, 155.3, 146.4, 140.9, 140.2, 136.5, 130.8, 130.2, 128.3, 127.8, 122.6, 116.0, 72.6, 18.7; IR (KBr) 3495 (OH), 1725 (C=O) cm^{-1}; MS (EI) *m*/*z* (%) 344 (M$^+$, 100), 299 (17), 272 (42), 255 (12), 243 (92), 236 (10), 215 (7), 208 (8), 192 (7), 179 (6), 163 (53), 152 (9), 136 (27), 127 (21), 124 (12), 110 (24), 100 (22), 97 (37), 85 (22), 83 (45), 81 (31), 73 (29), 71 (34), 69 (53), 67 (23), 60 (20), 57 (59), 55 (69); HRMS (EI) *m*/*z* 344.0563 (M$^+$, calcd for $C_{17}H_{13}N_2ClO_4$ 344.0564). Anal. ($C_{18}H_{15}N_2ClO_4$) C, N; H: calcd, 3.80; found, 4.45.

2-{4-[(7-Methyl-2-quinoxalinyl)oxy]phenoxy}propionic Acid (26c). The methyl ester of **26c** was prepared from **16b** (0.89 g, 5.0 mmol), **25** (1.08 g, 5.5 mmol), anhydrous K_2CO_3 (0.95 g, 6.9 mmol), and CH_3CN (25 mL) for 24 h (method A). Pure material (1.38 g, 82% yield) was obtained after chromatography (4:1 hexanes:AcOEt) and recrystallization from EtOH to give light yellow crystals: mp 138−140 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.59 (s, 1 H), 7.93 (d, J = 8.4 Hz, 1 H), 7.55 (s, 1 H), 7.43 (dd, J = 8.4, 1.5 Hz, 1 H), 7.23−7.15 (m, 2 H), 7.00−6.92 (m, 2 H), 4.79 (q, J = 6.9 Hz, 1 H), 3.80 (s, 3 H), 2.51 (s, 3 H), 1.66 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 157.2, 154.9, 147.1, 140.8, 140.0, 138.0, 129.3, 128.4, 126.8, 122.4, 116.1, 73.2, 52.2, 21.6, 18.6; IR (KBr) 1765 (C=O)

cm^{-1}; MS (EI) *m/z* (%) 338 (M^+, 100), 310 (2), 279 (53), 251 (19), 235 (13), 223 (96), 195 (10), 143 (95), 116 (43), 110 (11), 105 (10), 89 (60), 87 (10), 77 (19), 63 (24), 59 (36), 55 (17), 51 (12), 43 (14). Anal. ($C_{19}H_{18}N_2O_4$) C, H, N.

The methyl ester of **26c** (0.55 g, 1.6 mmol), dissolved in THF (15 mL), was hydrolyzed with 0.1 N NaOH (32 mL, 3.2 mmol) to give **26c** (0.50 g, 94% yield) as off-white crystals after recrystallization from EtOH−water: mp 178−180 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.07 (bs, 1 H), 8.72 (s, 1 H), 7.91 (d, J = 8.4 Hz, 1 H), 7.51 (s, 1 H), 7.49 (dd, J = 8.4, 1.5 Hz, 1 H), 7.25−7.16 (m, 2 H), 6.98−6.89 (m, 2 H), 4.83 (q, J = 6.6 Hz, 1 H), 2.44 (s, 3 H), 1.50 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 173.4, 157.6, 155.3, 146.7, 141.3, 139.8, 138.7, 137.9, 129.8, 128.6, 122.9, 116.2, 72.6, 21.5, 18.7; IR (KBr) 3495 (OH), 1730 (C=O) cm^{-1}; MS (EI) *m/z* (%) 324 (M^+, 99), 279 (13), 265 (10), 252 (21), 235 (8), 223 (100), 143 (68), 116 (23), 110 (9), 89 (27), 63 (9); HRMS (EI) *m/z* 324.1110 (M^+, calcd for $C_{18}H_{16}N_2O_4$ 324.1110). Anal. ($C_{18}H_{16}N_2O_4$) C, H, N.

2-{4-[(7-Methoxy-2-quinoxalinyl)oxy]phenoxy}propionic Acid (26d). The methyl ester of **26d** was prepared from **16c** (0.97 g, 5.0 mmol), **25** (1.08 g, 5.5 mmol), anhydrous K_2CO_3 (0.95 g, 6.9 mmol), and CH_3CN (25 mL) for 24 h (method A). Pure material (1.48 g, 84% yield) was obtained after chromatography (4:1 hexanes:AcOEt) and recrystallization from EtOH to give peach crystals: mp 107−109 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (s, 1 H), 7.91 (d, J = 9.6 Hz, 1 H), 7.24 (dd, J = 9.3, 2.7 Hz, 1 H), 7.23−7.16 (m, 2 H), 7.08 (d, J = 2.7 Hz, 1 H), 6.99−6.92 (m, 2 H), 4.79 (q, J = 6.6 Hz, 1 H), 3.89 (s, 3 H), 3.80 (s, 3 H), 1.66 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 161.2, 157.6, 154.9, 147.1, 141.8, 135.8, 135.4, 129.7, 122.4, 119.7, 116.1, 106.2, 73.1, 55.6, 52.2, 18.5; IR (KBr) 1755 (C=O) cm^{-1}; MS (EI) *m/z* (%) 354 (M^+, 100), 326 (4), 295 (36), 267 (8), 251 (10), 239 (48), 225 (10), 208 (4), 159 (45), 148 (8), 117 (14), 110 (4), 102 (5), 89 (5), 77 (8), 59 (7). Anal. ($C_{19}H_{18}N_2O_5$) C, H, N.

The methyl ester of **26d** (0.50 g, 1.4 mmol), dissolved in THF (15 mL), was hydrolyzed with 0.1 N NaOH (28 mL, 2.8 mmol) to give **26d** (0.49 g, 97% yield) as off-white crystals after recrystallization from EtOH−water: mp ∼110−140 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.07 (bs, 1 H), 8.61 (s, 1 H), 7.90 (d, J = 9.3 Hz, 1 H), 7.25 (dd, J = 9.3, 2.7 Hz, 1 H), 7.23−7.16 (m, 2 H), 7.07 (d, J = 2.7 Hz, 1 H), 6.98−6.89 (m, 2 H), 4.83 (q, J = 6.6 Hz, 1 H), 3.83 (s, 3 H), 1.50 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 173.4, 161.4, 158.0, 155.3, 146.7, 141.7, 136.5, 135.2, 130.0, 123.0, 119.9, 116.2, 106.7, 72.5, 56.3, 18.7; IR (KBr) 3505 (OH), 1745 (C=O) cm^{-1}; MS (EI) *m/z* (%) 340 (M^+, 90), 312 (8), 295 (10), 281 (13), 268 (21), 251 (9), 239 (85), 225 (22), 211 (6), 208 (7), 159 (100), 148 (9), 144 (12), 117 (58), 109 (22), 102 (22), 91 (24), 89 (29), 81 (26), 77 (50), 75 (19), 65 (26), 63 (33), 55 (32), 45 (47); HRMS (EI) *m/z* 340.1060, (M^+, calcd for $C_{18}H_{16}N_2O_5$ 340.1059). Anal. ($C_{18}H_{16}N_2O_5 \cdot H_2O$) C, H, N.

2-{4-[(7-Iodo-2-quinoxalinyl)oxy]phenoxy}propionic Acid (26e). The methyl ester of **26e** was prepared from **16d** (0.29 g, 1.0 mmol), **25** (0.21 g, 1.1 mmol), anhydrous K_2CO_3 (0.18 g, 1.3 mmol), and CH_3CN (10 mL) for 4 h (method A). Pure material (0.37 g, 82% yield) was obtained after chromatography (4:1 hexanes:AcOEt) and recrystallization from EtOH to give pale yellow crystals: mp 134−135 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (s, 1 H), 8.15 (d, J = 1.6 Hz, 1 H), 7.83 (dd, J = 8.8, 1.6 Hz, 1 H), 7.72 (d, J = 8.8 Hz, 1 H), 7.19−7.13 (m, 2 H), 6.97−6.91 (m, 2 H), 4.78 (q, J = 6.8 Hz, 1 H), 3.79 (s, 3 H), 1.65 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 157.5, 155.3, 146.7, 141.0, 140.0, 138.9, 136.8, 136.5, 130.3, 122.7, 116.3, 96.6, 73.3, 52.7, 18.9; IR (KBr) 1750 (C=O) cm^{-1}; MS (EI) *m/z* (%) 450 (M^+, 100), 404 (4), 402 (4), 391 (48), 364 (8), 347 (6), 335 (28), 255 (19), 228 (7), 220 (5), 208 (8), 128 (23), 101 (23), 81 (6), 75 (7), 63 (7), 59 (11), 55 (6), 50 (8), 45 (5). Anal. ($C_{18}H_{15}N_2IO_4$) C, H, N.

The methyl ester of **26e** (0.23 g, 0.51 mmol), dissolved in THF (10 mL), was hydrolyzed with 0.1 N NaOH (10.2 mL, 1.02 mmol) to give **26e** (0.21 g, 95% yield) as cream crystals after recrystallization from EtOH−water: mp 164−166 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.00 (bs, 1 H), 8.81 (s, 1 H), 8.07 (d, J = 1.6 Hz, 1 H), 7.91 (dd, J = 8.0, 1.6 Hz, 1 H), 7.76 (d, J = 8.8 Hz, 1 H), 7.22 (d, J = 8.8 Hz, 2 H), 6.94 (d, J = 8.8 Hz, 2 H), 4.83 (q, J = 6.8 Hz, 1 H), 1.52 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.8, 157.9, 155.6, 146.5, 141.1, 140.9, 138.8, 136.8, 136.2, 130.8, 123.2, 116.3, 98.1, 72.5, 19.0; IR (KBr) 3430 (OH), 1720 (C=O) cm^{-1}; MS (EI) *m/z* (%) 436 (M^+, 100), 391 (17), 377 (8), 364 (28), 347 (5), 335 (53), 255 (28), 228 (10), 208 (13), 182 (6), 128 (35), 110 (9), 101 (36), 75 (9), 63 (9), 50 (11); HRMS (EI) *m/z* 435.9928 (calcd for $C_{17}H_{13}N_2IO_4$ 435.9920). Anal. ($C_{17}H_{13}N_2IO_4$) C, H, N.

