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Synthesis of Indolylalkoxyiminoalkylcarboxylates as Leukotriene Biosynthesis Inhibitors

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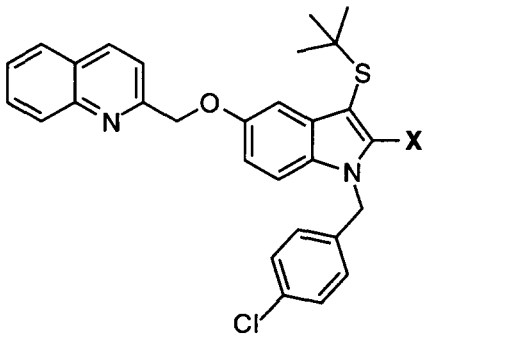
Abstract—A series of substituted indolylalkoxyiminoalkylcarboxylates were found to be potent leukotriene biosynthesis inhibitors. The structure–activity relationships were investigated. Representative potent inhibitors identified were the quinolyl **3a** (**A-86885**) and pyridyl **3b** (**A-86886**) congeners with in vitro IC_{50}s of 21 and 9 nM and in vivo leukotriene inhibition in the rat with oral ED_{50}s of 0.9 and 1.7 mg/kg, respectively. © 1997 Elsevier Science Ltd. All rights reserved.

Introduction

5-Lipoxygenase (5-LO) catalyzes the first two steps of the transformation of arachidonic acid into leukotrienes, known mediators of inflammation.[1] The 5-LO enzyme undergoes activation through an interaction with five-lipoxygenase activating protein (FLAP) at a nuclear membrane site.[2] Translocation of 5-LO to this activation site and the role of FLAP as an arachidonic acid carrier protein which enhances oxidative catalysis by 5-LO have been described.[3] Agents that interfere with the function of FLAP prevent leukotriene biosynthesis in intact cell systems. The reference FLAP inhibitor, MK-0591 (**1**) has demonstrated potent inhibition of leukotriene biosynthesis in both preclinical and clinical studies.[4-5]

In the course of structure–activity evaluations of various substituted indoles, we found that insertion of an oxime function into the alkylcarboxylate substituent of the reference inhibitor provided a congener **2**, with improved oral bioavailability.[6] This paper extends that initial finding by describing the biological properties of an interesting series of inhibitors exemplified by **3**, with the regio-isomeric oxime form referred to as the indolylalkoxyiminoalkylcarboxylate derivatives.



1 (MK-0591) X = CO_2H

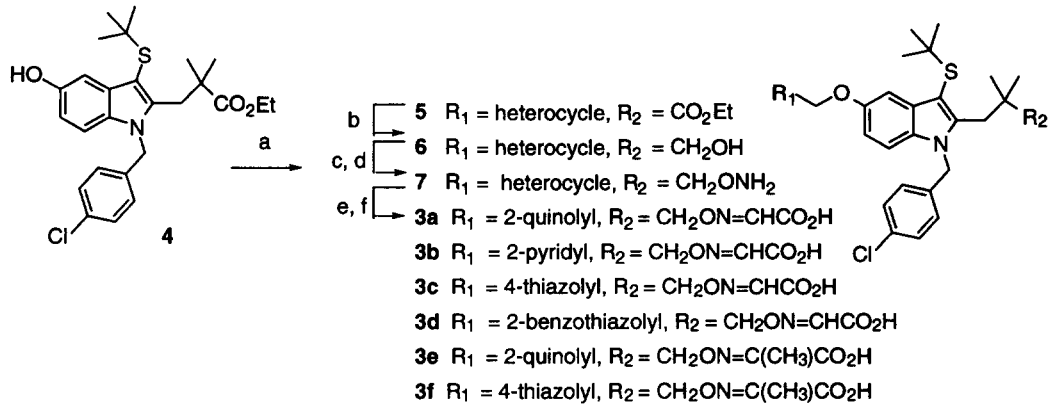
2 (A-81834) X = N, O, CO_2H

3a (A-86885) X = O, N, CO_2H

Chemistry

The indole intermediate **4** (Scheme 1, see also Experimental for preparation) was the key starting point for the synthesis of several potent leukotriene inhibitors. Alkylation of **4** with the requisite chloromethylheteroaryl group afforded the substituted indole esters **5** that were reduced to provide the corresponding alcohols **6**. A Mitsunobu reaction[7] with *N*-hydroxyphthalimide followed by hydrazinolysis of the phthaloyl derivative converted the alcohols **6** into the alkoxyamines **7**, which were transformed into the indolylalkoxyiminoalkylcarboxylate derivatives **3a–f** by reaction with the requisite carbonyl component under standard oxime formation conditions. The compounds were obtained as single isomers, presumably with the *E* oxime configuration. The absence of isolable amounts of the other isomers (*Z*) precluded confirmation of the configuration proposed.

The 2-alkyl substituent of the indole was simplified to a methylene unit as in indolylmethoxyiminoalkylcarboxylate analogues (**11a**, **b** and **12a**, **b**) that were synthesized from indole **8** (Scheme 2). Treatment with



Scheme 1. Reagents and conditions: (a) chloromethylheterocycle, K_2CO_3, DMF, 60 °C; (b) $NaBH_4$, $CaCl_2$, THF, EtOH, 0 °C to rt; (c) PhtNOH, Ph_3P, DIAD, THF; (d) H_2NNH_2, EtOH, reflux; (e) $RCOCO_2H$, AcOH, THF, H_2O; (f) NaOH, dioxane, MeOH, rt.

$AlCl_3$ in *t*-butylthiol provided the corresponding hydroxyindole intermediate that was directly alkylated with 2-chloromethylquinoline to provide a mixture of quinolylmethoxyindole **9** in 32% yield and the bisquinoline derivative **10** in 50% yield. These intermediates were separated and further transformed into the desired oxime derivatives **11a, b** (isolated as single isomers and the precise stereochemistry was not assigned) and **12a, b** according to the previously described methods. The **12a** was separated as a single isomer, probably *Z*, compared to the *Z*:*E* (4:1) ratio of less crowded **12b**. The preferred configuration as *Z* for these oximes is probably a result of the 3-thiomethylquinolyl substituent.

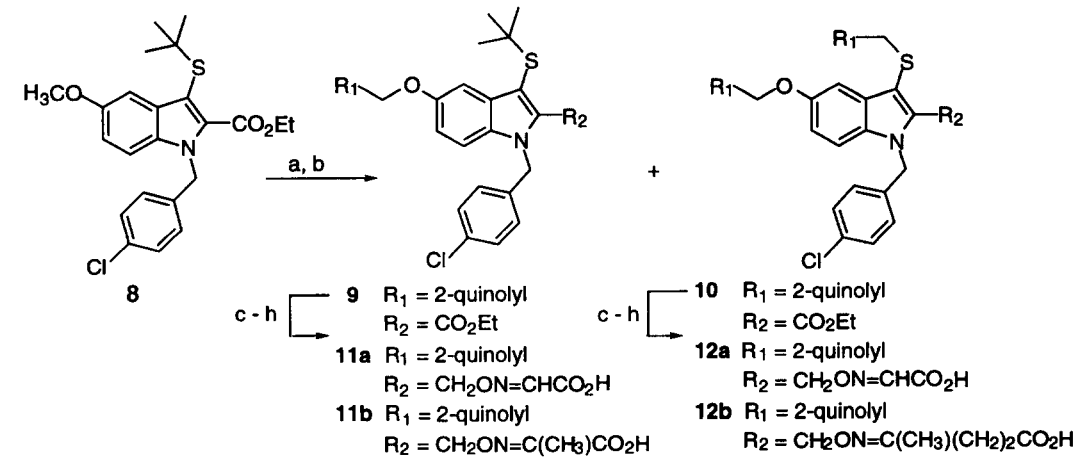
A series of analogues was prepared without the 3-thioalkyl substituent as shown in Scheme 3. Indolecarboxylate **13** was converted by standard methods into 1-(chlorobenzyl)-5-methoxyindole-2-carboxylic acid methyl ester **14** with 65% overall yield. The 2-quinolylmethoxy substituent was added as before and the resulting intermediate indole ester was saponified and reduced to the corresponding alcohol **15**, which was converted to the alkoxyamine by the methods previously described.

The oxime derivatives **17a, b** were prepared by reaction with the requisite carbonyl derivative under standard conditions. The major isomers were assigned as Z based on NMR studies. The **17a** was isolated from a mixture of 25:1, *Z*:*E* isomers and **17b** was separated from a mixture of 49:1, *Z*:*E* isomers.

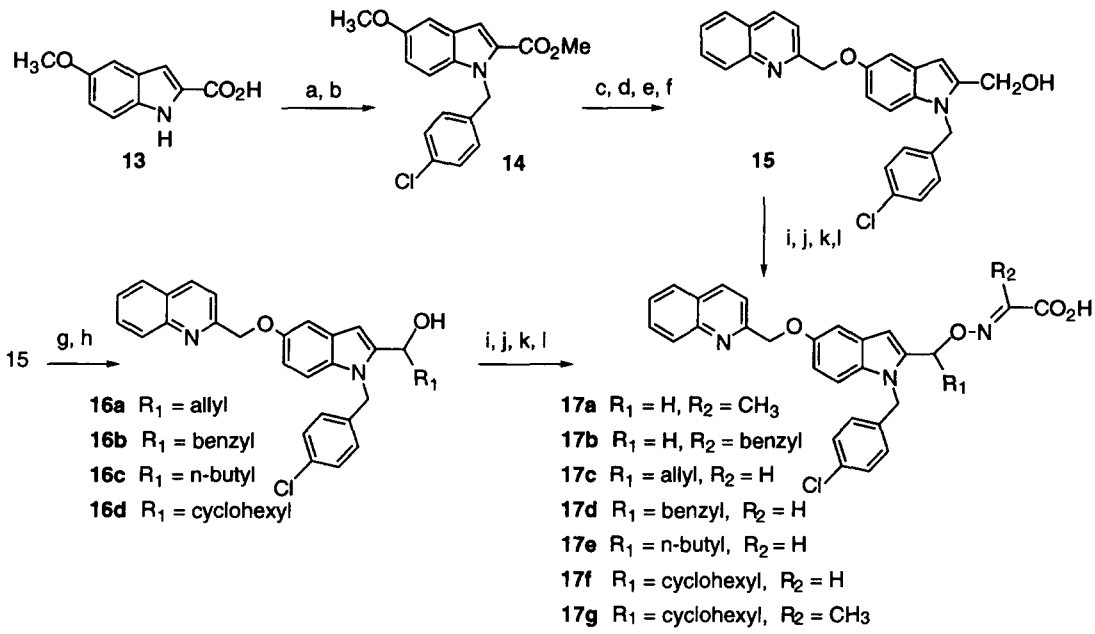
A series of secondary alcohol derivatives **16a–d** was prepared from the primary alcohol **15** by oxidation to the corresponding aldehyde followed by Grignard reaction (Scheme 3). The resulting secondary alcohols **16a–d** were then transformed into the racemic oxime derivatives **17c–g** as described previously. The compounds were isolated as single isomers, probably *E* (by 300 MHz ^1H NMR).

Results and Discussion

We previously demonstrated that inserting an oxime moiety into the 2-alkylcarboxylate substituent of **1** provided a leukotriene biosynthesis inhibitor **2** with improved oral bioavailability and in vivo pharmacological properties.[6] This result led us to examine the biological properties of the regioisomeric oxime form



Scheme 2. Reagents and conditions: (a) $AlCl_3$, *t*-BuSH, CH_2Cl_2, 0 °C, (91%); (b) 2-chloromethylquinoline, K_2CO_3, DMF, rt, **9** (32%) and **10** (50%); (c) NaOH, dioxane, MeOH, rt; (d) $ClCO_2Et$, Et_3N, THF, −15 °C, then $NaBH_4$, MeOH, 0 °C; (e) PhtNOH, Ph_3P, DEAD, THF; (f) H_2NNH_2, dioxane, EtOH, reflux; (g) $RCOCO_2Et$, AcOH, MeOH, dioxane; (h) NaOH, dioxane, MeOH, rt, overall yield (c–h): **11a** (21%), **11b** (73%), **12a** (53%), and **12b** (66%).



Scheme 3. Reagents: (a) MeI, $NaHCO_3$, DMF (69%); (b) *p*-ClBzlCl, NaH, DMF (94%); (c) $AlCl_3$, *t*-BuSH, CH_2Cl_2 (97%); (d) 2-chloromethylquinoline, K_2CO_3, DMF (64%); (e) NaOH, dioxane, MeOH (95%); (f) $ClCO_2Et$, Et_3N, THF, −15 °C, then $NaBH_4$, MeOH, 0 °C (93%); (g) $Ba(MnO_4)_2$, toluene, reflux (88%); (h) RMgX, THF, −78 °C; (i) PhtNOH, Ph_3P, DEAD, THF; (j) H_2NNH_2, dioxane, EtOH; (k) $CH_3COCO_2CH_3$, AcOH, dioxane, methanol; (l) NaOH, dioxane, MeOH. Overall yield from **15**: **17a** (10%), **17b** (4%), **17c** (15%), **17d** (13%), **17e** (35%), **17f** (9%), and **17g** (11%).

Table 1. Leukotriene inhibition results

Compound	Human neutrophil[a] IC_{50}, nM (95% CL)	In vivo rat anaphylaxis[b] ED_{50}, mg/kg (95% CL) or % inh (± SEM)
MK-0591	8 (7–10)	1.6 (0.8–2.5)
A-81834	12 (10–20)	0.24 (0.05–0.50)
3a	21 (20–20)	0.9 (0.7–3.7)
3b	9 (10–10)	1.7 (2.1–3.5)
3c	10 (10–20)	100 (± 0.4)
3d	18 (10–20)	99 (± 0.7)
3e	32 (30–40)	100 (0.0)
3f	8 (10–10)	100 (0.0)
11a	10 (10–20)	65 @ 5 μmol/kg
11b	30 (20–40)	100 (± 1.4)
12a	70 (60–80)	36 (± 89.8)
12b	110 (90–130)	0 (± 32.8)
17a	17 (12–21)	–
17b	24 (21–27)	–
17c	20 (13–25)	92 (± 9.4)
17d	40 (30–70)	100 (± 0.4)
17e	100 (80–130)	100 (0.0)
17f	25 (15–35)	–
17g	70 (50–160)	–

[a]Inhibition of calcium ionophore (A-23187) stimulated LTB_4 formation in human neutrophils, 95% confidence limits shown in parentheses.