2-{4-[(6-Nitro-2-quinoxalinyl)oxy]phenoxy}propionic Acid (26f). The methyl ester of **26f** was prepared from **18b** (0.42 g, 2.0 mmol), **25** (0.43 g, 2.2 mmol), anhydrous K_2CO_3 (0.38 g, 2.8 mmol), and CH_3CN (10 mL) for 2 h (method A). Pure material (0.69 g, 93% yield) was obtained after chromatography (3:1 hexanes:AcOEt) and recrystallization from EtOH to give light yellow crystals: mp 124−125 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (d, J = 2.4 Hz, 1 H), 8.80 (s, 1 H), 8.42 (dd, J = 9.2, 2.4 Hz, 1 H), 7.83 (d, J = 9.6 Hz, 1 H), 7.22−7.16 (m, 2 H), 6.99−6.93 (m, 2 H), 4.79 (q, J = 6.4 Hz, 1 H), 3.80 (s, 3 H), 1.66 (d, J = 7.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 158.9, 155.6, 146.3, 143.9, 142.2, 138.4, 130.2, 129.1, 125.5, 124.2, 122.7, 116.3, 73.3, 52.7, 18.9; IR (KBr) 1735 (C=O) cm^{-1}; MS (EI) *m/z* (%) 369 (M^+, 100), 339 (19), 310 (94), 283 (15), 266 (6), 254 (25), 236 (7), 225 (9), 220 (13), 208 (12), 174 (8), 144 (10), 132 (5), 128 (23), 117 (6), 110 (6), 101 (20), 91 (9), 75 (6), 69 (5), 63 (6), 59 (11), 57 (7), 55 (7), 50 (7). Anal. ($C_{18}H_{15}N_3O_6$) C, H, N.

The methyl ester of **26f** (0.33 g, 0.89 mmol), dissolved in THF (15 mL), was hydrolyzed with 0.1 N K_2CO_3 (22.5 mL, 2.25 mmol) to give **26f** (0.28 g, 88% yield) as a yellow solid: mp 167−169 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.01 (s, 1 H), 8.80 (d, J = 3.6 Hz, 1 H), 8.39 (dd, J = 8.8, 2.4 Hz, 1 H), 7.88 (d, J = 10.0 Hz, 1 H), 7.29−7.24 (m, 2 H), 6.99−6.93 (m, 2 H), 4.85 (q, J = 6.4 Hz, 1 H), 1.52 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.8, 159.4, 155.9, 146.1, 143.8, 143.5, 138.1, 129.4, 125.0, 124.6, 123.2, 116.3, 72.5, 19.0; IR (KBr) 3400 (OH), 1725 (C=O) cm^{-1}; MS (EI) *m/z* (%) 355 (M^+, 100), 339 (5), 325 (10), 310 (38), 296 (8), 283 (48), 266 (5), 254 (56), 236 (7), 225 (16), 220 (11), 208 (22), 192 (5), 182 (9), 174 (16), 144 (9), 128 (42), 109 (15), 101 (37), 91 (10), 83 (10), 81 (10), 75 (12), 69 (14), 65 (11), 63 (13), 57 (17), 55 (18), 50 (14); HRMS (EI) *m/z* 355.0804 (calcd for $C_{17}H_{13}N_3O_6$ 355.0804). Anal. ($C_{17}H_{13}N_3O_6$) C, H, N.

2-{4-[(7-Nitro-2-quinoxalinyl)oxy]phenoxy}propionic Acid (26g). The methyl ester of **26g** was prepared from **18d** (1.05 g, 5.0 mmol), **25** (1.08 g, 5.5 mmol), anhydrous K_2CO_3 (0.95 g, 6.9 mmol), and CH_3CN (25 mL) for 2 h (method A). Pure material (1.68 g, 91% yield) was obtained after chromatography (3:1 hexanes:AcOEt) to give a yellow liquid, which solidified very slowly: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.81 (s, 1 H), 8.62 (d, J = 2.4 Hz, 1 H), 8.36 (dd, J = 9.3, 2.4 Hz, 1 H), 8.18 (d, J = 9.3 Hz, 1 H), 7.25−7.16 (m, 2 H), 7.02−6.93 (m, 2 H), 4.80 (q, J = 6.9 Hz, 1 H), 3.81 (s, 3 H), 1.66 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 158.2, 155.4, 148.3, 146.2, 142.6, 142.0, 139.4, 130.3, 123.6, 122.4, 120.8, 116.2, 73.2, 52.3, 18.5; IR (film) 1755 (C=O) cm^{-1}; MS (EI) *m/z* (%) 369 (M^+, 80), 310 (100), 283 (16), 266 (7), 254 (25), 236 (8), 225 (7), 220 (13), 208 (13), 182 (5), 174 (9), 132 (4), 128 (27), 116 (4), 109 (5), 101 (18), 91 (8), 75 (8), 63 (7), 59 (17), 55 (6), 50 (7); HRMS (EI) *m/z* 369.0962 (M^+, calcd for $C_{18}H_{15}N_3O_6$ 369.0961).

The methyl ester of **26g** (0.52 g, 1.41 mmol), dissolved in THF (20 mL), was hydrolyzed with 0.1 N NaOH (28.5 mL, 2.85 mmol) to give **26g** (0.30 g, 60% yield) as a dark brown solid: mp ∼85 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.06 (bs, 1 H), 9.00 (s, 1 H), 8.41 (d, J = 2.4 Hz, 1 H), 8.36 (dd, J = 9.3, 2.4 Hz, 1 H), 8.25 (d, J = 9.0 Hz, 1 H), 7.33−7.23 (m, 2 H), 7.01−6.91 (m, 2 H), 4.84 (q, J = 6.6 Hz, 1 H), 1.51 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 173.3, 158.6, 155.6, 148.3, 146.2, 144.0, 142.0, 139.2, 130.8, 123.1, 122.8, 121.3, 116.3, 72.6, 18.7; IR (KBr) 3415 (OH), 1725 (C=O) cm^{-1}; MS (EI) *m/z* (%) 355 (M^+, 100), 339 (2), 325 (3), 310 (45), 296 (7), 283 (41), 266 (5), 254 (55), 236 (8), 225 (10), 220 (10), 208 (22), 182 (9),

174 (15), 128 (43), 116 (7), 109 (14), 101 (30), 91 (6), 81 (10), 75 (12), 63 (12); HRMS (EI) *m/z* 355.0802 (M^+, calcd for $C_{17}H_{13}N_3O_6$ 355.0804). Anal. ($C_{17}H_{13}N_3O_6$) C, H, N.

2-{4-[(7-Azido-2-quinoxalinyl)oxy]phenoxy}propionic Acid (26h). The methyl ester of **26h** was prepared from **21** (0.09 g, 0.4 mmol), **25** (0.09 g, 0.5 mmol), anhydrous K_2CO_3 (0.08 g, 0.6 mmol), and CH_3CN (5 mL) for 4 h (method A). Pure material (0.15 g, 94% yield) was obtained after chromatography (4:1 hexanes:AcOEt) to give a yellow liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.57 (s, 1 H), 7.98 (d, J = 8.7 Hz, 1 H), 7.37 (d, J = 2.4 Hz, 1 H), 7.21 (dd, J = 8.7, 2.4 Hz, 1 H), 7.20−7.13 (m, 2 H), 6.98−6.90 (m, 2 H), 4.77 (q, J = 6.9 Hz, 1 H), 3.79 (s, 3 H), 1.65 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 157.7, 155.1, 146.7, 142.4, 141.0, 138.2, 137.2, 130.4, 122.4, 120.0, 116.1, 115.6, 73.2, 52.2, 18.5; IR (Film) 2110 (N_3), 1755 (C=O) cm^{-1}; MS (EI) *m/z* (%) 365 (M^+, 76), 337 (40), 312 (6), 309 (9), 306 (12), 277 (58), 250 (46), 233 (23), 222 (55), 205 (7), 194 (32), 179 (8), 167 (9), 152 (6), 144 (15), 142 (25), 139 (30), 131 (10), 120 (10), 115 (100), 110 (14), 103 (14), 91 (22), 88 (44), 81 (13), 76 (34), 64 (68), 59 (56), 55 (25), 52 (14), 50 (16), 43 (12), 39 (10); HRMS (EI) *m/z* 365.1121 (M^+, calcd for $C_{18}H_{15}N_5O_4$ 365.1124).

The methyl ester of **26h** (0.15 g, 0.41 mmol), dissolved in THF (5 mL), was hydrolyzed with 0.1 N NaOH (8.2 mL, 0.82 mmol) to give **26h** (0.13 g, 93% yield) as a tan solid: mp 140−142 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.06 (bs, 1 H), 8.72 (s, 1 H), 8.01 (d, J = 8.4 Hz, 1 H), 7.39−7.30 (m, 2 H), 7.25−7.16 (m, 2 H), 6.97−6.87 (m, 2 H), 4.82 (q, J = 6.6 Hz, 1 H), 1.50 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 173.4, 158.0, 155.4, 146.4, 142.3, 140.7, 139.1, 137.1, 130.7, 122.9, 120.5, 116.2, 115.6, 72.5, 18.7; IR (KBr) 3440 (OH), 2230 (N_3), 1730 (C=O) cm^{-1}; MS (EI) *m/z* (%) 351 (M^+, 3), 323 (2), 279 (4), 251 (7), 222 (5), 195 (4), 182 (42), 137 (16), 115 (10), 110 (100), 93 (8), 81 (37), 74 (21), 65 (19), 55 (11), 53 (14), 44 (15), 39 (11); HRMS (EI) *m/z* 351.0974 (M^+, calcd for $C_{17}H_{13}N_5O_4$ 351.0968). Anal. ($C_{17}H_{13}N_5O_4$) C, H, N.