[b]Rat anaphylaxis in the peritoneal cavity, leukotrienes formed measured by enzyme-linked immunoassay, oral dose response determination ED_{50} or percentage leukotriene inhibition at a single dose of 30 μmol/kg with $n = 8$, 95% confidence limits shown in parentheses for oral dose response determinations or SEM for single dose studies. See ref 8 for a detailed description of the biological methods.

represented by the current series of substituted indolylalkoxyiminoalkylcarboxylates. The biological testing included a human neutrophil cellular assay involving calcium ionophore stimulated LTB_4 biosynthesis to measure in vitro leukotriene inhibition.[8] A rat anaphylaxis model involving antigen–antibody-stimulated leukotriene generation in the peritoneal cavity was used to evaluate in vivo leukotriene inhibition after oral administration of test compound.[8] The biological activity of these analogues in these two assays is shown in Table 1. The indolylalkoxyiminoalkylcarboxylate analogues **3a–f**, exhibited comparable in vitro inhibitory activity in the intact human neutrophil assay as **1**. These results indicated that several heteroaryl templates including quinolyl, pyridyl, thiazolyl, and benzothiazolyl provided potent leukotriene biosynthesis inhibitors. In the rat anaphylaxis model, **3a** was slightly more potent than **1** but less active than the oxime congener **2**. Preliminary pharmacokinetic evaluation of **3a** in dog, given orally at 7 mg/kg, showed a low plasma concentration ($T_{max} = 1.5$ h, $C_{max} = 0.67$ μM) and an estimated oral half-life of 3 h. For comparison, **2** given orally at 10 mg/kg provided more than 90% ex vivo inhibition of LTB_4 over an 8-h period. The change in oxime regiochemistry (comparing **2** with **3a**) invokes signficant changes in orientation of the respective heteroatoms which may result in potency differences. However only minor differences between **2** and **3a** were found both in vitro (IC_{50} values of 12 and 21 nM) and in vivo (ED_{50} values of 0.24 and 0.9 mg/kg). These results would imply that the oxime function in these inhibitors does not have specific strong binding interaction sites with FLAP.

Several other structural changes were examined. The nature of the alkyl group in the 2-position of the indole was examined due to the proximity to the newly introduced oxyimino moiety. The methoxyimino analogues **11a** and **11b** were also found to be potent leukotriene inhibitors. Replacement of the 3-indolyl-*S*-*t*-butyl group with more polar *S*-2-quinolylmethyl group as in **12a** and **12b** resulted in a decrease in in vitro inhibitory activity and a loss of in vivo activity. A series of analogues without the 3-indolyl-*S*-*t*-butyl substituent was evaluated. Analogues **17a–g** had in vitro activity in the 17–100 nM range and for those tested (**17c–e**) in vivo provided greater than 90% leukotriene inhibition in the rat with a single 30 μmol/kg oral dose 1 h prior to leukotriene measurement. In conclusion the regioisomeric oxime insertion led to congeners with potent in vitro and in vivo leukotriene inhibitory activity.

Experimental

Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded using a Nicolet QE-300 (300 MHz) instrument. Mass spectra were obtained with Hewlett Packard HP5985 spectrometer. Microanalyses were performed by the Robertson Microlit Laboratories, Inc., Madison, NJ, USA. Reagents were obtained from Aldrich and Lancaster chemical companies.

3-[3-*t*-Butylthio-1-(4-chlorobenzyl)-5-(2-quinolylmethoxy)indol-2-yl]-2,2-dimethylpropyloxyiminoacetic acid (3a). To a suspension of 4-methoxyphenylhydrazine:HCl (41 g, 230 mmol) in CH_2Cl_2 (1 L) under nitrogen was added diisopropylamine (79.8 g, 612 mmol), 4-chlorobenzyl chloride (40.25 g, 250 mmol), and tetrabutylammonium bromide (22.8 g, 70 mmol), and the mixture was stirred at rt for 48 h. The reaction mixture was washed with water, brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by chromatography (silica gel, 2.5% methanol in CH_2Cl_2) to provide 1-(4-chlorobenzyl)-1-(4-methoxyphenyl)hydrazine (43.5 g, 76%). Mp 55 °C. This hydrazine (38.25 g, 150 mmol) in toluene (250 mL) was treated with acetic acid (175 mL) and ethyl 5-*t*-butylthio-2,2-dimethyl-4-oxo-pentanoate (38.2 g, 150 mmol) and the resulting mixture was stirred in the dark at rt for four days. Water was added, the organic layer separated and washed with water, brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by chromatography (silica gel, 4:1, hexane:EtOAc) to provide ethyl 3-[3-*t*-butylthio-1-(4-chlorobenzyl)-5-methoxyindol-2-yl]-2,2-dimethylpropionate (36.5 g, 50%). To a suspension of $AlCl_3$ (26.3 g, 198 mmol) in *t*-butanthiol (60 mL) at 0 °C was added a solution of the ethyl ester (32 g, 66 mmol) in CH_2Cl_2 (90 mL) and the mixture was stirred at 0 °C for 10 min and at rt for 3 h. The mixture was poured on ice and acidified with 10% HCl. The organic layer was washed with water, brine, dried ($MgSO_4$), and concentrated in vacuo to provide ethyl 3-[3-*t*-butylthio-1-(4-chlorobenzyl)-5-hydroxyindol-2-yl]-2,2-dimethylpropionate (**4**) (21.8 g, 70%).

A mixture of chloromethylquinoline hydrochloride (1.07 g, 5 mmol), K_2CO_3 (2.07 g, 15 mmol) and **4** (2.37 g, 5 mmol) in DMF (30 mL) was refluxed at 60 °C for 3 h and stirred at rt for 15 h. The mixture was poured into water and extracted with ethyl acetate (80 mL), dried ($MgSO_4$) and concentrated in vacuo to provide ethyl 3-[3-*t*-butylthio-1-(4-chlorobenzyl)-5-(2-quinolylmethoxy)indol-2-yl]-2,2-dimethylpropionate (**5**) (2.6 g, 84%). To a solution of **5** (2.5 g, 4 mmol) in ethanol (30 mL) and THF (20 mL) was added powdered $CaCl_2$ (0.9 g, 8 mmol) and $NaBH_4$ (0.6 g, 16 mmol) and the mixture was stirred at 0 °C for 2 h and at rt for 14 h. The mixture was neutralized with 6 N HCl and extracted with ethyl acetate, washed with water, brine, dried ($MgSO_4$), and concentrated in vacuo to provide 3-[3-*t*-butylthio-1-(4-chlorobenzyl)-5-(2-quinolylmethoxy)indol-2-yl]-2,2-dimethylpropan-1-ol (**6**) (2.3 g, 99%). To a mixture of the alcohol **6** (2.3 g, 4 mmol), *N*-hydroxyphthalimide (0.75 g, 4.5 mmol) and triphenylphosphine (1.31 g, 5 mmol) in THF (100 mL) was added dropwise diisopropyl azodicarboxylate (DIAD, 1.01 g, 5 mmol) and the mixture was stirred at rt for 2 h. The mixture was concentrated and purified by chromatography (silica gel, 95:5, CH_2Cl_2:EtOAc) to provide *N*-phthaloyl-*O*-[3-[3-*t*-butylthio-1-(4-chlorobenzyl)-5-(2-quinolylmethoxy)-indol-2-yl]-2,2-dimethylpropyl]hydroxylamine. This *N*-phthaloyl derivative and hydrazine hydrate (1 mL) in ethanol was refluxed for 1 h and then concentrated in vacuo. The residue was partitioned between CH_2Cl_2 and 10% aqueous Na_2CO_3, and the organic layer was washed with water, brine, dried ($MgSO_4$), and concentrated in vacuo to provide *O*-[3-[3-*t*-butylthio-1-(4-chlorobenzyl)-5-(2-quinolylmethoxy)-indol-2-yl]-2,2-dimethylpropyl]hydroxylamine (**7**) (1.75 g, 80%). To amine **7** (700 mg, 1.3 mmol) in THF (35 mL) and water (10 mL) was added glyoxylic acid (240 mg, 2.6 mmol) and acetic acid (0.2 mL) and the mixture was stirred at rt for 14 h. The volatile organics were removed in vacuo and the residue was diluted with water to precipate a solid which was collected and purified by chromatography (silica gel, 9:1, CH_2Cl_2:MeOH) to provide **3a** (420 mg, 50%). Mp 152–155 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.87 (s, 6 H), 0.97 (s, 9 H), 2.90 (m, 2 H), 3.83 (s, 2 H), 5.39 (s, 2 H), 5.53 (s, 2 H), 6.83 (m, 3 H), 7.13 (d, J = 3 Hz, 1 H), 7.30 (m, 3 H), 7.40 (s, 1 H), 7.65 (m, 2 H), 7.78 (m, 1 H), 7.95 (d, J = 8 Hz, 1 H), 8.05 (d, J = 8 Hz, 1 H), 8.35 (d, J = 8 Hz, 1 H); MS (DCI-NH_3) *m/z* 644 $(M+H)^+$. Anal. calcd for $C_{36}H_{38}ClN_3O_4S{\cdot}2H_2O$: C, 63.52; H, 5.88; N, 6.17. Found: C, 63.04; H, 5.95; N, 5.88.

3-[3-(*t*-Butylthio)-1-(4-chlorobenzyl)-5-(2-pyridylmethoxy)-indol-2-yl]-2,2-dimethylpropyloxyiminoacetic acid (3b). Prepared by the method described for **3a**. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.91 (s, 6 H), 1.10 (s, 9 H), 2.93 (m, 2 H), 3.85 (s, 2 H), 5.20 (s, 2 H), 5.53 (s, 2 H), 6.83 (d, J = 9 Hz, 3 H), 7.09 (d, J = 3 Hz, 1 H), 7.32 (m, 4 H), 7.41 (s, 1 H), 7.49 (d, J = 8 Hz, 1 H), 7.79 (m,

1 H), 8.56 (m, 1 H); MS (DCI–NH_3) *m/z* 594 $(M+H)^+$. Anal. calcd for $C_{32}H_{36}ClN_3O_4S{\cdot}2H_2O$: C, 60.95; H, 6.20; N, 6.66. Found: C, 60.74; H, 5.89; N, 6.54.

3-[3-(*t*-Butylthio)-1-(4-chlorobenzyl)-5-(4-thiazolylmethoxy)-indol-2-yl]-2,2-dimethylpropyloxyiminoacetic acid (3c). Prepared by the method described for **3a**. Mp 125 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 0.92 (s, 6 H), 1.15 (s, 9 H), 2.95 (m, 2 H), 4.05 (s, 2 H), 5.22 (s, 2 H), 5.53 (s, 2 H), 6.85 (m, 3 H), 7.18 (d, *J*=3 Hz, 1 H), 7.31 (m, 3 H), 7.58 (s, 1 H), 7.73 (s, 1 H), 9.13 (s, 1 H); MS (FAB(–)) *m/z* 598 $(M-H)^+$. Anal. calcd for $C_{30}H_{34}ClN_3O_4S_2$: C, 59.89; H, 5.68; N, 6.99. Found: C, 59.31; H, 5.49; N, 6.81.

3-[3-*t*-Butylthio-1-(4-chlorobenzyl)-5-(2-benzothiazolylmethoxy)indol-2-yl]-2,2-dimethylpropyloxyiminoacetic acid (3d). Prepared by the method described for **3a**. Mp 154 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 0.92 (s, 6 H), 1.04 (s, 9 H), 2.95 (m, 2 H), 4.03 (s, 2 H), 5.53 (s, 2 H), 5.61 (s, 2 H), 6.85 (m, 3 H), 7.21 (d, *J*=3 Hz, 1 H), 7.31 (m, 3 H), 7.44 (m, 1 H), 7.54 (m, 1 H), 7.57 (s, 1 H), 8.03 (d, *J* = 9 Hz, 1 H), 8.08 (d, *J* = 9 Hz, 1 H); MS (FAB(+)) *m/z* 650 $(M+H)^+$. Anal. calcd for $C_{34}H_{36}ClN_3O_4S_2$: C, 62.79; H, 5.58; N, 6.46. Found: C, 62.70; H, 5.53; N, 6.30.

3-[3-*t*-Butylthio-1-(4-chlorobenzyl)-5-(2-quinolylmethoxy)indol-2-yl]-2,2-dimethylpropyloxyimino-2-propionic acid (3e). A mixture of **7** (700 mg, 1.3 mmol), methyl pyruvate (265 mg, 2.6 mmol), and acetic acid (0.2 mL) in methanol (20 mL), THF (35 mL), and water (10 mL) was stirred at rt for 12 h. The mixture was concentrated in vacuo and the residue was extracted with ethyl acetate, washed with water, dried ($MgSO_4$), and concentrated in vacuo. The residue was dissolved in methanol (25 mL) and treated with 1 N NaOH (3 mL) at rt for 14 h, concentrated in vacuo and the residue was acidified with 6 N HCl, extracted with ethyl acetate and purified by chromatography (silica gel, 9:1, CH_2Cl_2:MeOH) followed by crystallization from ethyl acetate–hexane to provide **3e** (375 mg, 44%). Mp 145–147 °C; ^1H NMR (300 MHz; DMSO-d_6) δ 0.89 (s, 6 H), 0.97 (s, 9 H), 1.85 (s, 3 H), 2.95 (m, 2 H), 3.86 (s, 2 H), 5.40 (s, 2 H), 5.52 (s, 2 H), 6.80 (d, *J* = 8 Hz, 1 H), 6.86 (d–d, *J* = 9 Hz and 3 Hz, 1 H), 7.14 (d, *J* = 3 Hz, 1 H), 7.30 (m, 3 H), 7.62 (m, 2 H), 7.78 (m, 1 H), 7.95 (d, *J* = 8 Hz, 1 H), 8.05 (d, *J* = 8 Hz, 1 H), 8.35 (d, *J* = 8 Hz, 1 H); MS (DCI–NH_3) *m/z* 658 $(M+H)^+$. Anal. calcd for $C_{37}H_{40}ClN_3O_4S{\cdot}2H_2O$: C, 64.06; H, 6.14; N, 6.06. Found: C, 63.56; H, 5.70; N, 6.01.