2-{4-[(7-Chloro-8-methoxy-2-quinoxalinyl)oxy]phenoxy}propionic Acid (26i). The methyl ester of **26i** was prepared from **24a** (0.17 g, 0.74 mmol), **25** (0.16 g, 0.82 mmol), anhydrous K_2CO_3 (0.14 g, 1.0 mmol), and CH_3CN (10 mL) for 4 h (method A). Pure material (0.22 g, 76% yield) was obtained after chromatography (4:1 hexanes:AcOEt) and recrystallization from EtOH−heptane to give white crystals: mp 115−116 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.65 (s, 1 H), 7.72 (d, J = 9.0 Hz, 1 H), 7.55 (d, J = 9.3 Hz, 1 H), 7.23−7.16 (m, 2 H), 6.99−6.91 (m, 2 H), 4.79 (q, J = 6.9 Hz, 1 H), 3.90 (s, 3 H), 3.78 (s, 3 H), 1.65 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 156.4, 155.1, 150.3, 146.9, 139.3, 138.7, 134.7, 128.3, 127.6, 124.2, 122.5, 116.1, 73.2, 62.1, 52.3, 18.5; IR (KBr) 1760 (C=O) cm^{-1}; MS (EI) *m/z* (%) 388 (M^+, 100), 359 (4), 329 (41), 313 (10), 311 (10), 301 (23), 285 (14), 273 (36), 270 (8), 255 (7), 209 (7), 193 (22), 180 (11), 163 (13), 151 (13), 136 (9), 121 (18), 110 (8), 102 (11), 88 (17), 76 (12), 63 (9), 59 (24), 55 (10), 50 (6). Anal. ($C_{19}H_{17}N_2ClO_5$) C, H, N.

The methyl ester of **26i** (0.18 g, 0.46 mmol), dissolved in THF (10 mL), was hydrolyzed with 0.1 N NaOH (9.2 mL, 0.92 mmol) to give **26i** (0.16 g, 94% yield) as off-white crystals after recrystallization from EtOH−water: mp 172−173 °C (softens at 120 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.02 (bs, 1 H), 8.81 (s, 1 H), 7.75 (d, J = 9.0 Hz, 1 H), 7.66 (d, J = 9.0 Hz, 1 H), 7.25 (d, J = 9.0 Hz, 2 H), 6.95 (d, J = 9.0, 2 H), 4.84 (q, J = 6.6 Hz, 1 H), 3.78 (s, 3 H), 1.50 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 173.4, 156.7, 155.4, 150.1, 146.4, 140.0, 139.3, 134.5, 128.4, 126.7, 124.7, 123.0, 116.1, 72.5, 62.2, 18.7; IR (KBr) 3440 (OH), 1720 (C=O) cm^{-1}; MS (EI) *m/z* (%) 374 (M^+, 100), 345 (6), 329 (12), 313 (10), 301 (22), 297 (42), 285 (12), 273 (45), 270 (9), 258 (11), 255 (11), 209 (12), 193 (32), 180 (12), 163 (19), 151 (19), 139 (9), 136 (14), 121 (15), 110 (14), 107 (8), 102 (16), 100 (9), 94 (12), 88 (27), 81 (11), 76 (16), 73 (8), 65 (15), 63 (15), 55 (13), 53 (9), 50 (10); HRMS (EI) *m/z* 374.0668 (M^+, calcd for $C_{18}H_{15}N_2ClO_5$ 374.0670). Anal. ($C_{18}H_{15}N_2ClO_5$) C, H, N.

2-{4-[(8-Chloro-7-methoxy-2-quinoxalinyl)oxy]phenoxy}propionic Acid (26j). The methyl ester of **26j** was prepared from **24b** (0.69 g, 3.0 mmol), **25** (0.65 g, 3.3 mmol), anhydrous K_2CO_3 (0.57 g, 4.1 mmol), and CH_3CN (15 mL) for 4 h (method A). Mostly pure material (0.84 g, 72% crude yield) was obtained after chromatography (2:1 hexanes:AcOEt) to give a yellow liquid, which gradually solidified. A sample was recrystallized from acetone−hexanes (2×) to give off-white crystals: mp 116−118 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.51 (s, 1 H), 7.94 (d, J = 9.0 Hz, 1 H), 7.36 (d, J = 9.0 Hz, 1 H), 7.37−7.31 (m, 2 H), 6.98−6.92 (m, 2 H), 4.80 (q, J = 6.9 Hz, 1 H), 4.04 (s, 3 H), 3.78 (s, 3 H), 1.65 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 157.4, 156.5, 155.0, 147.0, 138.2, 137.2, 135.3, 128.0, 122.4, 116.3, 116.0, 113.4, 73.2, 57.0, 52.6, 18.8; IR (KBr) 1730 (C=O) cm^{-1}; MS (EI) *m/z* (%) 388 (M^+, 100), 329 (39), 301 (13), 293 (5), 285 (11), 273 (58), 267 (5), 259 (21), 193 (30), 178 (14), 164 (8), 151 (10), 102 (8), 88 (8). Anal. ($C_{19}H_{17}N_2ClO_5$) C, H, N.

The crude methyl ester of **26j** (0.80 g, ∼2.0 mmol), dissolved in THF (25 mL), was hydrolyzed with 0.1 N NaOH (40 mL, 4.0 mmol) to give **26j** (0.70 g, 91% yield) as light yellow crystals after recrystallization from EtOH−water: mp 148−150 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.00 (bs, 1 H), 8.62 (s, 1 H), 7.95 (d, J = 9.6 Hz, 1 H), 7.58 (d, J = 9.6 Hz, 1 H), 7.31 (d, J = 9.2 Hz, 2 H), 6.95 (d, J = 8.8 Hz, 2 H), 4.85 (q, J = 6.4 Hz, 1 H), 3.98 (s, 3 H), 1.51 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.8, 157.9, 156.8, 155.4, 146.6, 138.1, 137.9, 135.2, 128.7, 123.0, 116.1, 115.1, 114.7, 72.5, 57.5, 19.0; IR (KBr) 3440 (OH), 1740 (C=O) cm^{-1}; MS (EI) *m/z* (%) 374 (M^+, 100), 329 (13), 302 (24), 293 (5), 285 (8), 273 (69), 267 (8), 259 (28), 236 (7), 193 (29), 178 (14), 164 (5), 151 (10), 110 (6), 102 (6), 97 (9), 83 (9), 69 (9), 55 (6); HRMS (EI) *m/z* 374.0672 (M^+, calcd for $C_{18}H_{15}N_2ClO_5$ 374.0670). Anal. ($C_{18}H_{15}N_2ClO_5$) C, H, N.

2-{4-[(7-Amino-2-quinoxalinyl)oxy]phenoxy}propionic Acid (26k). To the methyl ester of **26g** (1.29 g, 3.49 mmol), dissolved in AcOH (35 mL), was added iron powder (1.02 g, 17.4 mmol), and the mixture was stirred overnight at room temperature. After the mixture was concentrated, water and saturated $NaHCO_3$ were added until pH 7. Hot AcOEt (50 mL) was added, and the mixture was filtered and washed with AcOEt. The aqueous layer was extracted with AcOEt (50 mL), and the combined AcOEt was washed with saturated NaCl (25 mL), dried ($MgSO_4$), and concentrated. Pure material (0.93 g, 78% yield) was obtained after chromatography (1:1 hexanes:AcOEt) to give a yellow solid: mp 165−168 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (s, 1 H), 7.80 (d, J = 8.7 Hz, 1 H), 7.20−7.12 (m, 2 H), 6.98 (dd, J = 8.7, 2.4 Hz, 1 H), 6.97−6.90 (m, 2 H), 6.84 (d, J = 2.4 Hz, 1 H), 4.77 (q, J = 6.6 Hz, 1 H), 3.79 (s, 3 H), 3.75 (vbs, 2 H), 1.65 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5, 157.7, 154.8, 148.7, 147.3, 142.1, 134.3, 134.1, 129.8, 122.4, 118.6, 116.1, 107.6, 73.2, 52.3, 18.6; IR (KBr) 3360 (NH), 3250 (NH), 1735 (C=O) cm^{-1}; MS (EI) *m/z* (%) 339 (M^+, 100), 311 (10), 280 (20), 252 (7), 236 (12), 224 (54), 196 (8), 161 (11), 144 (55), 140 (5), 133 (6), 117 (37), 105 (10), 90 (28), 81 (12), 74 (10), 69 (15), 63 (21), 59 (26), 57 (18), 55 (21), 43 (22), 41 (26), 39 (16). Anal. ($C_{18}H_{17}N_3O_4$) C, H, N.

The methyl ester of **26k** (0.16 g, 0.47 mmol), dissolved in THF (10 mL), was hydrolyzed with 0.1 N NaOH (9.4 mL, 0.94 mmol) to give **26k** (0.05 g, 33% yield) as a yellow solid: mp 156−158 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.00 (bs, 1 H), 8.24 (s, 1 H), 7.63 (d, J = 9.0 Hz, 1 H), 7.14 (d, J = 9.0 Hz, 2 H), 6.98 (dd, J = 9.0, 2.1 Hz, 1 H), 6.90 (d, J = 9.0, 2 H), 6.54 (d, J = 2.1 Hz, 1 H), 5.94 (bs, 2 H), 4.81 (q, J = 6.6 Hz, 1 H), 1.49 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 173.5, 157.8, 155.0, 151.6, 147.0, 142.4, 133.4, 132.4, 129.7, 122.9, 119.2, 116.1, 105.2, 72.5, 18.7; IR (KBr) 3445 (OH), 3350 (NH), 3225 (NH), 1715 (C=O) cm^{-1}; MS (EI) *m/z* (%) 325 (M^+, 100), 297 (8), 280 (7), 266 (9), 253 (13), 236 (7), 224 (57), 196 (7), 182 (4), 144 (60), 140 (6), 117 (31), 110 (13), 105 (5), 90 (24), 81 (6), 63 (15), 55 (6); HRMS (EI) *m/z* 325.1061 (M^+, calcd for $C_{17}H_{15}N_3O_4$ 325.1063). Anal. ($C_{17}H_{15}N_3O_4$) C, H, N.

Methyl 2-[(7-Chloro-2-quinoxalinyl)oxy]propionate (28a). (Method B). Compound **27** (0.18 g, 1.0 mmol), methyl 2-bromopropionate (0.12 mL, 0.18 g, 1.05 mmol), anhydrous K_2CO_3 (0.17 g, 1.2 mmol), and acetone (25 mL) were refluxed

together for 8 h. After being concentrated it was mixed with AcOEt, filtered through silica gel, and concentrated. Pure **28a** (0.12 g, 44% yield) was obtained after chromatography (10:1−4:1 hexanes:AcOEt) and recrystallization from a small volume of hexanes (2×) to give white crystals: mp 70−72 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.56 (s, 1 H), 7.95 (d, J = 8.7 Hz, 1 H), 7.78 (d, J = 2.1 Hz, 1 H), 7.53 (dd, J = 8.7, 2.1, 1 H), 5.50 (q, J = 6.9 Hz, 1 H), 3.78 (s, 3 H), 1.71 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 156.4, 140.3, 139.3, 137.7, 135.9, 130.0, 127.7, 126.3, 70.5, 52.2, 17.4; IR (KBr) 1760 (C═O) cm^{-1}; MS (EI) *m*/*z* (%) 266 (M^+, 55), 251 (2), 235 (8), 207 (100), 180 (84), 163 (74), 152 (52), 136 (26), 124 (23), 100 (21), 75 (11), 59 (21). Anal. ($C_{12}H_{11}N_2ClO_3$) C, H, N.

Methyl 2-(7-Chloro-2-oxo-2*H*-quinoxalinyl)propionate (29). Compound **29** was also obtained after **28a** following chromatography of the crude mixture as yellow crystals, recrystallized from a small volume of hexanes (2×) (0.03 g, 11% yield): mp 122−124 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (s, 1 H), 7.85 (d, J = 8.4 Hz, 1 H), 7.34 (dd, J = 8.4, 1.8, 1 H), 7.19 (d, J = 1.8 Hz, 1 H), 5.62−5.50 (m, 1 H), 3.75 (s, 3 H), 1.73 (d, J = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.4, 153.8, 150.0, 137.1, 132.5, 132.4, 132.2, 124.3, 113.6, 52.8, 51.2, 13.9; IR (KBr) 1750 (C═O) cm^{-1}; MS (EI) *m*/*z* (%) 266 (M^+, 44), 234 (24), 207 (38), 179 (100), 163 (7), 152 (18), 144 (9), 124 (12), 117 (12), 111 (12), 89 (10), 75 (21), 63 (9), 59 (9). Anal. ($C_{12}H_{11}N_2ClO_3$) C, H, N.

2-[(7-Chloro-2-quinoxalinyl)oxy]propionic Acid (28b). Ester **28a** (0.07 g, 0.26 mmol), dissolved in THF (5 mL), was hydrolyzed with 0.1 N NaOH (5.2 mL, 0.52 mmol) to give **28b** (0.07 g, ∼100% yield) as an off-white solid: mp 152−154 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.11 (bs, 1 H), 8.66 (s, 1 H), 7.97 (d, J = 8.0 Hz, 1 H), 7.73 (d, J = 2.4 Hz, 1 H), 7.62 (dd, J = 9.2, 2.4 Hz, 1 H), 5.38 (q, J = 7.2 Hz, 1 H), 1.60 (d, J = 7.6 Hz, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.7, 157.2, 140.7, 140.5, 137.8, 135.6, 131.1, 128.2, 126.3, 70.9, 17.9; IR (KBr) 1720 (C═O) cm^{-1}; MS (EI) *m*/*z* (%) 252 (M^+, 32), 207 (19), 193 (63), 180 (81), 163 (54), 152 (100), 136 (24), 124 (29), 117 (12), 105 (18), 100 (20), 90 (10), 77 (12), 75 (10), 69 (20), 63 (12); HRMS (EI) *m*/*z* 252.0301 (M^+, calcd for $C_{11}H_9N_2ClO_3$ 252.0302). Anal. ($C_{11}H_9N_2ClO_3$) C, H, N.

Methyl 2-(3-Hydroxyphenoxy)propionate (31). (Method C). To a solution of sodium methoxide, prepared from sodium (2.30 g, 100 mmol) and CH_3OH (50 mL), was added **30** (5.50 g, 50 mmol), under an Ar atmosphere. Methyl 2-bromopropionate (3.8 mL, 5.7 g, 33 mmol) was added over 0.5 h at reflux. The mixture was refluxed overnight, and the CH_3OH was then removed by distillation. After drying, toluene (50 mL) was added, and the mixture was allowed to stand overnight. The toluene was decanted and the washing procedure repeated. Toluene (50 mL), AcOH (4 mL), and water (50 mL) were added, and the mixture was stirred until all the solid dissolved. The toluene layer was separated and the aqueous layer extracted with additional toluene (50 mL). The organic extract was washed with water (2 × 50 mL), dried ($MgSO_4$), and concentrated before purifying by chromatography (4:1 hexanes:AcOEt) to give **31** as a colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12 (t, J = 8.1 Hz, 1 H), 6.55−6.38 (m, 3 H), 4.95 (s, 1 H), 4.73 (q, J = 6.9 Hz, 1 H), 3.77 (s, 3 H), 1.62 (d, J = 6.9 Hz, 3 H).

Methyl 2-(2-Hydroxyphenoxy)propionate (33). Phenol **32** (1.83 mL, 2.09 g, 10.0 mmol), methyl 2-bromopropionate (1.25 mL, 1.87 g, 11.0 mmol), anhydrous K_2CO_3 (1.73 g, 12.5 mmol), and acetone (25 mL) were refluxed overnight (method B). The mixture was filtered hot and washed with hot acetone, and the filtrate was filtered through silica gel and concentrated to give methyl 2-(2-benzyloxyphenoxy)propionate as a brown liquid (2.08 g, 73% crude yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50−7.30 (m, 5 H), 7.00−6.82 (m, 4 H), 5.20−5.10 (m, 2 H), 4.80 (q, J = 6.9 Hz, 1 H), 3.72 (s, 3 H), 1.62 (d, J = 7.2 Hz, 3 H).

The intermediate (2.08 g, 7.2 mmol), 10% Pd/C (0.10 g), and CH_3OH (50 mL) were debenzylated by shaking with H_2 (30 psi) in a Parr apparatus for 8 h. The mixture was filtered, concentrated, and dissolved in toluene (50 mL) then washed with water (2 × 10 mL). After drying and concentrating, the residue was purified by chromatography (5:1 hexanes:AcOEt) to give **33** as a colorless liquid (1.03 g, 72% yield): ^{1}H NMR (300 MHz, CDCl3) δ 7.00−6.78 (m, 5 H), 4.69 (q, J = 6.9 Hz, 1 H), 3.78 (s, 3 H), 1.69 (d, J = 6.9 Hz, 3 H).

Methyl 2-(4,4′-Hydroxyphenylphenoxy)propionate (35). Sodium (0.46 g, 20 mmol), CH_3OH (25 mL), **34** (1.92 g, 10.0 mmol), and methyl 2-bromopropionate (1.14 mL, 1.71 g, 10.0 mmol) (method C). After being washed with toluene (2 × 25 mL) and mixed with AcOEt (50 mL), AcOH (1 mL), and water (25 mL). Extracted with AcOEt (2 × 25 mL), washed with saturated NaCl (25 mL), dried ($MgSO_4$), and concentrated before purifying by chromatography (aluminum oxide 150 mesh, 58 Å, Neutral, Brockmann 1 (Aldrich), AcOEt) to give **35** as an off-white solid: mp 115−120 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 6.4 Hz, 2 H), 7.38 (d, J = 7.2 Hz, 2 H), 6.90 (d, J = 6.4 Hz, 2 H), 6.85 (d, J = 6.4 Hz, 2 H), 5.20 (s, 1 H), 4.80 (bq, J = 6.4 Hz, 1 H), 3.78 (s, 3 H), 1.65 (d, J = 6.4 Hz, 3 H).

2-{3-[(7-Chloro-2-quinoxalinyl)oxy]phenoxy}propionic Acid (36). The methyl ester of **36** was prepared from **16a** (0.50 g, 2.5 mmol), **31** (0.61 g, 3.1 mmol), anhydrous K_2CO_3 (0.54 g, 3.9 mmol), and CH_3CN (15 mL) for 24 h (method A). Pure material (0.55 g, 61% yield) was obtained after chromatography (3:1 hexanes:AcOEt) and recrystallization from EtOH to give peach colored crystals: mp 167−169 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.66 (s, 1 H), 7.99 (d, J = 8.7 Hz, 1 H), 7.79 (d, J = 2.1 Hz, 1 H), 7.56 (dd, J = 8.7, 2.1 Hz, 1 H), 7.35 (t, J = 8.1 Hz, 1 H), 6.90 (dd, J = 7.8, 1.5 Hz, 1 H), 6.83 (d, J = 2.7 Hz, 1 H), 6.82 (dd, J = 13.8, 2.1 Hz, 1 H), 4.79 (q, J = 6.9 Hz, 1 H), 3.77 (s, 3 H), 1.65 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 158.7, 157.2, 153.6, 140.6, 139.3, 138.2, 136.3, 130.1, 130.0, 128.3, 126.8, 114.4, 112.3, 108.9, 72.9, 52.3, 18.4; IR (KBr) 1755 (C═O) cm^{-1}; MS (EI) *m*/*z* (%) 358 (M^+, 48), 299 (100), 271 (14), 255 (8), 244 (14), 192 (9), 163 (22), 136 (15), 119 (9), 100 (11), 92 (10), 64 (13), 59 (22). Anal. ($C_{18}H_{15}N_2ClO_4$) C, H, N.

The methyl ester of **36** (0.55 g, 1.53 mmol), dissolved in THF (25 mL), was hydrolyzed with 0.1 N NaOH (30.7 mL, 3.07 mmol) to give **36** (0.50 g, 94% yield) as a light tan solid: mp 132−135 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.75 (bs, 1 H), 8.76 (s, 1 H), 7.98 (d, J = 8.7 Hz, 1 H), 7.72 (s, 1 H), 7.61 (d, J = 9.0 Hz, 1 H), 7.40−7.30 (m, 1 H), 6.95−6.85 (m, 3 H), 4.83 (q, J = 6.6 Hz, 1 H), 1.49 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 173.3, 159.0, 157.5, 153.7, 140.5, 140.3, 138.1, 135.5, 130.7, 128.5, 126.5, 114.4, 112.5, 108.9, 72.3, 18.6; IR (KBr) 3525 (OH), 1725 (C═O) cm^{-1}; MS (EI) *m*/*z* (%) 344 (M^+, 0.1), 304 (21), 299 (2), 285 (4), 199 (32), 185 (18), 149 (16), 137 (16), 129 (9), 121 (11), 105 (82), 97 (10), 95 (15), 93 (10), 91 (11), 83 (14), 81 (48), 79 (11), 77 (48), 73 (12), 71 (12), 69 (100), 67 (14), 57 (21), 55 (28); HRMS (EI) *m*/*z* 299.0585 (M − CO_2H, calcd for $C_{16}H_{12}N_2ClO_2$ 299.0587). Anal. ($C_{17}H_{13}N_2ClO_4 \cdot H_2O$) C, H, N.