3-[3-*t*-Butylthio-1-(4-chlorobenzyl)-5-(4-thiazolylmethoxy)indol-2-yl]-2,2-dimethylpropyloxyimino-2-propionic acid (3f). Prepared by the method described for **3e**. Mp 110 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 0.95 (s, 6 H), 1.15 (s, 9 H), 1.93 (s, 3 H), 3.0 (m, 2 H), 4.05 (s, 2 H), 5.22 (s, 2 H), 5.53 (s, 2 H), 6.83 (m, 3 H), 7.18 (d, *J* = 3 Hz, 1 H), 7.30 (m, 3 H), 7.72 (d, *J* = 1.5 Hz, 1 H), 9.12 (d, *J* = 1.5 Hz, 1 H); MS (DCI-NH_3) *m/z* 614 $(M+H)^+$.

[3-*t*-Butylthio-1-(4-chlorobenzyl)-5-(2-quinolylmethoxy)-indol-2-yl]methoxyiminoacetic acid (11a). A mixture of 4-methoxyphenylhydrazine:HCl (5.95 g, 34 mmol) and ethyl 3-(*t*-butylthio)pyruvate (7.0 g, 34 mmol) in *t*-butanol (70 mL) was refluxed for 48 h, and then concentrated in vacuo. The residue was partioned between water and ethyl acetate and the organic layer was washed with water, brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by chromatography (silica gel, 2:1, hexane:EtOAc) to afford ethyl [3-(*t*-butylthio)-5-methoxyindo-2-yl]carboxylate (3.5 g, 34%). ^1H NMR (300 MHz, $CDCl_3$) δ 1.32 (s, 9 H), 1.45 (t, *J* = 7 Hz, 3 H), 3.88 (s, 3 H), 4.44 (q, *J* = 7 Hz, 2 H), 7.01 (d–d, *J* = 9 and 3 Hz, 1 H), 7.31 (m, 2 H), 9.10 (br s, 1 H); MS (DCI-NH_3) *m/z* 308 $(M+H)^+$, 325 $(M+NH_4)^+$. To a solution of this ester in DMF (50 mL) at 0 °C was added NaH (60% suspension in mineral oil, 460 mg, 11.5 mmol) and the mixture was stirred at rt for 15 min. Then *p*-chlorobenzyl chloride (1.93 g, 12 mmol) was added, the mixture was stirred at rt for 14 h, poured into water (200 mL), and extracted with ethyl acetate. The organic extract was washed with water, brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by chromatography (silica gel, 8:1, hexane:EtOAc) to provide ethyl [3-*t*-butylthio-1-(4-chlorobenzyl)-5-methoxyindol-2-yl]carboxylate (**8**) (4.1 g, 84%). ^1H NMR (300 MHz, $CDCl_3$) δ 1.30 (s, 9 H), 1.37 (t, *J* = 7 Hz, 3 H), 3.88 (s, 3 H), 4.35 (q, *J* = 7 Hz, 2 H), 5.65 (s, 2 H), 6.95 (m, 3 H), 7.20 (m, 3 H), 7.33 (d, *J* = 3 Hz, 1 H); MS (DCI-NH_3) *m/z* 432 $(M+H)^+$.

To a suspension of $AlCl_3$ (4.8 g, 36 mmol) in CH_2Cl_2 (15 mL) at 0 °C was added *t*-butylthiol (12 mL) followed by addition of **8** (3.77 g, 11 mmol) and the mixture was stirred for 45 min. The mixture was poured into ice-cold 1 N HCl (100 mL), extracted with ethyl acetate and concentrated in vacuo to provide crude ethyl [3-*t*-butylthio-1-(4-chlorobenzyl)-5-hydroxyindol-2-yl]carboxylate (4.2 g). To a solution of this hydroxyindole in DMF (60 mL) was added K_2CO_3 (1.66 g, 12 mmol) and 2-chloromethylquinoline (2.1 g, 12 mmol) and the mixture was stirred at 50 °C for 14 h. The mixture was partioned between water and ethyl acetate, and the organic extract was washed with water, brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed (silica gel, 2:1, hexane:EtOAc) to afford ethyl [3-*t*-butylthio-1-(4-chlorobenzyl)-5-(2-quinolylmethoxy)indol-2-yl] carboxylate (**9**) (1.7 g, 32%). ^1H NMR (300 MHz, $CDCl_3$) δ 1.15 (s, 9 H), 1.35 (t, *J* = 7 Hz, 3 H), 4.34 (q, *J* = 7 Hz, 2 H), 5.48 (s, 2 H), 5.63 (s, 2 H), 6.95 (d, *J* = 9 Hz, 2 H), 7.12 (d–d, *J* = 9 and 3 Hz, 1 H), 7.22 (m, 3 H), 7.44 (d, *J* = 3 Hz, 1 H), 7.56 (t, *J* = 8 Hz, 1 H), 7.73 (m, 2 H), 7.82 (d, *J* = 8 Hz, 1 H), 8.11 (m, 1 H), 8.20 (d, *J* = 8 Hz, 1 H); MS (DCI-NH_3) *m/z* 559 $(M+H)^+$ and ethyl [1-(4-chlorobenzyl)-5-(2-quinolylmethoxy)-3-(2-quinolylmethylthio)indol-2-yl]carboxylate **10** (3.0 g, 50%). A mixture of **9** (1.7 g, 3 mmol) and 1 N NaOH (10 mL, 10 mmol) in dioxane (15 mL) and methanol (30 mL) was refluxed for 6 h at 50 °C. The volatile organics were then removed in vacuo and the residue was acidified to pH 3 with