2-{2-[(7-Chloro-2-quinoxalinyl)oxy]phenoxy}propionic Acid (37). Method D. Compound **16a** (0.20 g, 1.0 mmol), compound **33** (0.22 g, 1.1 mmol), 60% NaH (0.06 g, 1.5 mmol), and DMF (5 mL) were stirred together overnight at room temperature. The mixture was poured into saturated NaCl (25 mL) containing AcOH (0.1 mL), extracted with AcOEt (2 × 25 mL), washed with saturated NaCl (25 mL), dried ($MgSO_4$), and concentrated. Pure material (0.28 g, 78% yield) was obtained after chromatography (4:1 hexanes:AcOEt) to give a light yellow liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.72 (s, 1 H), 8.00 (d, J = 9.0 Hz, 1 H), 7.74 (d, J = 2.4 Hz, 1 H), 7.55 (dd, J = 8.7, 2.4 Hz, 1 H), 7.30−7.22 (m, 2 H), 7.10 (dt, J = 7.8, 1.2 Hz, 1 H), 6.94 (dd, J = 7.8, 1.2 Hz, 1 H), 4.69 (q, J = 6.9 Hz, 1 H), 3.62 (s, 3 H), 1.29 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7, 157.4, 149.5, 142.3, 140.7, 139.0, 138.1, 135.9, 130.0, 128.0, 126.6, 123.3, 122.3, 73.8, 52.0, 18.3; IR (Film) 1760 (C═O) cm^{-1}; MS (EI) *m*/*z* (%) 358 (M^+, 14), 299 (16), 255 (100), 228 (5), 215 (6), 208 (6), 163 (19), 136 (13), 121 (10), 110 (5), 100 (8), 91 (13), 81 (5), 69 (5), 65 (6), 59 (11), 55 (7), 52 (6); HRMS (EI) *m*/*z* 358.0720 (M^+, calcd for $C_{18}H_{15}N_2ClO_4$ 358.0720).

The methyl ester of **37** (0.28 g, 0.78 mmol), dissolved in THF (10 mL), was hydrolyzed with 0.1 N NaOH (16 mL, 1.6 mmol) to give **37** (0.24 g, 89% yield) as off-white crystals after recrystallization from EtOH−water: mp 129−133 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.92 (bs, 1 H), 8.84 (s, 1 H), 8.00 (d, J = 8.7 Hz, 1 H), 7.69 (d, J = 2.1 Hz, 1 H), 7.60 (dd, J = 8.7, 2.1 Hz, 1 H), 7.34−7.27 (m, 1 H), 7.27−7.18 (m, 1 H), 7.08−6.98 (m, 2 H), 4.73 (q, J = 6.6 Hz, 1 H), 1.10 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.8, 157.6, 149.6, 141.9, 140.5, 140.0, 138.1, 135.5, 130.7, 128.4, 127.1, 126.4, 123.5, 122.1, 115.4, 73.0, 18.3; IR (KBr) 3485 (OH), 1715 (C═O) cm^{-1}; MS (EI) m/z (%) 344 (M$^+$, 1), 300 (5), 285 (3), 272 (14), 255 (100), 228 (6), 215 (11), 208 (7), 192 (31), 180 (4), 163 (23), 136 (18), 121 (7), 110 (13), 100 (10), 81 (5), 55 (5), 43 (5); HRMS (EI) m/z 344.0563 (M$^+$, calcd for $C_{17}H_{13}N_2ClO_4$ 344.0564). Anal. ($C_{17}H_{13}N_2ClO_4$) C, H, N.

2-{4-[4-[(7-Chloro-2-quinoxalinyl)oxy]phenyl]phenoxy}-propionic Acid (38). The methyl ester of **38** was prepared from **16a** (0.25 g, 1.26 mmol), **35** (0.37 g, 1.36 mmol), anhydrous K_2CO_3 (0.24 g, 1.7 mmol), and CH_3CN (10 mL) for 4 h (method A). Pure material (0.42 g, 76% yield) was obtained after chromatography (4:1 hexanes:AcOEt) and recrystallization from $CHCl_3$−EtOH to give white crystals: mp 149−151 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.70 (s, 1 H), 7.99 (d, J = 8.7 Hz, 1 H), 7.79 (d, J = 2.4 Hz, 1 H), 7.65−7.51 (m, 5 H), 7.35−7.28 (m, 2 H), 7.01−6.93 (m, 2 H), 4.84 (q, J = 6.9 Hz, 1 H), 3.80 (s, 3 H), 1.67 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5, 157.4, 157.2, 151.6, 140.5, 139.4, 138.1, 136.2, 133.8, 130.0, 128.2, 127.9, 126.8, 121.6, 115.5, 72.7, 52.3, 18.6; IR (KBr) 1755 (C═O) cm^{-1}; MS (EI) m/z (%) 434 (M$^+$, 37), 375 (12), 347 (24), 323 (5), 320 (11), 295 (18), 293 (6), 291 (5), 265 (6), 247 (5), 234 (6), 223 (9), 217 (18), 207 (5), 199 (100), 197 (9), 187 (10), 181 (8), 163 (6), 157 (6), 152 (7), 139 (18), 137 (7), 135 (11), 128 (5), 95 (5), 93 (5), 91 (7), 85 (76), 81 (19), 77 (12), 69 (20), 67 (10). Anal. ($C_{24}H_{19}N_2ClO_4$) C, H, N.

The methyl ester of **38** (0.38 g, 0.87 mmol), dissolved in THF (15 mL), was hydrolyzed with 0.1 N NaOH (17.5 mL, 1.75 mmol) to give **38** (0.31 g, 84% yield) as off-white crystals after recrystallization from EtOH−water: mp 183−185 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.05 (bs, 1 H), 8.86 (s, 1 H), 8.04 (d, J = 9.0 Hz, 1 H), 7.75 (d, J = 2.1 Hz, 1 H), 7.72−7.64 (m, 3 H), 7.60 (d, J = 8.7 Hz, 2 H), 7.36 (d, J = 8.7 Hz, 2 H), 6.94 (d, J = 8.7 Hz, 2 H), 4.86 (q, J = 6.6 Hz, 1 H), 1.50 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 173.4, 157.8, 157.6, 151.8, 140.6, 140.4, 138.1, 137.7, 135.5, 132.7, 130.7, 128.5, 128.2, 127.9, 126.4, 122.3, 115.7, 72.2, 18.7; IR (KBr) 3440 (OH), 1715 (C═O) cm^{-1}; MS (EI negative ion) m/z (%) 839 (2M − H, 7), 419 (M − H, 100), 347 (79), 189 (7), 81 (25). Anal. ($C_{23}H_{17}N_2ClO_4$) C, H, N.

Ethyl 2-(4-Hydroxyphenylamino)propionate (40a). Aniline **39a** (2.78 g, 25.0 mmol), methyl 2-bromopropionate (3.60 mL, 5.02 g, 27.5 mmol), and Na_2SO_3 (6.43 g, 50.0 mmol) were heated together under Ar at 125 °C for 8 h. After cooling, AcOEt (50 mL), water (25 mL), and saturated $NaHCO_3$ were added until pH 8. The layers were separated, and the aqueous layer was extracted with AcOEt (50 mL). The AcOEt layers were washed with saturated NaCl (25 mL), dried ($MgSO_4$), and concentrated. The residue was mixed with 1:2 hexanes:AcOEt, and the insoluble, unreacted **39a** was removed. After reconcentrating, the residue was purified by chromatography (3×) (1:2−2:1−3:1 hexanes:AcOEt) and recrystallized from AcOEt−hexanes to give **40a** as off-white crystals: mp 85−87 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.63−6.57 (m, 2 H), 6.52−6.46 (m, 2 H), 4.14 (q, J = 7.2 Hz, 2 H), 4.02 (q, J = 6.9 Hz, 1 H), 1.42 (d, J = 7.5 Hz, 3 H), 1.21 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.8, 149.2, 140.3, 116.5, 115.9, 61.5, 53.7, 19.1, 14.4.

Methyl 2-(4-Hydroxyphenylthio)propionate (40b). Thio **39a** (1.26 g, 10.0 mmol), methyl 2-bromopropionate (1.20 mL, 1.80 g, 10.5 mmol), anhydrous $KHCO_3$ (1.10 g, 11.0 mmol), and DMF (5 mL) were stirred together overnight at room temperature. Water (25 mL) was added, and the mixture was extracted with AcOEt (2 × 25 mL). The extracts were washed with saturated NaCl (20 mL) containing saturated $NaHCO_3$ (5 mL), followed by saturated NaCl (25 mL). After the extracts were dried ($MgSO_4$) and concentrated, the residue was purified by chromatography (3:1 hexanes:AcOEt) to give **40b** (2.10 g, 99% yield) as a colorless liquid, which solidified on cooling: mp 55−60 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.32 (m, 2 H), 6.80−6.72 (m, 2 H), 5.61 (s, 1 H), 3.69 (s, 3 H), 3.65 (q, J = 6.9 Hz, 1 H), 1.43 (d, J = 6.9 Hz, 3 H).

2-{4-*N*-[(7-Chloro-2-quinoxalinyl)oxy]phenylamino}-propionic Acid (41a). The ethyl ester of **41a** was prepared from **16a** (0.30 g, 1.5 mmol), **40a** (0.35 g, 1.7 mmol), anhydrous K_2CO_3 (0.29 g, 2.1 mmol), and CH_3CN (10 mL) for 6 h (method A). Pure material (0.47 g, 84% yield) was obtained after chromatography (3:1 hexanes:AcOEt) to give a yellow liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.60 (s, 1 H), 7.94 (d, J = 9.3 Hz, 1 H), 7.73 (d, J = 2.4 Hz, 1 H), 7.94 (dd, J = 9.0, 2.4 Hz, 1 H), 7.10−7.03 (m, 2 H), 6.69−6.62 (m, 2 H), 4.28 (bs, 1 H), 4.21 (q, J = 7.2 Hz, 2 H), 4.13 (q, J = 6.6 Hz, 1 H), 1.49 (d, J = 6.6 Hz, 3 H), 1.27 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.7, 158.2, 144.7, 144.4, 140.9, 139.6, 138.1, 136.3, 130.2, 128.2, 127.0, 122.5, 114.2, 61.5, 52.6, 19.2, 14.5; IR (NaCl film) 3375 (NH), 1730 (C═O) cm^{-1}; MS (EI) m/z (%) 371 (M$^+$, 16), 298 (100), 163 (3), 149 (4), 119 (7), 118 (7), 81 (5), 69 (10), 57 (7), 55 (6); HRMS (EI) m/z 371.1033 (calcd for $C_{19}H_{18}N_3ClO_3$ 371.1037).

The ethyl ester of **41a** (0.47 g, 1.3 mmol), dissolved in THF (25 mL), was hydrolyzed with 0.1 N NaOH (38 mL, 3.8 mmol) to give **41a** (0.14 g, 32% yield) as a brown solid after being washed with ether before being filtered and acidified: mp ∼135 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.76 (s, 1 H), 8.02 (d, J = 8.8 Hz, 1 H), 7.78 (d, J = 2.4 Hz, 1 H), 7.65 (dd, J = 8.8, 2.4 Hz, 1 H), 7.05−6.99 (m, 2 H), 6.63−6.57 (m, 2 H), 3.94 (q, J = 7.2 Hz, 1 H), 1.38 (d, J = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.6, 158.7, 146.3, 143.3, 140.9, 140.8, 138.1, 135.6, 130.9, 128.4, 126.6, 122.6, 113.5, 51.9, 18.9; IR (KBr) 3400 (NH), 1725 (C═O) cm^{-1}; MS (EI) m/z (%) 299 (84), 284 (100), 271 (7), 256 (27), 243 (4), 228 (5), 192 (4), 163 (11), 136 (27), 108 (12), 100 (10), 80 (15), 65 (7), 63 (5), 53 (6), 50 (5). Anal. ($C_{17}H_{14}N_3ClO_3$) C, H, N.

2-{4-[(7-Chloro-2-quinoxalinyl)oxy]phenylthio}propionic Acid (41b). The methyl ester of **41b** was prepared from **16a** (0.50 g, 2.5 mmol), **40b** (0.58 g, 2.7 mmol), anhydrous K_2CO_3 (0.47 g, 3.4 mmol), and CH_3CN (15 mL) for 6 h (method A). Pure material (0.94 g, 100% yield) was obtained after chromatography (4:1 hexanes:AcOEt) to give a yellow liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.68 (s, 1 H), 8.00 (d, J = 9.0 Hz, 1 H), 7.76 (d, J = 2.1 Hz, 1 H), 7.61−7.53 (m, 3 H), 7.28−7.21 (m, 2 H), 3.82 (q, J = 7.2 Hz, 1 H), 3.72 (s, 3 H), 1.53 (d, J = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5, 156.8, 152.4, 140.0, 139.1, 137.9, 135.9, 134.7, 129.9, 128.1, 126.4, 121.9, 52.0, 45.3, 17.3; IR (film) 1740 (C═O) cm^{-1}; MS (EI) m/z (%) 374 (M$^+$, 72), 315 (100), 298 (12), 287 (7), 259 (17), 239 (6), 211 (9), 163 (25), 153 (9), 136 (22), 125 (15), 123 (8), 100 (12), 97 (9), 91 (9), 81 (8), 73 (7), 69 (13), 59 (22), 57 (10), 55 (14); HRMS (EI) m/z 374.0492 (M$^+$, calcd for $C_{18}H_{15}N_2ClO_3S$ 374.0492).

The methyl ester of **41b** (0.94 g, 2.5 mmol), dissolved in THF (35 mL), was hydrolyzed with 0.1 N NaOH (50 mL, 5.0 mmol) to give **41b** (0.81 g, 90% yield) as off-white crystals after recrystallization from EtOH−water: mp 127−129 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.75 (bs, 1 H), 8.77 (s, 1 H), 7.97 (d, J = 8.7 Hz, 1 H), 7.67 (d, J = 1.8 Hz, 1 H), 7.60 (dd, J = 8.7, 2.1 Hz, 1 H), 7.50 (d, J = 8.7 Hz, 2 H), 7.29 (d, J = 8.4 Hz, 2 H), 3.89 (q, J = 6.9 Hz, 1 H), 1.37 (d, J = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 173.7, 157.5, 152.2, 140.5, 140.2, 138.1, 135.6, 133.5, 131.0, 130.7, 128.6, 126.5, 122.5, 45.0, 17.9; IR (KBr) 3485 (OH), 1710 (C═O) cm^{-1}; MS (EI) m/z (%) 360 (M$^+$, 85), 315 (87), 301 (17), 287 (28), 283 (52), 278 (11), 259 (94), 256 (40), 228 (14), 226 (12), 224 (13), 192 (16), 181 (9), 163 (76), 136 (100), 125 (27), 109 (16), 100 (39), 97 (28), 91 (20), 85 (10), 83 (15), 81 (14), 75 (13), 73 (16), 71 (14), 69 (27), 63 (12), 59 (14), 57 (21), 55 (26), 45 (22), 43 (25), 41 (17), 39 (10); HRMS (EI) m/z 360.0333 (M$^+$, calcd for $C_{17}H_{13}N_2ClO_3S$ 360.0335). Anal. ($C_{17}H_{13}N_2ClO_3S$) C, H, N.

2-{4-[(*N*-7-Chloro-2-quinoxalinyl)amino]phenoxy}propionic Acid (42a). To **16a** (0.40 g, 2.0 mmol) and **39a** (0.22 g, 2.0 mmol), dissolved in CH_3CN (15 mL), was added 0.2 N HCl (10 mL, 2.0 mmol), and the mixture was refluxed overnight. The volume of CH_3CN was reduced by distillation and, after cooling, diluted with water (50 mL), and saturated $NaHCO_3$ was added to adjust to pH 7. The mixture was extracted with AcOEt (2 × 50 mL), washed with saturated NaCl (25 mL), dried ($MgSO_4$), concentrated, and purified by chromatography (1:1 hexanes:AcOEt) to give 4-[(*N*-7-chloro-2-quinoxalinyl)amino]phenol as a yellow solid (0.36 g, 66% yield): mp 195−200 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.79 (s, 1 H), 9.23 (bs, 1 H), 8.43 (s, 1 H), 7.78−7.70 (m, 3 H), 7.60 (d, J = 1.6 Hz, 1 H), 7.30 (dd, J = 8.8, 1.6 Hz, 1 H), 6.80 (d, J = 8.0 Hz, 2 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 153.7, 150.8, 142.5, 141.8, 135.8, 134.7, 132.3, 130.5, 125.5, 125.0, 121.5, 115.9; IR (KBr) 3350 (OH), 3220 (NH) cm^{-1}; MS (EI) *m*/*z* (%) 270 (M − H, 100), 180 (4), 163 (3), 152 (17), 136 (4), 125 (4), 117 (4), 100 (4), 90 (3), 81 (4), 69 (4), 65 (5), 57 (5), 55 (6); HRMS (EI) *m*/*z* 270.0431 (M − H, calcd for $C_{14}H_9N_3ClO$ 270.0434).

The intermediate (0.41 g, 1.5 mmol), methyl 2-bromopropionate (0.22 mL, 0.33 g, 1.9 mmol), anhydrous K_2CO_3 (0.26 g, 1.9 mmol), and acetone (15 mL) were refluxed overnight (method B). The residue was purified by chromatography (1:1 hexanes:AcOEt) to give the methyl ester of **42a** as a brown-yellow liquid, which slowly solidified (0.48 g, 89% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (s, 1 H), 7.76 (d, J = 8.0 Hz, 1 H), 7.68 (d, J = 2.4 Hz, 1 H), 7.59−7.54 (m, 2 H), 7.32 (dd, J = 8.8, 2.4 Hz, 1 H), 7.30 (bs, 1 H), 6.89−6.83 (m, 2 H), 4.76 (q, J = 6.8 Hz, 1 H), 3.78 (s, 3 H), 1.63 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 154.0, 150.2, 142.1, 139.1, 136.0, 133.3, 129.8, 126.0 (2C), 122.0, 115.9, 73.0, 52.8, 18.9; IR (NaCl film) 3360 (NH), 1735 (C═O) cm^{-1}; MS (EI) *m*/*z* (%) 356 (M − H, 40), 297 (4), 269 (100), 253 (3), 163 (12), 152 (4), 136 (5); HRMS (EI) *m*/*z* 356.0800 (M − H, calcd for $C_{18}H_{15}N_3ClO_3$ 356.0802).

The methyl ester of **42a** (0.48 g, 1.3 mmol), dissolved in THF (15 mL), was hydrolyzed with 0.1 N NaOH (27 mL, 2.7 mmol) to give **42a** (0.38 g, 83% yield) as yellow crystals after recrystallization from EtOH−water: mp 244−246 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.85 (bs, 1 H), 9.93 (s, 1 H), 8.46 (s, 1 H), 7.87−7.81 (m, 2 H), 7.78 (d, J = 8.8 Hz, 1 H), 7.68 (d, J = 2.4 Hz, 1 H), 7.39 (dd, J = 8.8, 2.6 Hz, 1 H), 6.92−6.86 (m, 2 H), 4.78 (q, J = 6.4 Hz, 1 H), 1.49 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 174.0, 153.6, 150.7, 142.3, 141.7, 135.9, 134.8, 134.2, 130.6, 125.7, 125.3, 121.1, 115.7, 72.5, 19.0; IR (KBr) 3400 (OH), 3290 (NH), 1710 (C═O) cm^{-1}; MS (EI negative ion) *m*/*z* (%) 685 (2M − H, 3), 342 (M − H, 86), 298 (9), 270 (100), 265 (4), 214 (3), 166 (2), 150 (2), 134 (6), 121 (3), 111 (6), 97 (11), 62 (46). Anal. ($C_{17}H_{14}N_3ClO_3$) C, H, N.