aqueous 10% citric acid. The resulting solid was collected by filtration and dried in vacuo to afford [3-*t*-butylthio-1-(4-chlorobenzyl)-5-(2-quinolylmethoxy)-indol-2-yl]carboxylic acid (1.15 g, 72%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.98 (s, 9 H), 5.43 (s, 2 H), 5.69 (s, 2 H), 7.02 (d, J = 9 Hz, 2 H), 7.11 (d–d, J = 9 and 3 Hz, 1 H), 7.21 (d, J = 3 Hz, 1 H), 7.34 (d, J = 9 Hz, 2 H), 7.50 (d, J = 9 Hz, 1 H), 7.63 (m, 2 H), 7.80 (m, 1 H), 7.96 (m, 1 H), 8.04 (d, J = 8 Hz, 1 H), 8.36 (d, J = 8 Hz, 1 H); MS (DCI-NH_3) m/z 531 $(M+H)^+$. To a solution of this acid (360 mg, 0.66 mmol) in THF (20 mL) at −15 °C was added triethylamine (0.1 mL, 0.7 mmol) followed by dropwise addition of ethyl chloroformate (0.07 mL, 0.7 mmol). The mixture was stirred at −15 to −10 °C for 20 min and then $NaBH_4$ (76 mg, 2 mmol) was added and the mixture was warmed to 0 °C. Methanol (10 mL) was then added very slowly over a 20-min period. The mixture was acidified to pH 4 and extracted with ethyl acetate (70 mL), washed with water, brine, and concentrated in vacuo to provide [3-*t*-butylthio-1-(4-chlorobenzyl)-5-(2-quinolylmethoxy)-indol-2-yl]methanol (340 mg, 99%). To a mixture of this alcohol, triphenylphosphine (262 mg, 1 mmol), and *N*-hydroxyphthalimide (108 mg, 0.66 mmol) in THF (25 mL) was added dropwise diethylazodicarboxylate (DEAD, 0.16 mL, 1 mmol). The mixture was left at rt for 15 h and then concentrated in vacuo. The residue was purified by chromatography (silica gel, 3:1, hexane:EtOAc) to afford [3-*t*-butylthio-1-(4-chlorobenzyl)-5-(2-quinolylmethoxy)indol-2-yl]methoxy-*N*-phthaloylamine (360 mg, 82%). A mixture of the *N*-phthaloyl intermediate (300 mg, 0.44 mmol) and hydrazine hydrate (0.05 mL, 0.9 mmol) in ethanol (10 mL) and dioxane (5 mL) was refluxed for 30 min and then cooled to rt. Aq 10% Na_2CO_3 was added and the mixture was extracted with ethyl acetate to afford crude [3-*t*-butylthio-1-(4-chlorobenzyl)-5-(2-quinolylmethoxy)indol-2-yl]methoxyamine (230 mg, 98%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.17 (s, 9 H), 4.97 (s, 2 H), 5.34 (s, 2 H), 5.45 (m, 4 H), 6.92 (d, J = 9 Hz, 2 H), 7.00 (d–d, J = 9 and 3 Hz, 1 H), 7.10 (d, J = 9 Hz, 1 H), 7.24 (d, J = 9 Hz, 2 H), 7.40 (d, J = 3 Hz, 1 H), 7.55 (m, 1 H), 7.72 (m, 2 H), 7.81 (m, 1 H), 8.10 (m, 1 H), 8.18 (d, J = 8 Hz, 1 H); MS (DCI-NH_3) m/z 532 $(M+H)^+$. To this amine in methanol (25 mL) was added glyoxylic acid (92 mg, 1 mmol) and acetic acid (0.06 mL, 1 mmol) and the mixture was stirred at rt for 14 h, then poured into water and extracted with ethyl acetate. The organic extract was washed with water, brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by chromatography (silica gel, 4:1, CH_2Cl_2:EtOH) to afford **11a** (100 mg, 37%). Mp 155–157 °C (methylene chloride:ethyl ether); ^{1}H NMR (300 MHz; DMSO-d_6) δ 1.00 (s, 9 H), 5.32 (s, 2 H), 5.42 (s, 2 H), 5.5 (s, 2 H), 7.01 (m, 3 H), 7.16 (d, J = 3 Hz, 1 H), 7.19 (s, 1 H), 7.33 (m, 3 H), 7.62 (m, 2 H), 7.79 (m, 1 H), 7.96 (d, J = 8 Hz, 1 H), 8.04 (d, J = 8 Hz, 1 H), 8.35 (d, J = 8 Hz, 1 H); MS (FAB(+)) m/z 588 $(M+H)^+$.

[3-*t*-Butylthio-1-(4-chlorobenzyl)-5-(2-quinolylmethoxy)-indol-2-yl]methoxyimino-2-propionic acid (11b). A mixture of *O*-(3-(*t*-butylthio)-1-(4-chlorobenzyl)-5-(2-quinolylmethoxy)indole-2-methyl)hydroxylamine (266 mg, 0.5 mmol), methyl pyruvate (0.06 mL, 0.6 mmol), and acetic acid (0.04 mL, 0.6 mmol) in dioxane (10 mL), methanol (10 mL), and water (2 mL) was stirred at room temperature for 12 h to provide the desired oxime derivative that was converted by the method described for **3e** to provide the desired product **11b** (150 mg, 50%). Mp 135–137 °C (decomp); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.02 (s, 9 H), 1.53 (s, 3 H), 5.42 (s, 2 H), 5.52 (s, 2 H), 5.57 (s, 2 H), 6.93 (d, J = 9 Hz, 2 H), 7.0 (d–d, J = 9 and 3 Hz, 1 H), 7.20 (d, J = 3 Hz, 1 H), 7.34 (m, 3 H), 7.65 (m, 2 H), 7.80 (m, 1 H), 7.96 (d–d, J = 8 and 2 Hz, 1 H), 8.05 (d, J = 8 Hz, 1 H), 8.36 (d, J = 8 Hz, 1 H); MS (DCI-NH_3) m/z 602 $(M+H)^+$; IR (in $CDCl_3$) 3440, 1760, 1710, 1620, 1600 cm^{-1}. Anal. calcd for $C_{33}H_{32}ClN_3O_4S$: C, 65.82; H, 5.36; N, 6.98. Found: C, 65.49; H, 5.30; N, 6.74.

[1-(4-Chlorobenzyl)-5-(2-quinolylmethoxy)-3-(2-quinolylmethylthio)indol-2-yl]methoxyimino-2-propionic acid (12a). Prepared from **10** (2.9 g, 4.5 mmol) according to the methods described for **11b** to provide after recrystallization from ethyl acetate:hexane **12a** (360 mg, 53% overall). Mp 110–113 °C (dec); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.42 (s, 3 H), 4.15 (s, 2 H), 5.16 (s, 2 H), 5.2 (s, 2 H), 5.45 (s, 2 H), 6.8 (d, J = 9 Hz, 1 H), 6.93 (m, 1 H), 7.05 (d, J = 3 Hz, 1 H), 7.22 (m, 4 H), 7.5 (m, 1 H), 7.63 (m, 3 H), 7.82 (m, 4 H), 8.0 (d, J = 8 Hz, 1 H), 8.08 (t, J = 8 Hz, 2 H), 8.41 (d, J = 8 Hz, 1 H); MS (DCI-NH_3) m/z 688 $(M+H)^+$, 705 $(M+NH_4)^+$; IR (KBr pellet): 3440, 1710, 1615, 1600 cm^{-1}. Anal. calcd for $C_{39}H_{31}ClN_4O_4S$: C, 68.16; H, 4.55; N, 8.15. Found: C, 68.11; H, 4.58; N, 7.79.