2-{4-[(7-Chloro-2-quinoxalinyl)thio]phenoxy}propionic Acid (42b). Compound **16a** (0.50 g, 2.5 mmol), **39b** (0.32 g, 2.5 mmol), anhydrous $KHCO_3$ (0.28 g, 2.8 mmol), and DMF (5 mL) were stirred together overnight at room temperature. Water (25 mL) was added, and the mixture was extracted with AcOEt (2 × 25 mL). The extracts were washed with saturated NaCl (20 mL) containing saturated $NaHCO_3$ (5 mL), followed by saturated NaCl (25 mL). After drying ($MgSO_4$), the extract was concentrated to give 4-[(7-chloro-2-quinoxalinyl)thio]phenol as an orange solid (0.74 g, ∼100% crude yield). A sample was recrystallized from EtOH−heptane (2 ×) to give yellow-orange crystals: mp 188−190 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.09 (bs, 1 H), 8.44 (s, 1 H), 7.98 (d, J = 8.7 Hz, 1 H), 7.86 (d, J = 2.1 Hz, 1 H), 7.72 (dd, J = 8.7, 2.1, 1 H), 7.52−7.45 (m, 2 H), 6.97−6.87 (m, 2 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 159.8, 159.6, 143.5, 142.1, 138.2, 137.5, 135.5, 131.0, 129.6, 126.8, 117.5, 115.5; IR (KBr) 3485 (OH) cm^{-1}; MS (EI) *m*/*z* (%) 288 (M$^+$, 100), 271 (4), 253 (6), 163 (23), 136 (27), 126 (25), 100 (25), 97 (32), 81 (14), 75 (16), 69 (11), 63 (12), 53 (14), 50 (10), 45 (10), 39 (13). Anal. ($C_{14}H_9N_2ClOS$) C, H, N.

The intermediate (0.74 g, 2.5 mmol), methyl 2-bromopropionate (0.35 mL, 0.52 g, 3.1 mmol), anhydrous K_2CO_3 (0.43 g, 3.1 mmol), and acetone (15 mL) were refluxed together for 21 h (method B). The residue was purified by chromatography (4:1 hexanes:AcOEt) and recrystallized from EtOH−heptane (2×) to give the methyl ester of **42b** as yellow crystals (0.56 g, 60% yield): mp 112−114 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (s, 1 H), 7.91 (d, J = 8.7 Hz, 1 H), 7.85 (d, J = 2.4 Hz, 1 H), 7.63−7.54 (m, 2 H), 7.57 (dd, J = 9.0, 2.4 Hz, 1 H), 7.02−6.95 (m, 2 H), 4.84 (q, J = 6.9 Hz, 1 H), 3.80 (s, 3 H), 1.68 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0, 159.1, 159.0, 143.1, 142.4, 138.3, 137.1, 136.1, 130.3, 129.3, 127.1, 119.6, 116.4, 72.7, 52.4, 18.5; IR (KBr) 1735 (C═O) cm^{-1}; MS (EI) *m*/*z* (%) 374 (M$^+$, 100), 315 (26), 287 (99), 271 (13), 259 (13), 163 (45), 136 (22), 125 (10), 100 (13), 59 (17). Anal. ($C_{18}H_{15}N_2ClO_3S$) C, H, N.

The methyl ester of **42b** (0.19 g, 0.51 g, 1.3 mmol), dissolved in THF (5 mL), was hydrolyzed with 0.1 N NaOH (10.2 mL, 1.02 mmol) to give **42b** (0.12 g, 66% yield) as yellow crystals after recrystallization from EtOH−water: mp 159−163 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.15 (bs, 1 H), 8.42 (s, 1 H), 7.90 (d, J = 8.7 Hz, 1 H), 7.74 (d, J = 2.1 Hz, 1 H), 7.62 (dd, J = 8.7, 2.1 Hz, 1 H), 7.56 (d, J = 8.7 Hz, 2 H), 7.00 (d, J = 8.7 Hz, 2 H), 4.91 (q, J = 6.6 Hz, 1 H), 1.52 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 173.1, 159.4, 159.0, 143.7, 142.1, 138.3, 137.2, 135.6, 131.0, 129.7, 126.8, 118.4, 116.8, 72.2, 18.6; IR (KBr) 3485 (OH), 1735 (C═O) cm^{-1}; MS (EI) *m*/*z* (%) 360 (M$^+$, 78), 315 (7), 301 (11), 287 (100), 271 (8), 259 (14), 163 (50), 136 (24), 125 (15), 100 (14), 97 (9), 75 (7), 69 (8), 63 (6), 55 (6), 50 (5); HRMS (EI) *m*/*z* 360.0333 (M$^+$, calcd for $C_{17}H_{13}N_2ClO_3S$ 360.0335). Anal. ($C_{17}H_{13}N_2ClO_3S$) C, H, N.

2-{4-[(7-Chloro-2-quinoxalinyl)oxy]phenoxy}propionamide (43). To a solution of **2** (0.18 g, 0.50 mmol) in CH_3OH (20 mL) was added NH_3 gas for 1 h, and the mixture was stirred overnight. The solvent was removed, and the crude material was recrystallized from AcOEt to give **43** as white crystals (0.12 g, 70% yield): mp 210−211 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.82 (s, 1 H), 8.04 (d, J = 9.0 Hz, 1 H), 7.77 (d, J = 2.1 Hz, 1 H), 7.67 (dd, J = 8.7, 2.1 Hz, 1 H), 7.56 (s, 1 H), 7.27 (s, 1 H), 7.27−7.19 (m, 2 H), 7.02−6.94 (m, 2 H), 4.62 (q, J = 6.6 Hz, 1 H), 1.44 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 173.8, 158.0, 155.4, 146.4, 140.6, 140.4, 138.0, 135.5, 130.7, 128.4, 126.4, 122.9, 116.6, 74.5, 19.1; IR (KBr) 3375 (NH), 3185 (NH), 1665 (C═O) cm^{-1}; MS (EI) *m*/*z* (%) 343 (M$^+$, 69), 325 (9), 299 (100), 272 (34), 255 (18), 244 (46), 192 (8), 163 (45), 136 (28), 110 (9), 100 (16), 91 (6), 75 (7), 63 (7), 55 (7), 44 (29). Anal. ($C_{17}H_{14}N_3ClO_3$) C, H, N.

2-{4-[(7-Chloro-2-quinoxalinyl)oxy]phenoxy}propionhydrazide (44). To a solution of **3** (0.36 g, 1.0 mmol) in EtOH (25 mL) was added hydrazine (0.66 mL, 0.67 g, 20 mmol) dropwise, and the mixture was stirred overnight at room temperature. After cooling, the mixture was filtered and washed with cold EtOH to give **44** as white crystals (0.31 g, 86% yield): mp 201−203 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.39 (s, 1 H), 8.80 (s, 1 H), 8.01 (d, J = 8.7 Hz, 1 H), 7.72 (d, J = 2.4 Hz, 1 H), 7.65 (dd, J = 8.7, 2.1 Hz, 1 H), 7.21 (d, J = 9.0 Hz, 2 H), 6.97 (d, J = 9.0 Hz, 2 H), 4.71 (q, J = 6.6 Hz, 1 H), 4.30 (s, 2 H), 1.43 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 170.5, 158.0, 155.2, 146.4, 140.6, 140.4, 138.0, 135.5, 130.7, 128.4, 126.4, 122.9, 116.6, 73.6, 19.2; IR (KBr) 3290 (NH), 1660 (C═O) cm^{-1}; MS (EI) *m*/*z* (%) 358 (M$^+$, 22), 299 (33), 272 (100), 255 (20), 244 (40), 207 (6), 192 (10), 163 (34), 136 (24), 124 (5), 110 (11), 100 (16), 91 (7), 87 (22), 81 (6), 75 (9), 65 (9), 59 (30), 55 (10), 50 (7). Anal. ($C_{17}H_{15}N_4ClO_3$) C, H, N.

General Procedure for Methyl and Dimethyl Amides. To the acid dissolved in THF containing catalytic quantity of pyridine was added $(COCl)_2$ (2 N in CH_2Cl_2) dropwise at 0 °C, and the mixture was stirred until the evolution of gas ceased and then stirred overnight at room temperature. The amine (2 N in THF) was added until the mixture was basic, and it was concentrated. Water and saturated $NaHCO_3$ were added until pH 8, and the mixture was extracted with AcOEt. The extract was washed with saturated NaCl, dried ($MgSO_4$), and concentrated.

2-{4-[(7-Chloro-2-quinoxalinyl)oxy]phenoxy}propionmethylamide (45a). Acid **1** (0.52 g, 1.5 mmol), THF (5 mL), pyridine (12 μL), $(COCl)_2$ (1.88 mL, 3.76 mmol), and methylamine were reacted to give **45a** as white crystals after recrystallizing from AcOEt (0.48 g, 89% yield): mp 181−182 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.65 (s, 1 H), 7.97 (d, J = 8.7 Hz, 1 H), 7.74 (d, J = 2.1 Hz, 1 H), 7.54 (dd, J = 9.0, 2.4 Hz, 1 H), 7.23−7.15 (m, 2 H), 7.00−6.92 (m, 2 H), 6.53 (bs, 1 H), 4.69 (q, J = 6.6 Hz, 1 H), 2.88 (d, J = 4.8 Hz, 3 H), 1.61 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5, (165.6), 157.5, 154.5, 146.9, 140.5, 139.2, 138.1, 136.2, 130.0, 128.2, 126.7, 122.6, 116.4, 75.8, (29.6), 25.8, 18.7; IR (KBr) 3370 (NH), 1650 (C=O) cm^{-1}; MS (EI) m/z (%) 357 (M^+, 85), 299 (91), 285 (8), 272 (27), 255 (24), 244 (41), 192 (13), 163 (50), 136 (34), 124 (7), 110 (12), 100 (25), 91 (12), 86 (94), 81 (15), 75 (14), 69 (28), 63 (16), 58 (100), 55 (23), 50 (13). Anal. ($C_{18}H_{16}N_3ClO_3$) C, H, N.