[1-(4-Chlorobenzyl)-5-(2-quinolylmethoxy)-3-(2-quinolylmethylthio)indol-2-yl]methoxyimino-4-pentanoic acid (12b). Prepared from **10** according to the methods described for **11b** using ethyl levulinate for oxime formation resulting in **12b** as a 4:1 mixture of Z and E isomers (120 mg, 66%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.36 and 1.70 (two s, 4:1, 3 H), 2.29 (m, 4 H), 4.11 (s, 2 H), 4.92 (m, 2 H), 5.18 and 5.20 (two s, 1:4, 2 H), 5.42 (broad s, 2 H), 6.82 (d, J = 9 Hz, 2 H), 6.90 (m, 1 H), 7.05 and 7.08 (two d, 1:4, J = 3 Hz, 1 H), 7.24 (m, 4 H), 7.50 (m, 1 H), 7.65 (m, 3 H), 7.82 (m, 3 H), 8.00 (d, J = 8 Hz, 1 H), 8.10 (m, 2 H), 8.41 (d, J = 8 Hz, 1 H), 12.09 (br s, 1 H); MS (DCI-NH_3) m/z 715 $(M+H)^+$; IR (in $CDCl_3$) 3680, 1710, 1620, 1600 cm^{-1}. Anal. calcd for $C_{41}H_{35}ClN_4O_4S$: C, 68.85; H, 4.93; N, 7.83. Found: C, 68.11; H, 4.90; N, 7.53.

(*Z*)-2-{[1-(4-chlorobenzyl)-5-(2-quinolylmethoxy)indol-2-yl]methoxyimino}propionic acid (17a). A mixture of 5-methoxyindole-2-carboxylic acid (**13**) (9.55 g, 50 mmol), $NaHCO_3$ (4.2 g, 50 mmol), and iodomethane (12.5 mL, 200 mmol) in DMF (50 mL) was stirred at rt for 28 h and then poured into ice-water (500 mL). The mixture was extracted with ethyl acetate (200 mL), washed with water, brine, dried ($MgSO_4$), and concentated in vacuo to provide 5-methoxyindole-2-carboxylic acid methyl ester (7.1 g, 69%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.76 (s, 3 H), 3.86 (s, 3 H),

6.91 (d–d, $J = 9$ and 3 Hz, 1 H), 7.06 (m, 1 H), 7.11 (d, $J = 3$ Hz, 1 H), 7.34 (d, $J = 9$ Hz, 1 H), 11.79 (br s, 1 H); MS (DCI-NH_3) m/z 206 $(M+H)^+$. This ester was converted by the methods previously described for **11b** to provide after recrystallization from ethyl acetate:hexane **17a** (80 mg, 10% overall). Mp 158–160 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 1.63 (s, 3 H), 5.36 (s, 4 H), 5.48 (s, 2 H), 6.59 (s, 1 H), 6.94 (m, 3 H), 7.30 (m, 4 H), 7.62 (m, 1 H), 7.70 (d, $J = 8$ Hz, 1 H), 7.80 (m, 1 H), 8.00 (m, 2 H), 8.40 (d, $J = 8$ Hz, 1 H), 13.00 (broad s, 1 H); MS (FAB(+)) m/z 514 $(M+H)^+$. Anal. calcd for $C_{29}H_{24}ClN_3O_4 \cdot 0.25\ H_2O$: C, 67.18; H, 4.76; N, 8.10. Found: C, 67.15; H, 4.40; N, 7.95.

(*Z*)-2-{[1-(4-chlorobenzyl)-5-(2-quinolylmethoxy)indol-2-yl]methoxyimino}-3-phenylpropionic acid (17b). Prepared by the method described for **17a** and oxime formation with phenylpyruvic acid provided after recrystallization from ethyl acetate–hexane **17b** (20 mg, 4% overall). Mp 133–136 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 3.53 (s, 2 H), 5.35 (s, 2 H), 5.38 (s, 2 H), 5.40 (s, 2 H), 6.57 (s, 1 H), 6.92 (m, 3 H), 7.02 (m, 2 H), 7.25 (m, 7 H), 7.62 (m, 1 H), 7.70 (d, $J = 8$ Hz, 1 H), 7.78 (m, 1 H), 8.00 (m, 2 H), 8.40 (d, $J = 8$ Hz, 1 H); MS (FAB(+)) m/z 590 $(M+H)^+$. Anal. calcd for $C_{35}H_{28}ClN_3O_4 \cdot 1.5\ H_2O$: C, 68.12; H, 5.06; N, 6.81. Found: C, 67.71; H, 4.23; N, 6.53.

{1-[1-(4-Chlorobenzyl)-5-(2-quinolylmethoxy)indol-2-yl]-1-but-3-enyloxyimino}acetic acid (17c). Prepared by the method described for **17e** substituting allylmagnesium chloride for *n*-butylmagnesium chloride. Mp 90–92 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 2.80 (m, 2 H), 3.62 (m, 1 H), 5.12 (m, 1 H), 5.45 (m, 5 H), 6.54 (s, 1 H), 6.94 (m, 3 H), 7.18 (d, $J = 3$ Hz, 1 H), 7.30 (m, 4 H), 7.60 (m, 1 H), 7.68 (d, $J = 9$ Hz, 1 H), 7.78 (m, 1 H), 8.0 (m, 2 H), 8.40 (d, $J = 9$ Hz, 1 H); MS (DCI-NH_3) m/z 540 $(M+H)^+$. Anal. calcd for $C_{31}H_{26}ClN_3O_4 \cdot H_2O$: C, 66.82; H, 5.05; N, 7.53. Found: C, 67.41; H, 5.46; N, 7.23.

{1-[1-(4-Chlorobenzyl)-5-(2-quinolylmethoxy)indol-2-yl]-2-phenylethyloxyimino}acetic acid (17d). Prepared according to the method described for **17e** substituting benzylmagnesium chloride for *n*-butylmagnesium chloride: mp 94–96 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 1.91 (s, 2 H), 5.36 (m, 4 H), 5.6 (t, $J = 7$ Hz, 1 H), 6.65 (s, 1 H), 6.85 (m, 3 H), 7.23 (m, 9 H), 7.61 (m, 1 H), 7.68 (d, $J = 9$ Hz, 1 H), 7.78 (m, 1 H), 8.01 (m, 3 H), 8.40 (d, $J = 9$ Hz, 1 H); MS (DCI-NH_3) m/z 590 $(M+H)^+$. Anal. calcd for $C_{35}H_{28}ClN_3O_4 \cdot 2\ H_2O$: C, 67.14; H, 5.11; N, 6.70. Found: C, 66.43; H, 5.00; N, 6.37.

{1-[1-(4-Chlorobenzyl)-5-(2-quinolylmethoxy)indol-2-yl]-1-pentyloxyimino}acetic acid (17e). A suspension of [1-(4-chlorobenzyl)-5-(2-quinolylmethoxy)indol-2-yl]-methanol (**15**) (3.9 g, 9.1 mmol) and barium manganate[9] (23 g, 90 mmol) in toluene (250 mL) was refluxed at 100 °C for 18 h. The reaction mixture was then cooled to rt and the solids were removed by filtration, washed with ethyl acetate, and THF. The filtrate and washings were combined and concentrated in vacuo to afford [1-(4-chlorobenzyl)-5-(2-quinolylmethoxy)indol-2-yl]carboxaldehyde (3.4 g, 88%). ^1H NMR (300 MHz, DMSO-d_6) δ 5.40 (s, 2 H), 5.80 (s, 2 H), 7.05 (d, $J = 9$ Hz, 2 H), 7.23 (d–d, $J = 9$ and 3 Hz, 1 H), 7.33 (d, $J = 9$ Hz, 2 H), 7.39 (d, $J = 3$ Hz, 1 H), 7.46 (m, 1 H), 7.60 (m, 2 H), 7.71 (d, $J = 8$ Hz, 1 H), 7.80 (m, 1 H), 8.01 (m, 2 H), 8.41 (d, $J = 8$ Hz, 1 H); MS (DCI-NH_3) m/z 427 $(M+H)^+$.

To a solution of aldehyde (852 mg, 2 mmol) in THF (50 mL) at −78 °C was added *n*-butylmagnesium chloride (2 M solution in ethyl ether, 1.5 mL, 3 mmol) and the resulting mixture was stirred at rt for 12 h. It was then quenched with aqueous saturated NH_4Cl and extracted with ethyl acetate (100 mL). The organic extract was dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed (silica gel, 2:1, hexane:ethyl acetate) to afford 900 mg (93%) of 1-[1-(4-chlorobenzyl)-5-(2-quinolylmethoxy)indol-2-yl]-1-pentanol (**16c**). ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, $J = 7$ Hz, 3 H), 1.30 (m, 3 H), 1.61 (m, 1 H), 1.90 (m, 2 H), 4.68 (m, 1 H), 5.44 (m, 4 H), 6.44 (s, 1 H), 6.88 (d, $J = 9$ Hz, 2 H), 6.95 (d–d, $J = 9$ and 3 Hz, 1 H), 7.06 (d, $J = 9$ Hz, 1 H), 7.17 (d, $J = 3$ Hz, 1 H), 7.22 (d, $J = 9$ Hz, 2 H), 7.55 (m, 1 H), 7.73 (m, 2 H), 7.83 (d, $J = 8$ Hz, 1 H), 8.10 (d, $J = 8$ Hz, 1 H), 8.19 (d, $J = 8$ Hz, 1 H); MS (DCI-NH_3) m/z 485 $(M+H)^+$.

To a solution of **16c** (650 mg, 1.3 mmol), triphenylphosphine (470 mg, 1.6 mmol) and *N*-hydroxyphthalimide (260 mg, 1.6 mmol) in THF (45 mL) was added dropwise DIAD (0.35 mL, 1.8 mmol) and the mixture was stirred at rt for 10 h. The THF was removed in vacuo and the residue was chromatographed (silica gel, 3:1, hexane:ethyl acetate) to provide 1-[1-(4-chlorobenzyl)-5-(2-quinolylmethoxy)indol-2-yl]-1-pentoxyl-*N*-phthaloylamine (630 mg, 77%). A mixture of the phthaloyl intermediate and hydrazine hydrate (0.2 mL, 3 mmol) in ethanol (20 mL) was refluxed for 30 min and then cooled to rt. Aq 10% Na_2CO_3 was added and the resulting mixture was extracted with ethyl acetate (75 mL). The organic layer was washed with water, brine, dried ($MgSO_4$), and concentrated in vacuo to provide 450 mg (90%) of 1-[1-(4-chlorobenzyl)-5-(2-quinolylmethoxy)indol-2-yl]1-pentoxyamine. A solution of amine, glyoxylic acid hydrate (165 mg, 1.8 mmol) and acetic acid (0.1 mL) in THF (60 mL), methanol (30 mL) and water (15 mL) was stirred at rt for 12 h. The volatile organics were removed in vacuo and the resulting residue was extracted with ethyl acetate, dried ($MgSO_4$), concentrated, and chromatographed (silica gel, 19:1, methylene chloride:methanol) followed by crystallization from ethyl acetate:hexane to afford **17e** (310 mg, 62%). Mp 125–127 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 0.78 (m, 3 H), 1.22 (m, 4 H), 1.95 (m, 2 H), 5.40 (m, 5 H), 6.54 (s, 1 H), 6.95 (m, 3 H), 7.20 (d, $J = 3$ Hz, 1 H), 7.30 (m, 4 H), 7.52 (m, 1 H), 7.70 (d, $J = 9$ Hz, 1 H), 7.80 (m, 1 H), 8.02 (m, 2 H), 8.42 (d, $J = 9$ Hz, 1 H); MS (DCI-NH_3) m/z 556 $(M+H)^+$. Anal. calcd for $C_{32}H_{30}ClN_3O_4$: C, 69.11; H, 5.43; N, 7.55. Found: C, 69.00; H, 5.50; N, 7.47.

{1-[1-(4-Chlorobenzyl)-5-(2-quinolylmethoxy)indol-2-yl]-1-cyclohexylmethoxyimino}acetic acid (17f). Prepared by the method of **17e** using cyclohexylmagnesium chloride. Mp 182–185 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.11 (m, 6 H), 1.72 (m, 5 H), 4.98 (d, J = 9 Hz, 1 H), 5.34 (s, 2 H), 5.45 (d, J = 9 Hz, 2 H), 6.36 (s, 1 H), 6.85 (m, 1 H), 7.05 (d, J = 9 Hz, 2 H), 7.15 (m, 2 H), 7.31 (m, 3 H), 7.61 (m, 1 H), 7.69 (d, J = 9 Hz, 1 H), 7.78 (m, 1 H), 8.00 (m, 2 H), 8.40 (d, J = 9 Hz, 1 H); MS (FAB(+)) m/z 582 $(M+H)^+$.

{1-[1-(4-Chlorobenzyl)-5-(2-quinolylmethoxy)indol-2-yl]-1-cyclohexylmethoxyimino}-2-propionic acid (17g). Prepared by the method of **17e** with oxime formation as described for **3e**. Mp 140 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.05 (m, 6 H), 1.55 (m, 3 H), 1.75 (s, 3 H), 1.95 (m, 2 H), 5.1 (d, J = 9 Hz, 1 H), 5.35 (s, 2 H), 5.45 (s, 2 H), 6.38 (s, 1 H), 6.85 (dd, J = 9 and 2 Hz, 1 H), 7.05 (d, J = 9 Hz, 2 H), 7.16 (m, 2 H), 7.30 (m, 2 H), 7.61 (m, 1 H), 7.70 (d, J = 8 Hz, 1 H), 7.78 (m, 1 H), 8.02 (m, 2 H), 8.40 (d, J = 8 Hz, 1 H); MS (DCI-NH_3) m/z 596 $(M+H)^+$. Anal. calcd for $C_{35}H_{34}ClN_3O_4 \cdot H_2O$: C, 68.51; H, 5.81; N, 6.85. Found: C, 68.72; H, 5.48; N, 6.75.

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