2-{4-[(7-Chloro-2-quinoxalinyl)oxy]phenoxy}propiondimethylamide (45b). Acid **1** (0.52 g, 1.5 mmol), in THF (5 mL), pyridine (12 μL), $(COCl)_2$ (1.8 mL, 3.6 mmol), and dimethylamine gave **45b**. This was purified by chromatography (1:2 hexanes:AcOEt) and recrystallization from EtOH−hexanes to give pale yellow crystals (0.45 g, 82% yield): mp 122−124 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (s, 1 H), 7.95 (d, J = 8.8 Hz, 1 H), 7.73 (d, J = 1.6 Hz, 1 H), 7.52 (dd, J = 8.8, 2.4 Hz, 1 H), 7.19−7.13 (m, 2 H), 6.97−6.92 (m, 2 H), 4.97 (q, J = 6.4 Hz, 1 H), 3.15 (s, 3 H), 2.97 (s, 3 H), 1.63 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 157.6, 154.8, 146.4, 140.5, 139.3, 137.9, 136.1, 130.0, 128.1, 126.7, 122.5, 115.7, 74.1, 36.5, 36.3, 17.6; IR (KBr) 1635 (C=O) cm^{-1}; MS (EI) m/z (%) 371 (M^+, 28), 299 (30), 272 (6), 255 (11), 244 (7), 192 (6), 163 (15), 136 (11), 100 (100), 91 (6), 81 (11), 72 (50), 69 (22), 55 (11), 45 (8). Anal. ($C_{19}H_{18}N_3ClO_3$) C, H, N.

2-{4-[(7-Chloro-2-quinoxalinyl)oxy]phenoxy}propionhydroxamic Acid (45c). Acid **1** (0.17 g, 0.5 mmol) and $SOCl_2$ (0.35 mL, 0.57 g, 4.8 mmol) were refluxed for 1 h. After cooling, the mixture was concentrated in vacuo and the acid chloride dissolved in toluene (10 mL). $(TMS)_2NOTMS$ (0.14 g, 0.56 mmol) was added, and the mixture was stirred for 0.25 h before it was concentrated. The residue was dissolved in toluene (10 mL) and stirred overnight in the open. The resulting solid was washed with AcOEt and dried to give **45c** as an off-white solid (0.14 g, 79% yield): mp 190 °C (dec); ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.88 (s, 1 H), 8.96 (bs, 1 H), 8.81 (s, 1 H), 8.02 (d, J = 8.7 Hz, 1 H), 7.74 (d, J = 2.1 Hz, 1 H), 7.66 (dd, J = 8.7, 2.1 Hz, 1 H), 7.22 (d, J = 8.7 Hz, 2 H), 6.98 (d, J = 8.7 Hz, 2 H), 4.67 (q, J = 6.6 Hz, 1 H), 1.44 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 168.1, 158.0, 155.2, 146.4, 140.6, 140.4, 138.0, 135.5, 130.7, 128.4, 126.4, 122.9, 116.6, 73.0, 19.2; IR (KBr) 3415 (OH), 3165 (NH), 1650 (C=O) cm^{-1}; MS (EI) m/z (%) 359 (M^+, 1), 344 (18), 299 (9), 272 (100), 255 (6), 244 (100), 237 (10), 216 (19), 209 (18), 181 (16), 163 (57), 152 (19), 136 (61), 124 (19), 110 (59), 100 (54), 88 (10), 81 (47), 75 (27), 70 (21), 65 (24), 63 (33), 59 (19), 53 (19), 50 (21). Anal. ($C_{17}H_{14}N_3ClO_4$) C, H, N.

2-(4-Hydroxyphenoxy)propionitrile (47). A mixture of phenol **46** (2.04 g, 10.0 mmol), 2-bromopropionitrile (1.33 mL, 2.06 g, 15.0 mmol), anhydrous K_2CO_3 (1.73 g, 12.5 mmol), and acetone (25 mL) was refluxed overnight. The reaction mixture was filtered hot and washed with hot acetone, and the filtrate was filtered through silica gel and then concentrated in vacuo to give 2-(4-benzyloxyphenoxy)propionitrile as a pale brown liquid, which solidified (2.41 g, 95% crude yield): mp 86−87 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47−7.30 (m, 5 H), 7.00−6.90 (m, 4 H), 5.04 (s, 2 H), 4.79 (q, J = 6.9 Hz, 1 H), 1.77 (d, J = 6.9 Hz, 3 H).

To the intermediate (2.41 g, 9.51 mmol) in CH_2Cl_2 (10 mL) was added $BBr_3{\cdot}S(CH_3)_2$ (3.11 g, 10.0 mmol), and the solution was stirred for 2 h at room temperature. The solution was diluted with AcOEt (25 mL), saturated $NaHCO_3$ (15 mL), and water (10 mL). The layers were separated, and the aqueous layer was extracted with AcOEt (25 mL). The extracts were washed with saturated NaCl (10 mL), dried ($MgSO_4$), and concentrated before purifying by chromatography (4:1 hexanes:AcOEt) to give **47** as a light yellow liquid, which solidified on cooling (1.30 g, 84% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.96−6.86 (m, 2 H), 6.86−6.77 (m, 2 H), 5.01 (s, 1 H), 4.78 (q, J = 6.6 Hz, 1 H), 1.76 (d, J = 6.9 Hz, 3 H).

2-{4-[(7-Chloro-2-quinoxalinyl)oxy]phenoxy}propionitrile (48). Compound **16a** (0.40 g, 2.0 mmol), compound **47** (0.36 g, 2.2 mmol), anhydrous K_2CO_3 (0.38 g, 2.7 mmol), and CH_3CN (10 mL) were reacted for 4 h (method A), and the product was purified by chromatography (4:1 hexanes:AcOEt) and recrystallized from heptane to give **48** as off-white crystals (0.57 g, 87% yield): mp 135−137 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (s, 1 H), 7.97 (d, J = 9.2 Hz, 1 H), 7.75 (d, J = 2.4 Hz, 1 H), 7.54 (dd, J = 8.8, 2.4 Hz, 1 H), 7.27−7.22 (m, 2 H), 7.12−7.07 (m, 2 H), 4.91 (q, J = 6.4 Hz, 1 H), 1.83 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 154.0, 148.0, 140.7, 139.5, 138.3, 136.5, 130.3, 128.6, 127.0, 123.1, 118.4, 117.3, 63.3, 20.2; MS (EI) m/z (%) 325 (M^+, 41), 271 (26), 243 (100), 215 (7), 208 (11), 179 (5), 163 (78), 136 (55), 124 (12), 109 (19), 100 (52), 81 (28), 75 (25), 69 (15), 63 (38), 54 (43), 52 (26), 50 (24). Anal. ($C_{17}H_{12}N_3ClO_2$) C, H, N.

7-Chloro-2-{4-[1-(1*H*-tetazol-5-yl)ethoxy]phenoxy}quinoxaline (49). Nitrile **48** (0.48 g, 1.5 mmol), NH_4Cl (0.10 g, 1.9 mmol), NaN_3 (0.12 g, 1.8 mmol), and DMF (5 mL) were heated at 80 °C overnight. The mixture was concentrated, and dilute NH_4OH (10 mL) was added. The mixture was heated, adding more dilute NH_4OH to maintain pH 8. The filtered mixture was washed with water, and the filtrate was acidified to pH 3−4 with 0.25 N HCl. After cooling, the solid was collected, washed with ice−water, dried, and recrystallized from AcOEt−heptane to give **49** as brown crystals (0.38 g, 70% yield): mp 198−199 °C (dec); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.81 (s, 1 H), 8.03 (d, J = 8.0 Hz, 1 H), 7.73 (d, J = 2.4 Hz, 1 H), 7.67 (dd, J = 9.2, 2.4 Hz, 1 H), 7.27−7.22 (m, 2 H), 7.12−7.07 (m, 2 H), 5.98 (q, J = 6.4 Hz, 1 H), 1.72 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.2, 154.8, 147.0, 140.9, 140.6, 138.2, 135.7, 131.0, 128.7, 126.6, 123.4, 117.4, 67.8, 20.8; IR (KBr) 2620 (OH) cm^{-1}; MS (EI negative ion with NH_4OH) m/z (%) 735 (2M − H,5), 367 (M − H,100), 271 (2), 95 (14). Anal. ($C_{17}H_{13}N_6ClO_2$) C, H, N.

Biology. Methods. In Vitro. Our "disk diffusion soft agar colony formation assay"[23] is designed to compare the relative cytotoxicity of an agent against leukemia cells, solid tumor cells (including mutlidrug resistant solid tumors), and normal cells.[2,4,23] 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 or normal cells in the soft agar assay to be of interest. Normal fibroblasts were used in current studies. For the operation of the assay, the tumor cells are isolated from live tissue, i.e., 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 #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.

In Vivo. Treatment was carried out against early stage Pancreatic Ductal Adenocarcinoma-03[24] and/or Mammary Adenocarcinoma-17/Adr.[25,26] The general methods of tumor transplantation, drug treatment, endpoint determination, and interpretation of data have been published.[2−4,24−28] A brief summary follows:

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

b. Chemotherapy of Solid Tumors. The animals were pooled, implanted subcutaneously with 30 to 60 mg tumor

fragments by a 12-gauge trocar, and again pooled before unselective distribution to the various treatment and control groups (5 mice or 6 mice per group). For early stage treatment, chemotherapy was started 1 to 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.

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

d. Quantified End Points for Assessing Antitumor Activity for Solid Tumors. The following quantified end points are used to assess antitumor activity.

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.

2. Calculation of Tumor Cell Kill. For subcutaneously (sc) growing tumors, the log cell kill is calculated from the following formula: $\log_{10}$ cell kill total (gross) $= T - C$ value in days/$3.32T_d$, 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 posttreatment (Rx) approximates the T_d values of the tumors in untreated control mice.

Duration of treatment: 5−20 days

antitumor activity		gross $\log_{10}$ tumor cell kill
highly active	++++	>2.8
	+++	2.0−2.8
	++	1.3−1.9
	+	0.7−1.2
inactive	−	<0.7

e. Activity Rating for Leukemia L1210/0. Because the L1210 leukemia was markedly more sensitive to the antitumor agents than the solid tumors, an expanded activity rating was required. This rating was used in Tables 1 and 2 for L1210 only.

Duration of treatment: 1−9 days

antileukemic activity		gross log10 tumor cell kill
highly active	+++++	>5.0
	++++	4.0−4.9
	+++	3.0−3.9
	++	2.0−2.9
	+	1.0−1.9
inactive	−	<1.0

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 of <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.

Acknowledgment. Thanks are due to the Resource Laboratory of the Chemistry Department, Wayne State University, Detroit, MI, wherein all instrumental analyses were performed. The authors are grateful for the support of this research through grants from the National Institutes of Health (CA 82341), the Virtual Discovery Program of the Barbara Ann Karmanos Cancer Institute, and the Jack and Miriam Shenkman Cancer Research Fund.

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JM0005149